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DFT Calculations and Statistical Mechanics Applied to Isomerization of Pseudosaccharins

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Abstract

In the present work, molar fractions were obtained as a function of temperature with different levels of theory for the most representative isomers of three systems belonging to the family of pseudosaccharins. The choice of those three systems was due to the fact that it is known in the scientific literature that these systems present very small differences in their relative energies which make a complicated experimental characterization, in addition these compounds are of interest in the biological area. These systems represent challenges not only from an experimental point of view but also from a theoretical point of view. From the theoretical perspective, this study is also complicated since several possible isomers with very similar energies are presented. The diagrams of species distribution (molar fractions) provide information that cannot be accessed through the electronic structure calculations at T = 0. Here, this tool was useful to identify the most probable isomer from several quasi-degenerate isomers and to discern if thermal effects favor any of them, as well as to find trends despite the different results of each level of theory. Additionally, an analysis was performed on vibrational, rotational and electronic data in order to know the reason of the behavior of molar fractions as function of temperature.

Keywords: molar fractions, pseudosaccharin, isomerism, DFT calculations, statistical mechanics

1. Introduction

Having the same chemical composition, a molecule can present different geometrical arrangements of atoms, leading to distinct chemical and physical properties. Here lies the importance

of knowing the arrangement of the atoms inside molecules. The different atomic arrangements in a molecule are known as isomers and their study gives rise to isomerization or isomerism. Computational chemistry is one of the most used tools in this branch of research. Through the analysis of stabilities by means of the electronic energy, the isomers that could be found in an experiment can be known. However, when the energetic differences between isomers are very small, it is difficult to assure that the lower energy isomer is the only one present in the experiment. Existing models, both in the framework of methods of electronic structure or molecular dynamics, have contributed greatly to the study of the different types of isomerization, and have been improved taking into account, for example, the inclusion of solvents. Despite advances in theory and technology, no current theoretical methodology is 100% accurate. This leads to the fact that it is not sufficient to consider only the results yielded by these methods, mainly in molecules whose isomers have very similar energies, which could be considered as part of the error associated to the level of theory.

For this reason, given the importance of elucidating the isomerism of a molecular system with very small energy differences, it is important to make use of other tools. In this chapter, we will obtain diagrams of species predominance (molar fractions) as a function of the temperature (assuming that the equilibrium has been reached) for some systems of the pseudosaccharin family that have isomeric structures with small energy differences and are of great importance in various fields of applied sciences.

Pseudosaccharins, also known as benzisothiazoles, are molecular systems with a wide variety of properties. Their structures are derived from saccharin, which is the first synthetic sweetener that is still used with that aim, but also has many industrial applications. Its photosensitive properties have aroused interest in the derivatives of this system for applications of synthesis of coordination compounds and bioorganic synthesis [1]. Its general structure can be seen in **Figure 1**, where **R** can be any other functional group or molecule. Additionally, these structures may present a tautomerism known as Chapman rearrangement [2]; this internal reaction of the structure consists in the movement of the **R** group to the oxygen of the carbonyl group as the temperature increases. Depending on the degrees of freedom that the **R** group possesses, different structures can be formed with different properties, reason
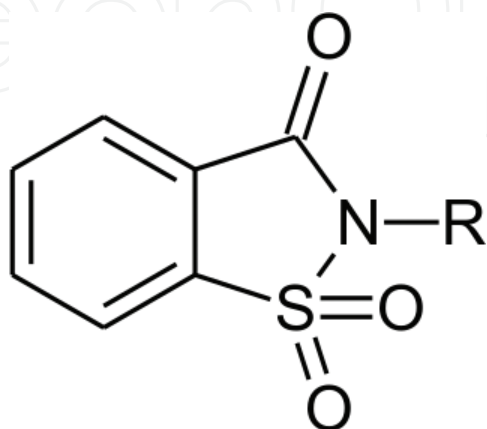

Figure 1. General structure for the family of pseudosaccharins.

why such rearrangement has awakened the interest to elucidate the mechanism of isomerization [3]. Moreover, pseudosaccharins are receptors of a quite potent electronic density that has called attention in research areas of synthesis of organic compounds.

Pseudosaccharins are compounds of interest in several fields of research, specifically in biologically active systems [4]. Their usage has been reported in the treatment of cardiac and hepatic diseases [5, 6], and even for the treatment of breast cancer, as antibiotic agents and herbicides [7–9]. Adding to these applications, Hlasta et al. [10] proposed a series of compounds of the pseudosaccharins family as inhibitors of the human leukocyte elastase protein, which causes the destruction of the connective tissue of the lungs in people with pulmonary emphysema. They also found how this series of compounds have therapeutic usage in people with this condition [10, 11].

