

Conformers of diheteroaryl ketones and thioketones: a quantum chemical study of their properties and fundamental intramolecular energetic effects

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Abstract The conformational behavior of ten diheteroaryl ketones and thioketones is investigated using various quantum chemical methods. These ketones and thioketones are formed by the disubstitution of formaldehyde and thioformaldehyde with such a heteroaryl group as 2-furanyl, 2-thiophenyl, 2-selenophenyl, 2-pyrrolyl or 1-methyl-2-pyrrolyl. For these compounds, their conformational preference and the energetic ordering of their conformers are determined at the MP2 and B3LYP levels of theory. Energetic barriers resulting from the interconversion between conformations are also estimated. The natural bond orbital (NBO) and interacting quantum atoms (IQA) methods are used to study fundamental intramolecular energetic effects influencing the stability of individual conformers. The results of the two methods indicate the great significance of the effect associated with electron delocalization (in the form of either NBO donor–acceptor interactions or the IQA interatomic exchange–correlation interaction energy) in governing the conformational behavior of the investigated diheteroaryl ketones and thioketones.

Keywords Diheteroaryl ketones · Diheteroaryl thioketones · Conformation · Quantum chemical calculations

Introduction

Chemical compounds exhibit many physical, chemical and biological properties that are closely related to the molecular structure of the compounds. The molecular structure of a chemical compound is characterized by the spatial arrangement of atoms in the molecules of this compound and by the bonds holding together atoms in the molecules. For some compounds, it is possible to change the spatial arrangement of atoms in their molecules by rotations about formally single bonds. In consequence, conformational isomerism is observed for such compounds, which means that the different molecular geometries of a given chemical compound, that is, its conformers, can be interconverted exclusively by rotations about formally single bonds [1, 2]. Interestingly, different conformers may possess quite distinct properties [3–5], and therefore, investigating the conformational behavior of chemical compounds is important from a practical point of view. From a more fundamental standpoint, the information about the preferred conformer of a given compound is helpful in understanding the intramolecular forces governing the conformational behavior of this compound [6–8].

In this work, the conformation of ten diheteroaryl ketones and thioketones is studied using a variety of quantum chemical methods. We focus on formaldehyde and thioformaldehyde disubstituted with such a five-membered heteroaryl group as 2-furanyl, 2-thiophenyl, 2-selenophenyl, 2-pyrrolyl or 1-methyl-2-pyrrolyl. Part of the compounds considered here have been synthesized only

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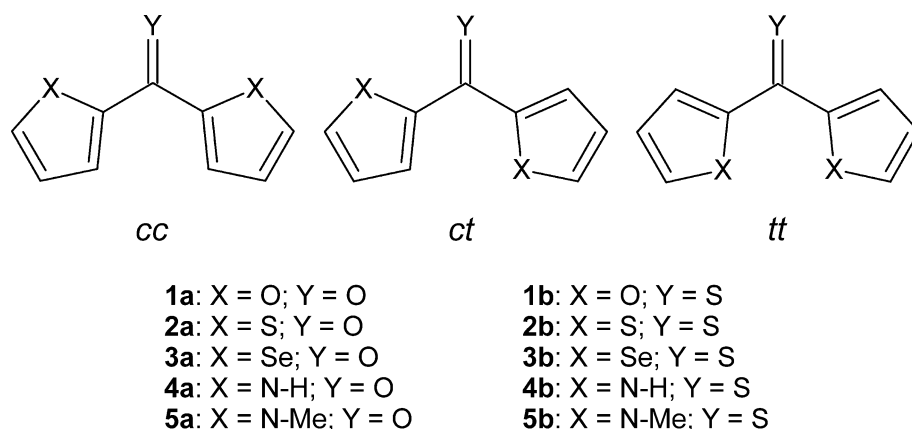
recently [9]. The structure of the investigated diheteroaryl ketones **1a–5a** is sketched in Scheme 1. This scheme also represents the corresponding diheteroaryl thioketones **1b–5b** if $Y=S$ is assumed. For compounds **1a–5a** and **1b–5b**, the occurrence of conformational isomerism in their molecules results from the rotations of the whole heteroaryl substituents about the single bonds between these substituents and the carbon atom of (thio)carbonyl group. Both for **1a–5a** and for **1b–5b**, it is possible to distinguish four characteristic rotatory conformations, depending on the relative orientation of the Y atom and the heteroatoms present in X. Three of the conformations are shown in Scheme 1. The X,Y-*cis* orientations for X in both heteroaryl substituents yield the conformation denoted by *cc* in the scheme. The occurrence of the X,Y-*cis* orientation for X belonging to one substituent, together with the X,Y-*trans* orientation involving X from another heteroaryl substituent, leads to the mixed conformation, marked by the abbreviation *ct* in Scheme 1. Because **1a–5a** and **1b–5b** possess two identical heteroaryl substituents, we consider the other mixed conformer, that is, the *tc*-one, to be equivalent to the *ct*-conformer for the purposes of the present study. Finally, the X,Y-*trans* orientations found for X in both heteroaryl substituents refer to the *tt*-conformation.

For some of the diheteroaryl ketones and thioketones considered here, their conformational behavior has previously been studied experimentally [10–13]. From dipole moment measurements, it is inferred that the *cc*-conformation is preferred for **2a** [10]. A more recent analysis of the dipole moments of **2a** and **2b** in benzene solutions suggests a mixture of *cc*-conformer and mixed conformers, with the former being more abundant (72 and 91 % for **2a** and **2b**, respectively) [11]. In the case of **1a** in benzene solution, its dipole moment is consistent with a mixture of *cc*-conformer and mixed conformers, with the latter being more abundant (73 %) [11]. Dipole moment measurements also show that the molecules of **4a** and **4b** tend to adopt the

cc-conformation in several nonpolar solvents [12]. The X-ray analysis of crystal **2a** indicates that the S atoms are always on the same side of the carbonyl group, and therefore, the *cc*-conformer of **2a** seems to display an attractive interaction between sulfur and oxygen [13]. Results from NMR spectra and lanthanide-induced shift measurements suggest that the O,O-*trans* orientation is largely preferred for **1a** in chloroform solution [13]. No definite conclusion on the preference of the *tt*-conformer relative to the *ct*-one can, however, be reached from the lanthanide-induced shift measurements for **1a**. The coexistence of various conformers also shows that the energy difference between the *ct*- and *tt*-conformers is relatively small for **1a**. In addition, the conformational behavior of **1a** in solution is expected to be dependent on the solvent applied and the *ct*-conformer is likely to become more stable in solvents of increasing polarity [13].

Molecular properties of various diheteroaryl ketones and thioketones have previously been investigated using theoretical methods [13–19]. In particular, the conformational behavior of such compounds has been the subject of many theoretical investigations because theoretical methods are an effective tool for detecting different conformers and determining their relative stabilities. The results of quantum chemical conformational analysis have so far been reported only for a small part of the compounds considered in this work. The results of early quantum chemical calculations performed at the HF/3-21G level of theory indicate that for **1a** its *ct*-conformer is slightly more stable than the *tt*-conformer, while the *cc*-conformer turns out to be the least stable in the gas phase [13]. For the conformations of **2a**, the ordering of relative energies calculated at the HF/3-21G* level follows $cc < ct < tt$ [13]. On the one hand, the prevalence of the *cc*-conformer for **2a** is confirmed by the results of calculations carried out using MP2/6-311G** [15], but, on the other hand, the most recent B3LYP/6-311G* calculation designates the *ct*-conformer as the global energy minimum [18]. In the above-mentioned

Scheme 1 Skeletal structural formulas of the investigated diheteroaryl ketones and thioketones in their three conformations



theoretical investigations, the conformational behavior of **1a** and **2a** is characterized by specifying the molecular geometries, relative energies and dipole moments of conformers.

In the present work, we start with providing the geometrical and energetic description of the conformations occurring in **1a–5a** and **1b–5b**. Standard wave function theory (WFT) and density functional theory (DFT) methods are used for this routine description. Next, we extend the analysis of the conformational behavior of the compounds in question and two quantum chemical methods with great interpretative potential, namely the natural bond order (NBO) analysis and the interacting quantum atoms (IQA) method, are employed to explain the conformational behavior from different perspectives. It is of great interest for us to establish whether these methods yield a consistent view of the conformational behavior of **1a–5a** and **1b–5b**. The fundamental intramolecular energetic effects that play stabilizing and destabilizing roles in individual conformations are also characterized in detail.

Computational details

The geometries of three gas-phase conformers for **1a–5a** and **1b–5b** in their ground electron states have been optimized at the WFT level using the Møller–Plesset second-order perturbation theory (MP2) [20, 21] and at the DFT level using Becke's three-parameter global hybrid density functional with the Vosko–Wilk–Nusair V local correlation and the Lee–Yang–Parr non-local correlation part (B3LYP) [22–24]. The def2-TZVP basis set [25] has been assigned to the atoms of all conformers optimized by MP2, whereas the B3LYP method has been combined with both def2-TZVP and def2-QZVPP [25]. For selected compounds, additional calculations have been carried out using B3LYP with Grimme's dispersion corrections (DFT-D) [26–28], MP2, SCS-MP2 [29], CCSD [30] and CCSD(T) [30]. These calculations involve the def2-QZVPP basis set. All WFT calculations take advantage of the resolution of the identity approximation [31]. The optimized geometries of all conformers have been confirmed to be local minima on the potential energy surface by calculating harmonic vibrational normal modes. All WFT and DFT calculations are done with TURBOMOLE 6.3.1 and 6.6 [32].

The wave functions of all conformers optimized at the B3LYP/def2-QZVPP level of theory are used for the NBO [33] and IQA [34] analyses. The NBO calculations have been carried out with the NBO 6.0 program [35], whereas the IQA calculations make use of the implementation available in AIMALL 14.06.21 [36]. NBO archive files (*.47) and AIM extended wave function files (*.wfx) required by the

above-mentioned programs have been generated by GAUSSIAN 09 D.01 [37].

Results and discussion

Relative energies

Let us begin the analysis of the conformational behavior of **1a–5a** and **1b–5b** with establishing the energetic preference of individual conformations. For each compound, the sequence of its three conformations is ordered with respect to increasing energy and then the energy of each conformation in the sequence is calculated relative to the energy of the preferred conformation, that is, the lowest energy one. The energy of each conformer is expressed as its total electron energy E and its Gibbs free energy G at 298.15 K. The former does not include the zero-point vibrational energy. For the preferred conformation, its relative energies ΔE and ΔG are obviously equal to zero, whereas less energetically favorable conformations exhibit positive values of ΔE and ΔG . The values of ΔE and ΔG for ketones **1a–5a** and thioketones **1b–5b** in three conformations are listed in Tables 1 and 2. The tabulated results have been obtained from MP2/def2-TZVP and B3LYP/def2-QZVPP. Calculations at the B3LYP/def2-TZVP level have also been carried out, but they do not give any new insights over those of B3LYP/def2-QZVPP; therefore, they are not presented and discussed in this section (the results of the B3LYP/def2-TZVP calculations can be found in Tables S1 and S2, see Electronic Supplementary Material).

It is evident that there is no single conformation that is preferred for the whole set of investigated compounds. Both energetic criteria, that is, ΔE and ΔG , indicate that the *ct*-conformation is most favorable for **1a** and **1b**, while the *cc*-conformation is designated as the preferred one for the remaining compounds. The preference of the *ct*-conformation detected in this work for **1a** and the preference of the *cc*-conformation for **2a** agree with the findings reported in two previous theoretical investigations of these compounds [13, 15].

Three conformations found for **1a** can be ordered in the following sequence $ct < tt < cc$ with respect to the growing values of ΔE and ΔG . The same is observed for **1b**, although the ΔE criterion obtained from the MP2/def2-TZVP method predicts that the *tt*-conformation is less favorable than the *cc*-conformation. In this case, the difference between the ΔE values of these two conformations is, however, very small and, what is more important, the ordering is corrected when the ΔG values are considered. We will return to the issue of the quality of the MP2/def2-TZVP results further in this section. For **2a–5a** and **2b–5b**, the increases in ΔE and ΔG follow the ordering

Table 1 Some selected energetic (ΔE and ΔG in kcal/mol) and structural (τ_1 and τ_2 in $^\circ$) parameters calculated for three conformations of **1a–5a**

Conformer	MP2/def2-TZVP					B3LYP/def2-QZVPP				
	ΔE	ΔG	P	τ_1	τ_2	ΔE	ΔG	P	τ_1	τ_2
<i>cc-1a</i>	1.24	2.73	1	−19.1	−19.1	2.14	2.84	1	−17.7	−17.7
<i>ct-1a</i>	0.00	0.00	80	0.0	180.0	0.00	0.00	67	−0.1	179.9
<i>tt-1a</i>	0.51	0.84	19	180.0	180.0	0.34	0.44	32	180.0	180.0
<i>cc-2a</i>	0.00	0.00	55	−20.5	−20.5	0.00	0.00	55	−18.6	−18.6
<i>ct-2a</i>	0.83	0.21	39	−20.4	156.2	0.77	0.17	41	−15.9	157.9
<i>tt-2a</i>	1.58	1.28	6	156.8	156.8	1.85	1.56	4	159.2	159.2
<i>cc-3a</i>	0.00	0.00	71	−20.1	−20.1	0.00	0.00	80	−18.1	−18.1
<i>ct-3a</i>	1.22	0.61	26	−20.6	153.8	1.41	0.84	19	−16.0	154.6
<i>tt-3a</i>	2.15	1.90	3	154.5	154.5	2.93	2.73	1	155.9	155.9
<i>cc-4a</i>	0.00	0.00	99	−10.5	−10.5	0.00	0.00	100	−4.9	−4.9
<i>ct-4a</i>	3.20	2.91	1	−15.5	159.7	3.82	3.69	0	−12.6	161.8
<i>tt-4a</i>	8.09	7.91	0	154.4	154.4	8.99	8.94	0	156.4	156.4
<i>cc-5a</i>	0.00	0.00	100	−21.0	−21.0	0.00	0.00	100	−19.7	−19.7
<i>ct-5a</i>	4.54	3.42	0	−19.3	143.3	5.37	4.35	0	−17.5	142.5
<i>tt-5a</i>	6.36	5.33	0	143.4	143.4	9.63	6.89	0	143.1	143.1

Populations of individual conformers (P in %) are also tabulated

Table 2 Some selected energetic (ΔE and ΔG in kcal/mol) and structural (τ_1 and τ_2 in $^\circ$) parameters calculated for three conformations of **1b–5b**

Conformer	MP2/def2-TZVP					B3LYP/def2-QZVPP				
	ΔE	ΔG	P	τ_1	τ_2	ΔE	ΔG	P	τ_1	τ_2
<i>cc-1b</i>	0.49	1.22	9	−22.0	−22.0	1.46	2.58	1	−21.4	−21.4
<i>ct-1b</i>	0.00	0.00	74	−13.0	163.8	0.00	0.00	82	−6.4	172.5
<i>tt-1b</i>	0.55	0.88	17	160.1	160.1	0.31	0.92	17	164.5	164.5
<i>cc-2b</i>	0.00	0.00	69	−24.0	−24.0	0.00	0.00	65	−22.8	−22.8
<i>ct-2b</i>	1.13	0.52	28	−25.3	150.0	0.99	0.42	32	−21.5	149.7
<i>tt-2b</i>	2.24	1.91	3	149.5	149.5	2.22	1.92	3	150.6	150.6
<i>cc-3b</i>	0.00	0.00	77	−23.6	−23.6	0.00	0.00	80	−22.2	−22.2
<i>ct-3b</i>	1.37	0.75	22	−24.8	147.8	1.44	0.85	19	−19.9	146.3
<i>tt-3b</i>	2.62	2.29	1	148.0	148.0	3.00	2.71	1	148.9	148.9
<i>cc-4b</i>	0.00	0.00	99	−15.9	−15.9	0.00	0.00	100	−13.9	−13.9
<i>ct-4b</i>	3.37	2.94	1	−17.7	155.9	3.92	3.40	0	−15.3	157.3
<i>tt-4b</i>	8.54	8.21	0	152.2	152.2	9.41	8.91	0	154.0	154.0
<i>cc-5b</i>	0.00	0.00	77	−27.9	−27.9	0.00	0.00	97	−27.8	−27.8
<i>ct-5b</i>	2.05	1.05	13	−29.6	142.9	3.05	1.99	3	−27.6	142.0
<i>tt-5b</i>	2.01	1.22	10	142.7	142.7	5.04	3.81	0	142.0	142.0

Populations of individual conformers (P in %) are also tabulated

$cc < ct < tt$. Again, an exception occurs for MP2/def2-TZVP, whose ΔE results for **5b** suggest that the *tt*-conformation is slightly more favorable than the *ct*-conformation. In general, the differences in energies in all sequences of conformations span the range of several kcal/mol and they divide the investigated compounds into two groups. Taking the values of ΔG obtained from B3LYP/def2-QZVPP into consideration, we can see that the ΔG values of the least favorable conformers do not exceed 3 kcal/mol for **1a–3a** and **1b–3b**. In particular, the

ΔG values for the *tt*-conformers of **2a** and **2b** are lower than 2 kcal/mol. On the other hand, the ΔG values calculated for the *tt-4a*, *tt-4b*, *tt-5a* and *tt-5b* are significantly larger, with the maximal value amounting to 8.94 kcal/mol for *tt-4a*.

The existence of both N,O-*cis* and N,O-*trans* conformations has been detected by FTIR for a series of 2-pyrrolyl chloromethyl ketones and 1-methyl-2-pyrrolyl chloromethyl ketones in cyclohexane solution [38]. In this case, the conformational stability is, however, governed

mainly by intermolecular hydrogen bonding interactions. Theoretical calculations for isolated molecules of these ketones [38], as well as of several related compounds [39–45], indicate that their N,O-*cis* conformers possess lower total electron energies than the respective N,O-*trans* conformers, which fully corresponds with the energetic ordering of the *cc*- and *tt*-conformers for **4a** and **5a**.

It is also expedient to compare our ΔE values for the conformers of **1a** and **2a** with the results of previous quantum chemical calculations [13, 15]. The comparison reveals that there is one significant discrepancy between our ΔE values and the previous ones. For the *cc*-conformer of **1a**, Benassi et al. [13] have predicted that the ΔE value amounts to 7.55 kcal/mol, whereas our values are 1.24 and 2.14 kcal/mol, depending on the level of theory applied. The ΔE value of 7.55 kcal/mol seems to be severely overestimated, which most probably results from the poor accuracy and simplifications of the computational methodology used by Benassi et al.

Populations of individual conformers for each compound are also shown in Tables 1 and 2. These populations are based on the ΔG values inserted into the well-known Boltzmann formula. Expressing the ΔG values of individual conformations in terms of the populations of the corresponding conformers allows us to collate our results for **1a**, **2a** and **2b** with the experimental data. Although the absolute values of the populations calculated in this work differ from those deduced from the experimental dipole moment measurements [11], two main findings are shared. First, the population of the *ct*-conformation is predominant for **1a**, while the percentage of the *cc*-conformer outnumbers that of the *ct*-conformer for **2a** and **2b**. In all these cases, the populations of the dominating conformer exceed 50 %. Second, the population of the *cc*-conformer grows on going from **2a** to **2b**. Our results do not support the conjecture made by Lumbroso et al. [11] about the noticeable contribution of the *cc*-conformation in **1a**. According to the results of our calculations, the population of the *cc*-conformer is negligible (1 %). Instead of the *cc*-conformer, the *tt*-conformer becomes abundant, with its population of 19 and 32 % at the MP2/def2-TZVP and B3LYP/def2-QZVPP levels, respectively.

As stated previously, the ΔE values yielded by MP2/def2-TZVP and the corresponding B3LYP/def2-QZVPP values lead to the reverse ordering of two higher-energy conformations for **1b** and **5b**. In order to establish whether the reverse ordering is a consequence of the quantum chemical method applied or the basis set effect, additional calculations using several quantum chemical methods in conjunction with the def2-QZVPP basis set have been performed. It is known that DFT methods do not account for dispersive interactions and, for that reason, B3LYP is combined with three versions of Grimme's dispersion

correction. Selected representatives of WFT methods are also taken into account. Of them, the CCSD(T) method is used to provide reference results. Two reasons argue for selecting CCSD(T)/def2-QZVPP to be an appropriate level of theory for calculating reference energies reliably. The first reason is that the def2-QZVPP basis set is close to the complete basis set limit [46]. The second one relies on a highly likely assumption that post-CCSD(T) effects are insignificant [47]. Because of the very high computational cost of CCSD(T), only two compounds, namely **1b** and its ketone counterpart, are considered here and the CCSD(T) method is used to calculate single-point energies for the conformers in their B3LYP/def2-QZVPP-optimized geometries. Table 3 presents the ΔE values obtained by the aforementioned DFT and WFT methods for **1a** and **1b** in three conformations. Perusing the tabulated results leads to several findings. First, the B3LYP/def2-QZVPP level of theory is able to reproduce the reference ordering of three conformations in **1a** and **1b**. On this basis, it can be assumed that the sequences of conformations for **2a–5a** and **2b–5b** are also predicted by this method reliably. However, the comparison of the absolute ΔE values calculated by B3LYP/def2-QZVPP with the CCSD(T)/def2-QZVPP ones reveals that B3LYP/def2-QZVPP underestimates the ΔE values for the *tt*-conformers of **1a** and **1b**, while the ΔE values of the *cc*-conformers are overestimated by ca. 0.5 kcal/mol. In other words, B3LYP/def2-QZVPP overestimates the energy gap between the conformer of the lowest energy and the conformer of the highest energy. It is in line with previous reports for such energy gaps in *n*-alkanes [47] and cyclohexane derivatives [48]. Second, the addition of Grimme's dispersion correction to B3LYP has a noticeable influence on ΔE values, but it does not change the ordering in the sequences of conformations for both compounds. It is rather difficult to answer a question whether the presence of Grimme's dispersion correction improves the accuracy of the calculated ΔE values. It seems to be heavily dependent on the version of such a correction. B3LYP-D3/def2-QZVPP is outperformed by B3LYP/def2-QZVPP, while the other two B3LYP-D methods yield the ΔE values that are closer to the reference ones than those of B3LYP/def2-QZVPP. In particular, the D2 correction provides a noticeable improvement in the calculated ΔE values. Interestingly, D2 is the simplest dispersion correction of those considered here. A cursory review of literature reveals an ambiguous effect of dispersion correction on relative energies of conformers. On the one hand, Grimme's dispersion corrections considerably improve relative energies for selected conformers of 4-ethyl-4-methyloctane [49] and melatonin [50], but, on the other hand, the presence of such a correction leads to qualitatively wrong conformer ordering in alkanes [47]. Third, for all three B3LYP-D methods, the differences

Table 3 Relative energies between conformers (ΔE in kcal/mol) calculated at various levels of theory for **1a** and **1b**

Method	ΔE					
	<i>cc-1a</i>	<i>ct-1a</i>	<i>tt-1a</i>	<i>cc-1b</i>	<i>ct-1b</i>	<i>tt-1b</i>
B3LYP/def2-QZVPP ^a	2.14	0.00	0.34	1.46	0.00	0.31
B3LYP-D2/def2-QZVPP ^b	1.84	0.00	0.62	1.09	0.00	0.46
B3LYP-D3/def2-QZVPP ^b	2.25	0.00	0.47	1.59	0.00	0.30
B3LYP-D3(BJ)/def2-QZVPP ^b	1.91	0.00	0.58	1.37	0.00	0.43
MP2/def2-QZVPP ^b	1.29	0.00	0.64	0.40	0.00	0.62
SCS-MP2/def2-QZVPP ^b	1.32	0.00	0.76	0.39	0.00	0.70
CCSD/def2-QZVPP ^b	1.56	0.00	0.89	0.82	0.00	0.79
CCSD(T)/def2-QZVPP ^b	1.60	0.00	0.79	0.97	0.00	0.70
B3LYP-D2/def2-QZVPP ^c	1.71	0.00	0.63	1.00	0.00	0.48
B3LYP-D3/def2-QZVPP ^c	2.25	0.00	0.48	1.59	0.00	0.31
B3LYP-D3(BJ)/def2-QZVPP ^c	1.90	0.00	0.59	1.36	0.00	0.43
MP2/def2-QZVPP ^c	1.22	0.00	0.65	0.51	0.00	0.61

^a Repeated after Tables 1 and 2

^b The values of ΔE are calculated for the structures optimized at the B3LYP/def2-QZVPP level of theory

^c The same method is used for geometry optimization and calculating ΔE

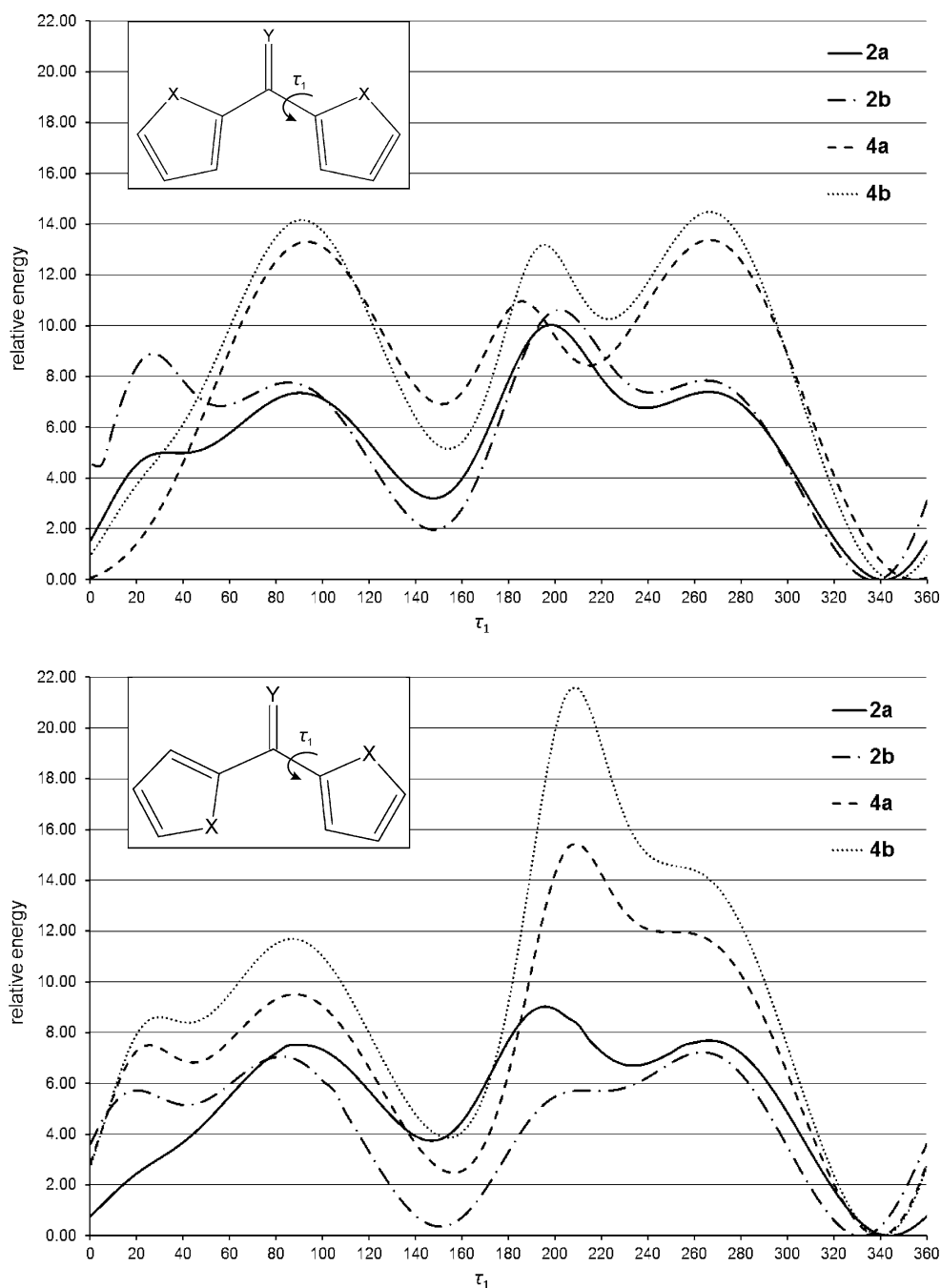
between the ΔE values obtained for the B3LYP/def2-QZVPP-optimized conformers and for the geometries optimized using the dispersion-corrected versions of B3LYP are small, which indicates that the geometries of the conformers are not strongly affected by intramolecular dispersion. Fourth, the WFT results in Table 3 facilitate the assessment of the MP2/def2-TZVP results. One could suspect that the basis set effect is responsible for the quality of the MP2/def2-TZVP calculations. It is known that WFT methods generally require extended basis sets, while the def2-TZVP basis set is relatively modest, which may be the reason of inaccuracies in E . However, MP2/def2-QZVPP still predicts the reverse ordering of *cc-1b* and *tt-1b*; hence, it excludes the basis set effect. In consequence, the MP2 method itself exhibits a deficiency in the values of E for the conformers of **1b** and **5b**. Fifth, the spin-component scaled variant of MP2 demonstrates poor accuracy in the calculated ΔE value for the *cc-1b*, which results in the wrong ordering of the *cc*- and *tt*-conformers. On the other hand, SCS-MP2 shows an improvement in ΔE for **1a** over MP2, which in turn is in line with previous reports on the improved performance of SCS-MP2 in providing the structural and energetic description of conformations for molecules [50, 51] and molecular complexes [52–54].

Interconversion barriers

Energy barriers for the interconversion between individual conformations in a molecule give an indication on how easy a change in the conformations occurs, and on this basis, a conclusion on the flexibility of molecular structure can be drawn. Now we attempt to establish what changes in

the total electron energy E are associated with the rotation of the whole heteroaryl substituent about the single C–C bond linking this substituent with the C atom of (thio)-carbonyl group. However, we are interested in estimating roughly the order of magnitude of changes in E for the molecular motion involving such a rotation rather than in calculating the accurate values of energy barriers for the interconversion between individual conformations. In order to determine the relation between the E energy and the rotation of heteroaryl substituent, a fragment of potential energy surfaces (PESs) for **2a**, **2b**, **4a** and **4b** has been examined. To be precise, a one-dimensional variant of the PESs has been probed with respect to the X–C–C=O dihedral angle, ranging from 0° to 360° (in the case of **4a** and **4b**, the N atom of their 2-pyrrolyl substituents corresponds to X in the X–C–C=O angle). This angle will be denoted here by τ_1 , and its changes define the rotation of one heteroaryl substituent about the single C–C bond. The arrangement of the other heteroaryl substituent is kept fixed, and it corresponds to either the X,Y-*cis* orientation found in the fully optimized *cc*-conformer or the X,Y-*trans* orientation of the fully optimized *tt*-conformer. As a result, two sets of geometries with different τ_1 angles have been generated for each of the four above-mentioned compounds, and then for each geometry, its single-point energy is calculated at the B3LYP/def2-QZVPP level of theory. Such a computational procedure allows us to express E as a function of τ_1 , and the PESs obtained in this manner are shown in Fig. 1. To make the analysis of the PESs easy, the energy scales in Fig. 1 present relative energies. In the upper plot, the E energies of *cc-2a*, *cc-2b*, *cc-4a* and *cc-4b* are assumed to be zero, whereas *ct-2a*, *ct-2b*, *ct-4a* and *ct-*

Fig. 1 PESs for the rotation of heteroaryl substituent in **2a**, **2b**, **4a** and **4b**. Relative energies are given in kcal/mol, and the angle of rotation (τ_1 in $^\circ$) is assumed to change in the range from 0° to 360°



4b occupy the zero level in energy in the bottom plot. It should be stressed that in general the relative energy shown in Fig. 1 is not identical to the ΔE energy discussed in the previous section because the latter is determined for fully optimized geometries.

A quick glance at the plots in Fig. 1 reveals that several local minima and maxima appear on the PESs. The relatively complex shape of the PESs suggests that the rotation of one heteroaryl substituent is affected by the presence of the other heteroaryl substituent, and it is dependent on the

orientation of the other substituent. The local minima occurring for τ_1 around 150° in the upper and bottom plots correspond to the *ct*- and the *tt*-conformations, respectively (although these minima are not the conformers whose structures are fully optimized). The upper plot shows that the interconversion from the *cc*-conformation to the *ct*-conformation requires surmounting the barriers of at least several kcal/mol, while the bottom plot indicates that the barriers of the interconversion from the *tt*-conformation to the *ct*-conformation are even higher. The values of relative

energy at the highest energy points on the PESs are 10.02, 10.61, 15.43 and 21.56 kcal/mol for **2a**, **2b**, **4a** and **4b**, respectively. These maximal values of relative energy allow us to estimate the magnitude of energy barriers for the rotation of the 2-thiophenyl and 2-pyrrolyl groups. The maximal values of relative energy for **2a** and **2b** occur for the transition of the 2-thiophenyl group from the S,Y-*cis* to S,Y-*trans* orientation, with the second 2-thiophenyl group being in the S,Y-*cis* orientation. The other orientation of the second 2-thiophenyl group lowers slightly the maximal values of relative energy on going from the *ct*-conformer to the *tt*-conformer. The rotation of the 2-pyrrolyl group is accompanied by larger values of relative energy than those observed for the rotation of the 2-thiophenyl group. The maximal values of relative energy in **4a** and **4b** are found for the transition from the *ct*-conformation to the *tt*-conformation, which indicates that the latter is not easily adopted. It correlates with the negligible population of the *tt*-conformer for these compounds. The maximal relative energy predicted here for the rotation from *cc*-**2a** to *ct*-**2a** (9.02 kcal/mol) is not very far from the experimental activation energy of 7.48 kcal/mol found for the transition between the *ct*-conformation and the *tt*-conformation in the ketyl radical generated from di-2-thiophenyl ketone [55]. The presence of a heteroaryl group may hinder the rotation of another heteroaryl group in diheteroaryl ketone or thioketone. The comparison of the difference in relative energy at the highest and lowest energy points on the PESs for **4a** with the energy barrier calculated previously for 2-pyrrolyl aldehyde [56, 57] shows that the former is approximately twice as large as the latter. Similarly, the energy barrier for **2a** demonstrates a higher value when it is collated with the values of energy barriers calculated for 2-thiophenyl aldehyde [58] and thiophene-2-carbonyl fluoride [59].

In principle, the magnitude of maximal relative energies for **2a** and **2b** is different from that for **4a** and **4b**. Irrespective of whether one 2-thiophenyl group is in its S,Y-*cis* or S,Y-*trans* orientation, the rotation of the other 2-thiophenyl group leads to smaller energy barriers than those occurring for the rotation of the 2-pyrrolyl group in **4a** and **4b**. It is in line with the division of the investigated compounds into two groups with respect to the magnitude of ΔE , as it was mentioned in the previous section. The heights of the energy barriers in Fig. 1 correlate qualitatively with the previously presented values of ΔE . The values of ΔE for the conformers of **2a** and **2b** are smaller than the ΔE values for **4a** and **4b**. Similarly, the maximal relative energies for **2a** and **2b** do not exceed 10.6 kcal/mol, whereas the maximal values of relative energy for **4a** and **4b** are much greater. It generally leads to the conclusion that **2a** and **2b** are more flexible systems than **4a** and **4b**. The higher-energy barrier for the rotation of 2-pyrrolyl

group compared to the rotational barrier of 2-thiophenyl group is also observed for 2-heteroaryl chromium aminocarbene [60].

The magnitude of energy barriers in **2a**, **2b**, **4a** and **4b** is also affected by the kind of the Y atom. For the transition from the *cc*-conformation to the *ct*-conformation, thioketones exhibit higher relative energies of local maxima and lower relative energies of local minima around τ_1 of 150° on the PESs than the corresponding ketones.

To conclude the discussion on the interconversion barriers, we can expect that the rotation of heteroaryl substituents in **4a**, **4b**, **5a** and **5b** is more restricted than the rotation of heteroaryl substituents in the remaining compounds. Furthermore, the rotation of heteroaryl fragments in thioketones turns out to be more hindered than in the corresponding ketones.

Geometries

Let us now describe briefly the optimized geometries of the conformers found for **1a–5a** and **1b–5b**. For all these compounds, their *cc*- and *tt*-conformers exhibit the C_2 point group symmetry, with the twofold rotation axis lying along the double bond of (thio)carbonyl group. As for the *ct*-conformers of the compounds, their optimized geometries do not manifest the presence of any rotation axis or mirror plane. We will focus on one characteristic feature of the geometries of the investigated compounds, namely on the spatial orientation of the heteroaryl groups with respect to the (thio)carbonyl group. Two dihedral X–C–C=Y angles define such an orientation and their changes dictate to the rotation of the heteroaryl rings about the single C–C bonds (as it was described in the previous section). These two angles will be referred to as τ_1 and τ_2 , and their values occurring in the conformers of **1a–5a** and **1b–5b** are listed in Tables 1 and 2. For the *cc*- and *tt*-conformers, whose geometries belong to the C_2 point group, the values of τ_1 and τ_2 are obviously identical. In general, two heteroaryl substituents being a part of each conformer in the investigated compounds prefer a non-planar orientation and their planes are leaned outward in the opposite directions. The values of τ_1 and τ_2 additionally give us an indication on the deviation of the heteroaryl rings from a coplanar arrangement with the (thio)carbonyl group. There are, however, two exceptions to the non-planar arrangement of the heteroaryl rings. *tt*-**1a** demonstrates a strictly planar molecular geometry. The orientation of two 2-furanyl groups in *ct*-**1a** is also very close to coplanarity both with each other and with the carbonyl group.

It is interesting to analyze some possible relations between τ_1 or τ_2 and the kind of X and Y in the investigated compounds. For the *cc*-conformation, the distortion of the heteroaryl groups from a coplanar arrangement with

the (thio)carbonyl group diminishes gradually along the sequence of X: N–Me > S > Se > O > N–H. In the case of the *tt*-conformation, the decrease in the distortion from planarity follows the sequence in X: N–Me > Se > S > N–H > O. It is rather obvious that the bulkiest X of those considered here, that is N–Me, prevents both *cc*- and *tt*-conformers from adopting a planar structure. When X is a group 16 heteroatom and it changes from O to Se, the distortion in the *tt*-conformation correlates with the growing size of the heteroatoms. For this conformation, the heteroatoms are close to each other, and thus, their lone electron pairs are in the immediate neighborhood, which seems to directly affect the distortion of the heteroaryl substituents. The magnitude of the distortion of conformer geometry from planarity is also dependent on the kind of the Y atom. Ketones **1a–5a** possess the heteroaryl substituents whose planes are leaned less outward than it is in the corresponding thioketones **1b–5b**.

We end the analysis of the calculated τ_1 and τ_2 structural parameters by comparing them with the available experimental data. According to an early experimental dipole moment measurement for the preferred conformer of **2a** in solution, a dihedral angle of $45^\circ \pm 10^\circ$ between the planes of two 2-thiophenyl rings has been inferred [10]. A more recent experimental study of the crystal structure of **2a** reports that the S–C–C=O angle in the *cc*-conformer amounts to -21.6° [13]. Our values of τ_1 and τ_2 calculated for *cc*-**2a** in the gas phase predict a slightly less distorted geometry.

NBO analysis

In order to better understand the reasons for the conformational behavior of **1a–5a** and **1b–5b**, the NBO analysis of their conformers has been carried out. Within the framework of the NBO analysis, the total energy of a molecule can be decomposed into a Lewis-type component E^L and a non-Lewis-type component E^{NL} . The former represents the energy of an idealized structure with all bonds and lone pair orbitals perfectly localized and doubly occupied. The latter describes the energetic effect arising from the deviation of the molecule from its idealized structure, and thus, it can be used as a measure of electron delocalization [33].

Here, the B3LYP/def2-QZVPP total energy of each conformer for **1a–5a** and **1b–5b** is decomposed into the E^L and E^{NL} components, and their values are expressed relative to E^L and E^{NL} found for the preferred conformer of each compound. The resulting ΔE^L and ΔE^{NL} values are presented in Tables 4 and 5. They allow us to estimate the relative importance of E^L and E^{NL} in establishing the energetic ordering of individual conformers for each

compound. According to the values of ΔE^L , the *cc*-conformation turns out to be least stable for all investigated compounds except **1b**. However, this conformation is favored by E^{NL} and the values of ΔE^{NL} evolve in the sequence *cc* < *ct* < *tt* for the majority of the compounds. The greatest stabilization of the *cc*-conformation by the E^{NL} component can be clarified in terms of electron delocalization. Strictly speaking, a significant π -conjugation is expected for a trans arrangement of the C=Y bond and the adjacent C=C bond of the heterocyclic ring (for this bond, there is a high π -electron density) [10, 61]. This π -conjugation can be illustrated by the energies of specific donor–acceptor interactions $E^{(2)}$ estimated using a standard second-order perturbation treatment [33]. As a matter of fact, the values of $E^{(2)}$ for the delocalizing interactions between the π - and π^* -orbitals of the C=Y group and of the heteroaryl rings most often become less and less negative in the sequence from *cc* to *ct* and to *tt*, which means that the *cc*-conformation is stabilized by these interactions most effectively. In addition, the trend in the inner stabilization of the heteroaryl substituents (that is, the delocalization between the lone pairs of the heteroatoms and the π^* -orbitals of the rings) imitates this sequence strictly. The $LP_{Xs} \rightarrow \pi^*_{rings}$ interaction and generally the interactions taking place between the orbitals of each heteroaryl substituents are large in magnitude, which is obviously a consequence of the strong delocalization over every aromatic ring. In the case of **1a** and **1b**, the values of $E^{(2)}$ also give a clear indication on the reasons for the low stabilization of their *cc*-conformers. For these two compounds, the stabilization resulting from the $\pi_{rings} \rightarrow \pi^*_{C=Y}$ delocalization shows less negative $E^{(2)}$ values for the *cc*-conformers than for the other conformers. The difference in the $E^{(2)}$ values of the $LP_{Xs} \rightarrow \pi^*_{rings}$ delocalization for the *cc*- and *tt*-conformers of **1a** and **1b** is also smaller than for the remaining compounds. The trend in the $E^{(2)}$ values of the π -conjugative interactions that favor the *cc*-conformation in **2a–5a** and **2b–5b** is usually opposite to that observed for the $E^{(2)}$ values of σ -hyperconjugative interactions. In general, the hyperconjugative interaction between $\sigma_{C=Y}$ and σ^*_{rings} stabilizes the *tt*-conformation most effectively.

The values of the delocalizing interactions between the orbitals of the heteroaryl substituents and the orbitals of the C=Y groups are less negative for the ketones than for the corresponding thioketones, and therefore, the stabilization resulting from these interactions is diminished for **1a–5a** relative to the corresponding **1b–5b**. The σ , σ^* , π and π^* orbitals of carbonyl group lie much higher in energy than those of thiocarbonyl group, while the energies of the orbitals of the heteroaryl substituents change only slightly while going from the ketones to the corresponding

Table 4 Relative energies (ΔE) and some selected results of the NBO analysis for **1a–5a** in three conformations

Conformer	ΔE^a	ΔE^L	ΔE^{NL}	ΔE^{SX}	$E^{(2)}$				
						$\sigma_{C=Y} \rightarrow \sigma_{rings}^*$	$\pi_{C=Y} \rightarrow \pi_{rings}^*$	$\sigma_{rings} \rightarrow \sigma_{C=Y}^*$	$\pi_{rings} \rightarrow \pi_{C=Y}^*$
<i>cc-1a</i>	1.24	2.49	-0.35	-4.79	-2.80	-11.60	-2.88	-35.70	-118.04
<i>ct-1a</i>	0.00	0.00	0.00	0.00	-3.63	-11.64	-2.56	-40.80	-113.91
<i>tt-1a</i>	0.51	-0.75	1.10	-2.62	-4.28	-10.44	-2.26	-41.78	-114.18
<i>cc-2a</i>	0.00	0.00	0.00	0.00	-3.48	-10.82	-3.04	-37.44	-97.90
<i>ct-2a</i>	0.77	-8.82	9.59	-5.39	-3.56	-9.75	-3.43	-37.90	-94.77
<i>tt-2a</i>	1.85	-5.50	7.35	-4.18	-3.62	-8.40	-4.06	-37.88	-92.16
<i>cc-3a</i>	0.00	0.00	0.00	0.00	-3.62	-11.10	-3.04	-37.80	-74.08
<i>ct-3a</i>	1.41	-7.74	9.15	-6.78	-3.75	-9.77	-3.83	-37.05	-71.70
<i>tt-3a</i>	2.93	-5.96	8.89	-6.99	-3.90	-8.32	-4.90	-36.50	-69.02
<i>cc-4a</i>	0.00	0.00	0.00	0.00	-3.98	-12.08	-3.02	-48.18	-158.38
<i>ct-4a</i>	3.82	-14.73	18.54	-22.18	-3.83	-10.97	-2.86	-42.57	-153.88
<i>tt-4a</i>	8.99	-25.26	34.25	-27.56	-3.76	-9.50	-2.64	-38.04	-132.62
<i>cc-5a</i>	0.00	0.00	0.00	0.00	-3.24	-10.32	-3.84	-44.06	-156.42
<i>ct-5a</i>	5.37	-9.12	14.49	-3.16	-3.40	-8.94	-2.95	-36.55	-146.11
<i>tt-5a</i>	9.63	-19.82	29.45	-4.34	-3.72	-7.62	-2.10	-31.14	-141.20

The NBO quantities are described in the text. All values in kcal/mol

^a Repeated after Table 1

Table 5 Relative energies (ΔE) and some selected results of the NBO analysis for **1b–5b** in three conformations

Conformer	ΔE^a	ΔE^L	ΔE^{NL}	ΔE^{SX}	$E^{(2)}$				
						$\sigma_{C=Y} \rightarrow \sigma_{rings}^*$	$\pi_{C=Y} \rightarrow \pi_{rings}^*$	$\sigma_{rings} \rightarrow \sigma_{C=Y}^*$	$\pi_{rings} \rightarrow \pi_{C=Y}^*$
<i>cc-1b</i>	1.47	-2.72	4.18	-4.08	-6.96	-20.44	-3.82	-41.20	-118.58
<i>ct-1b</i>	0.00	0.00	0.00	0.00	-8.79	-20.47	-3.38	-48.63	-114.08
<i>tt-1b</i>	0.31	-0.73	1.04	-7.88	-9.14	-17.62	-3.10	-48.34	-114.32
<i>cc-2b</i>	0.00	0.00	0.00	0.00	-7.48	-17.72	-4.14	-43.72	-97.84
<i>ct-2b</i>	0.99	-5.91	6.90	-3.74	-7.46	-16.13	-4.70	-42.49	-94.50
<i>tt-2b</i>	2.21	-6.08	8.30	-13.19	-7.36	-14.58	-5.62	-41.62	-91.54
<i>cc-3b</i>	0.00	0.00	0.00	0.00	-7.56	-18.02	-4.34	-44.76	-73.88
<i>ct-3b</i>	1.43	-5.82	7.25	-4.97	-7.58	-16.26	-5.21	-41.90	-71.30
<i>tt-3b</i>	2.99	-6.72	9.71	-15.79	-7.84	-14.72	-6.66	-40.80	-68.48
<i>cc-4b</i>	0.00	0.00	0.00	0.00	-8.72	-18.42	-4.14	-59.60	-161.60
<i>ct-4b</i>	3.92	-8.66	12.58	-5.54	-8.87	-17.77	-3.69	-51.78	-152.82
<i>tt-4b</i>	9.41	-24.86	34.26	-20.30	-8.48	-16.36	-3.42	-45.58	-134.20
<i>cc-5b</i>	0.00	0.00	0.00	0.00	-6.74	-15.06	-4.92	-50.52	-155.48
<i>ct-5b</i>	3.06	-5.77	8.83	-7.06	-7.36	-14.46	-3.93	-43.54	-150.62
<i>tt-5b</i>	5.04	-13.30	18.35	-9.90	-8.22	-13.80	-2.96	-38.58	-143.22

The NBO quantities are described in the text. All values in kcal/mol

^a Repeated after Table 2

thioketones. It leads to larger energy gaps between the donor and acceptor orbitals for the ketones. Since each value of $E^{(2)}$ depends inversely on the energy gap between

the respective donor and acceptor orbitals, the larger energy gaps encountered in the ketones result in less negative $E^{(2)}$ values and hence the smaller stabilization of the

ketones. It emphasizes that the delocalization due to the conjugative and hyperconjugative interactions with the carbonyl group is less efficient than that involving the interactions with the thiocarbonyl group. It is in line with the findings reported in previous comparative NBO studies of various carbonyl and thiocarbonyl compounds [62–64]. The larger stabilization through the π -conjugative orbital interactions occurs in **1b–5b** in spite of the spatial arrangement of their heteroaryl substituents. The heteroaryl substituents in **1b–5b** are more leaned outward than in the corresponding **1a–5a**, and it actually should reduce the π -conjugation between the heteroaryl substituents and the C=S group.

The importance of electron delocalization in governing the conformational behavior of the investigated compounds can also be deduced from the values of ΔE^{SX} . Within the framework of the NBO steric analysis [65], donor–donor orbital interactions are taken into consideration in order to estimate the magnitude of steric exchange energy E^{SX} in a molecule. Tables 4 and 5 present the ΔE^{SX} energies that are calculated relative to the E^{SX} energy of the preferred conformer for each compound. It should be noted here that the use of DFT wave functions may sometimes lead to unphysical artifacts in NBO steric calculations [66], and therefore, the correctness of the findings presented in this paragraph has been also confirmed at the HF/def2-QZVPP level (see Tables S3 and S4, Electronic Supplementary Material). It is evident from the tabulated values of ΔE^{SX} that the conformers other than the preferred ones exhibit negative values of ΔE^{SX} (the E^{SX} values themselves are positive, so the negative values of ΔE^{SX} for these other conformers correspond to E^{SX} that are less positive than the E^{SX} values of the preferred conformers). It means that for each compound its preferred conformer is characterized by the largest steric repulsion. However, the stabilization energy of donor–acceptor delocalization more than compensate for such an unfavorable effect. It implies that the delocalizing orbital interactions acting in **1a–5a** and **1b–5b** are a very important factor influencing the stability and ordering of their conformers.

IQA analysis

Having analyzed the natural orbital viewpoint on the conformational stability of the investigated ketones and thioketones, let us now examine the fundamental intramolecular energetic effects governing the conformational behavior of these compounds from a different (that is, orbital free) perspective.

The results of the IQA analysis performed for charge density distributions calculated at the B3LYP/def2-QZVPP level of theory are given in Tables 6 and 7. The ΔE values calculated using the IQA method differ slightly from the

corresponding values obtained from ordinary single-point B3LYP/def2-QZVPP calculations (see Tables 1 and 2). The deviations in the IQA values of ΔE amount to 0.37 kcal/mol at the very most, and these deviations result from numerical inaccuracies in integrations over atomic basins. Because IQA calculations generally are very time-consuming, the basin quadratures and integration methods used in our IQA calculations have been of standard quality in order to lower slightly the computational cost of these calculations. In Tables 6 and 7, several IQA energy components are presented relative to the values of these components found for the preferred conformer of each compound. All the IQA energy components shown in the tables are described in detail in Section S1; see Electronic Supplementary Material.

In general, two monotonous regularities in the values of IQA energy components are clearly evident for **1a–3a** and **1b–3b**. The values of ΔE^{intra} become more and more negative while going from the *cc*-conformers of these compounds to their *ct*-conformers and further to their *tt*-conformers, which means that the stabilizing influence of the intraatomic energy E^{intra} is largest for the *tt*-conformers. The opposite trend occurs for the values of ΔE^{inter} , and the interatomic interaction energy E^{inter} is most energetically favorable for the *cc*-conformers of **1a–3a** and **1b–3b**. From the trends in E^{intra} and E^{inter} , it can be concluded that the E^{inter} component is responsible for the preference of the *cc*-conformation in **2a**, **2b**, **3a** and **3b**.

Within the framework of the IQA theory, various intramolecular energetic effects can be classified with respect to their physical nature. Accordingly, the values of ΔE are partitioned into the kinetic energy component ΔE_{kin} , the classical electrostatic component ΔE_{elst} and the purely quantum mechanical, exchange–correlation component ΔE_{xc} . For all investigated compounds, the ΔE_{kin} component definitely disfavors their preferred conformers. In consequence, the conformational preference for the majority of the compounds is established on grounds of electrostatic and exchange–correlation interactions. For a few higher-energy conformers, their ΔE_{elst} values are negative, but in such cases the large and positive ΔE_{xc} component outweighs and shifts these conformers higher in ΔE . Although the E_{xc} energy is regarded as a quantum mechanical correction whose order of magnitude is one or two times smaller than that of E_{elst} , the importance of ΔE_{xc} in ordering the higher-energy conformers is usually comparable to that of ΔE_{elst} . The trend in the values of ΔE_{xc} always remains in qualitative agreement with that observed for ΔE .

Tables 6 and 7 also show the interatomic components of electrostatic energy $E_{\text{elst}}^{\text{inter}}$ and exchange–correlation energy $E_{\text{xc}}^{\text{inter}}$. The magnitude of $E_{\text{elst}}^{\text{inter}}$ is much smaller than its

Table 6 Some selected results of the IQA analysis for **1a–5a** in three conformations

Conformer	ΔE	ΔE^{intra}	ΔE^{inter}	ΔE_{kin}	ΔE_{elst}	ΔE_{xc}	$E_{\text{elst}}^{\text{inter}}$	$E_{\text{xc}}^{\text{inter}}$
<i>cc-1a</i>	1.99	11.58	−9.58	−2.07	1.87	2.19	−938.23	−4279.71
<i>ct-1a</i>	0.00	0.00	0.00	0.00	0.00	0.00	−931.39	−4276.97
<i>tt-1a</i>	0.12	−4.90	5.02	−1.17	0.80	0.49	−926.38	−4276.96
<i>cc-2a</i>	0.00	0.00	0.00	0.00	0.00	0.00	−77.79	−4393.68
<i>ct-2a</i>	0.99	−5.32	6.31	0.05	0.38	0.55	−73.80	−4391.36
<i>tt-2a</i>	1.86	−9.77	11.63	−1.90	2.11	1.66	−69.81	−4390.03
<i>cc-3a</i>	0.00	0.00	0.00	0.00	0.00	0.00	−201.02	−4298.63
<i>ct-3a</i>	1.31	−7.59	8.90	0.29	−0.48	1.51	−194.38	−4296.37
<i>tt-3a</i>	2.87	−14.94	17.82	−1.70	0.74	3.84	−187.30	−4294.53
<i>cc-4a</i>	0.00	0.00	0.00	0.00	0.00	0.00	−885.25	−4691.47
<i>ct-4a</i>	4.05	−0.11	4.17	−2.81	3.66	3.20	−881.08	−4691.47
<i>tt-4a</i>	9.33	−16.68	26.01	−8.53	10.36	7.50	−859.98	−4690.73
<i>cc-5a</i>	0.00	0.00	0.00	0.00	0.00	0.00	−769.17	−5867.63
<i>ct-5a</i>	5.00	−10.28	15.29	−4.23	5.12	4.12	−754.74	−5866.77
<i>tt-5a</i>	9.59	−5.82	15.41	−8.32	10.44	7.47	−754.57	−5866.82

The IQA quantities are explained in the text. All values in kcal/mol

Table 7 Some selected results of the IQA analysis for **1b–5b** in three conformations

Conformer	ΔE	ΔE^{intra}	ΔE^{inter}	ΔE_{kin}	ΔE_{elst}	ΔE_{xc}	$E_{\text{elst}}^{\text{inter}}$	$E_{\text{xc}}^{\text{inter}}$
<i>cc-1b</i>	1.45	21.85	−20.40	−1.63	2.00	1.08	−563.36	−4309.08
<i>ct-1b</i>	0.00	0.00	0.00	0.00	0.00	0.00	−546.97	−4305.08
<i>tt-1b</i>	0.42	−13.97	14.39	−0.69	−0.83	1.93	−533.95	−4303.71
<i>cc-2b</i>	0.00	0.00	0.00	0.00	0.00	0.00	320.31	−4424.92
<i>ct-2b</i>	1.06	−10.22	11.28	0.09	−0.01	0.99	328.07	−4421.40
<i>tt-2b</i>	2.23	−19.11	21.34	−1.94	1.53	2.64	334.29	−4417.56
<i>cc-3b</i>	0.00	0.00	0.00	0.00	0.00	0.00	204.81	−4329.54
<i>ct-3b</i>	1.41	−10.54	11.95	0.18	−0.45	1.69	213.41	−4326.19
<i>tt-3b</i>	3.18	−22.85	26.03	−1.55	0.52	4.20	223.98	−4322.68
<i>cc-4b</i>	0.00	0.00	0.00	0.00	0.00	0.00	−485.58	−4713.31
<i>ct-4b</i>	4.16	7.80	−3.63	−3.11	5.79	1.48	−487.26	−4715.25
<i>tt-4b</i>	9.67	−5.10	14.77	−9.13	14.83	3.98	−466.69	−4717.42
<i>cc-5b</i>	0.00	0.00	0.00	0.00	0.00	0.00	−350.90	−5893.21
<i>ct-5b</i>	3.14	8.17	−5.02	−1.30	3.21	1.23	−355.36	−5893.78
<i>tt-5b</i>	4.88	12.91	−8.02	−3.95	6.36	2.48	−357.72	−5894.41

The IQA quantities are explained in the text. All values in kcal/mol

intraatomic counterpart, but the differences between the $E_{\text{elst}}^{\text{inter}}$ values for the conformers of each compound are close to the differences between the values of the intraatomic electrostatic component. The same is valid for $E_{\text{xc}}^{\text{inter}}$ and its intraatomic counterpart. From the values of $E_{\text{elst}}^{\text{inter}}$, the preference of the *cc*-conformation can be deduced for all the compounds except **4b** and **5b**. For these two compounds, the preference of the *cc*-conformation is recovered after the inclusion of the intraatomic electrostatic component, as it can be evidenced by the ΔE_{elst} values for **4b** and **5b**. Interestingly, the positive values of $E_{\text{elst}}^{\text{inter}}$ are detected for **2b** and **3b**, which indicates that the interatomic

electrostatic interaction destabilizes the conformers of **2b** and **3b**. Of the $E_{\text{elst}}^{\text{inter}}$ and $E_{\text{xc}}^{\text{inter}}$ components, the latter contributes the main share to the interatomic stabilization E^{inter} (the percentage of $E_{\text{xc}}^{\text{inter}}$ in E^{inter} always far exceeds 80 %). There is no single regularity in the values of $E_{\text{xc}}^{\text{inter}}$ for all the investigated compounds. However, the combination of the intra- and interatomic exchange–correlation components yields the ΔE_{xc} values that perfectly mimic the trends in ΔE . The values of $E_{\text{xc}}^{\text{inter}}$ are usually most negative for the *cc*-conformation, which is in line with the significant π -conjugation expected for this conformation. The $E_{\text{xc}}^{\text{inter}}$ component is regarded as an energetic signature of

electron delocalization, and its values indeed reflect the increasing π -conjugative interactions while going from the *tt*-conformation to the *ct*-conformation and further to the *cc*-conformation. The NBO and IQA energetic quantities evaluating the electron delocalization effect in the conformers of the investigated compounds seem to be closely related to one another (the coefficient of determination for the linear regression between E_{xc}^{inter} and E^{NL} for all conformers amounts to 0.87).

To end up this section, the IQA results confirm that the classical electrostatic effects contribute significantly to the determination of the preference and ordering of the investigated conformers, but the comprehensive explanation of the conformational behavior of all the investigated compounds indisputably requires the combination of the classical electrostatic energy component with the quantum mechanical, exchange–correlation energy component. The latter component includes the effects associated with electron delocalization.

Conclusions

In this work, the conformational behavior of five diheteroaryl ketones **1a–5a** and the corresponding thioketones **1b–5b** has been established using quantum chemical WFT and DFT methods. The intramolecular energetic effects governing the conformational behavior of these compounds have been studied by means of the NBO and IQA methods. The conformational isomerism in the molecules of the investigated compounds stems from the possibility of rotation about two C–C bonds linking the C=Y group with the heteroaryl substituents. The results presented in this work lead to the following findings.

1. The molecules of the investigated diheteroaryl ketones and thioketones can exist in three conformations, denoted here as *cc*, *ct* and *tt* in order to indicate the spatial arrangement of the heteroatoms with respect to the Y atom. The overwhelming majority of the conformers found for the investigated compounds exhibit a non-planar geometry, with their heteroaryl substituents leaned outward in the opposite directions. The picture of the conformational behavior for all ten compounds is not uniform. The *ct*-conformation is most energetically favorable for **1a** and **1b**, and the energetic stability of three conformations in the two compounds decreases in the sequence $ct > tt > cc$. In contrast to the two compounds, the remaining diheteroaryl ketones and thioketones order their conformers relative to the decreasing energetic stability as $cc > ct > tt$. Thus, the *cc*-conformation is designated as the preferred one for **2a–5a** and **2b–5b**.

2. The differences in energy between the individual conformers of each investigated compound span a range of several kcal/mol. The calculated energetic profiles for the interconversion between the conformations of **2a**, **2b**, **4a** and **4b** show that the resulting energy barriers for **2a** and **2b** are much smaller than those of **4a** and **4b**. Thus, the rotation of the heteroaryl substituents in the molecules of **4a**, **4b**, **5a** and **5b** seems to be rather restricted and the remaining compounds are more flexible in their conformational interconversions. Furthermore, the rotation of the heteroaryl fragments in the thioketones turns out to be hindered to a greater extent than it is in the corresponding ketones.

3. The results of the NBO and IQA analyses clearly point out that the electrostatic effects are not solely responsible for the preference and ordering of the conformers. For each compound, its preferred conformer is heavily destabilized by either the steric repulsion (from the NBO perspective) or the kinetic energy component (from the IQA perspective). Such an effect is compensated totally or at least to a great extent by the stabilization resulting from either donor–acceptor delocalizing interactions (from the NBO perspective) or the exchange–correlation energy component (from the IQA perspective). It proves the importance of the energetic effect associated with electron delocalization in governing the conformational behavior of the investigated compounds.

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