Due to the importance of this type of compounds, studies have been carried out to characterize experimentally and theoretically both their structure and properties. A high reactivity can be found mainly in the junction of the heterocyclic ring and **R**, due to an electron-withdrawing effect of the pseudosaccharyl ring system, which is the reason of the Chapman-like rearrangement. The properties of the pseudosaccharins can be modified depending on which structures are combined with saccharin. In the case of tetrazole-saccharin, the properties of tetrazole, which can be very reactive, have been combined with saccharin, resulting in a greater stability of the tetrazole [12]. Furthermore, the combination of an allyl group with saccharin can also form compounds with the properties mentioned in previous paragraphs.

In previous studies [4, 13, 14], the importance of isomerization in these systems has been demonstrated. As the **R** group can be very flexible, it gives rise to several possible isomers. This can lead to challenges in the characterization of these compounds, since there could be a mixture of isomers whose population can become significant during the synthesis. As a result, there are signals in spectrophotometry [4, 12, 13] that cannot be associated with a precise isomer. Theoretical analysis can ease to obtain the different spectra of the possible isomers and the spectra could be weighted by a number or parameter, for example, a calculated molar fraction. However, when there are small energy differences, it is important to consider the methodology used to obtain the most probable isomers to study; that is, having the challenge of solving structures whose differences in energy are small, methodology becomes very important, because a different functional and basis set (BS) could give rise to different relative stabilities between the isomers.

Due to all the previously mentioned, in the present chapter a systematic study of the isomerization of three pseudosaccharins, which have very small energy differences between them and that have also been previously studied experimentally and theoretically, is performed. For this study, a variation of functional and BS is carried out, however, considering that a better comparison can be made between experimental and theoretical results if thermal effects are taken into account, molar fractions are obtained for the different isomers of pseudosaccharins. It is important to mention that, unlike previous studies on these compounds, populations are obtained as a function of temperature, taking into account different contributions through the vibrational, rotational and electronic partition functions. From this, it is possible to observe the effects of methodology in the molar fractions, as well as to find the reason of behavior of molar fractions plots.

2. Theoretical background

All calculations were performed with Gaussian09 suite of programs [15], while the construction of graphics of molar fractions as a function of temperature was made with a program designed by Professor Slanina et al. [16]. Relaxation of molecular structures, vibrational frequencies, rotational constants and excited states were obtained through B3LYP [17, 18], M06-2X [19] and PBE [20] exchange-correlation (XC) functionals, along with 6-311++G(3df,3pd), 6-31++G(3df,3pd), 6-311+G(d,p) and 6-31+G(d,p) [21, 22] basis. The choice of the methodology was made taking as a starting point the level of theory used in previous studies [4, 13, 14]. Additionally, the other functionals and BSs were used in order to be able to compare the results and analyze the importance of the methodology. It is important to mention that, for selected cases, total electronic energies were refined through the second-order Møller-Plesset perturbation theory, MP2, along with 6-311++G(3df,3pd) and 6-31+G(d,p) level of calculation.

In this work, calculations of molar fractions (x_i) including thermal effects for n isomers have been obtained through their partition functions q_i and the enthalpies at the absolute zero temperature or ground-state energies $\Delta H^0_{0,i}$ (i.e. the relative potential energies corrected for the vibrational zero-point energies) by the formula:

$$x_i = \frac{q_i\, exp\left(-\Delta H^0_{0,i}/RT\right)}{\sum_{j=1}^{n} q_j\, exp\left(-\Delta H^0_{0,j}/RT\right)} \tag{1}$$

where R is the gas constant and T the absolute temperature. It is worth to mention that, as it is expected, single point calculations (MP2 results) are not corrected by the vibrational zero-point energies. Eq. (1) is an exact formula of the isomers, supposing the conditions of the inter-isomeric thermodynamic equilibrium. Rotational-vibrational partition functions were constructed from the calculated structural and vibrational data using the rigid rotator and harmonic oscillator (RRHO) approximation. The electronic partition function was constructed by 10 time-dependent electronic excitation energies. All calculations were performed taking into account a tight convergence in the self-consistent field calculation, and an ultrafine mesh in the integration.

3. Results and discussion

From previous studies on pseudosaccharins, three isomers were reported for 2-allyl-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide (ABIOD) [4], five isomers for allyl ether 3-(allyloxy)-1,2-benzisothiazole1,1-dioxide (ABID) [13] and six isomers for tetrazole-saccharyl [14]. The isomers for each pseudosaccharyl molecule were obtained through the rotation of two dihedral angles as will be explained in the next subsections. It is shown in **Figure 2(a)** the ABIOD pseudosaccharyl, in **Figure 2(b)** the ABID pseudosaccharyl and in **Figure 2(c)** and **(d)** tetrazole saccharine. The numbers are needed to understand the formation of the different isomers through dihedral angles.
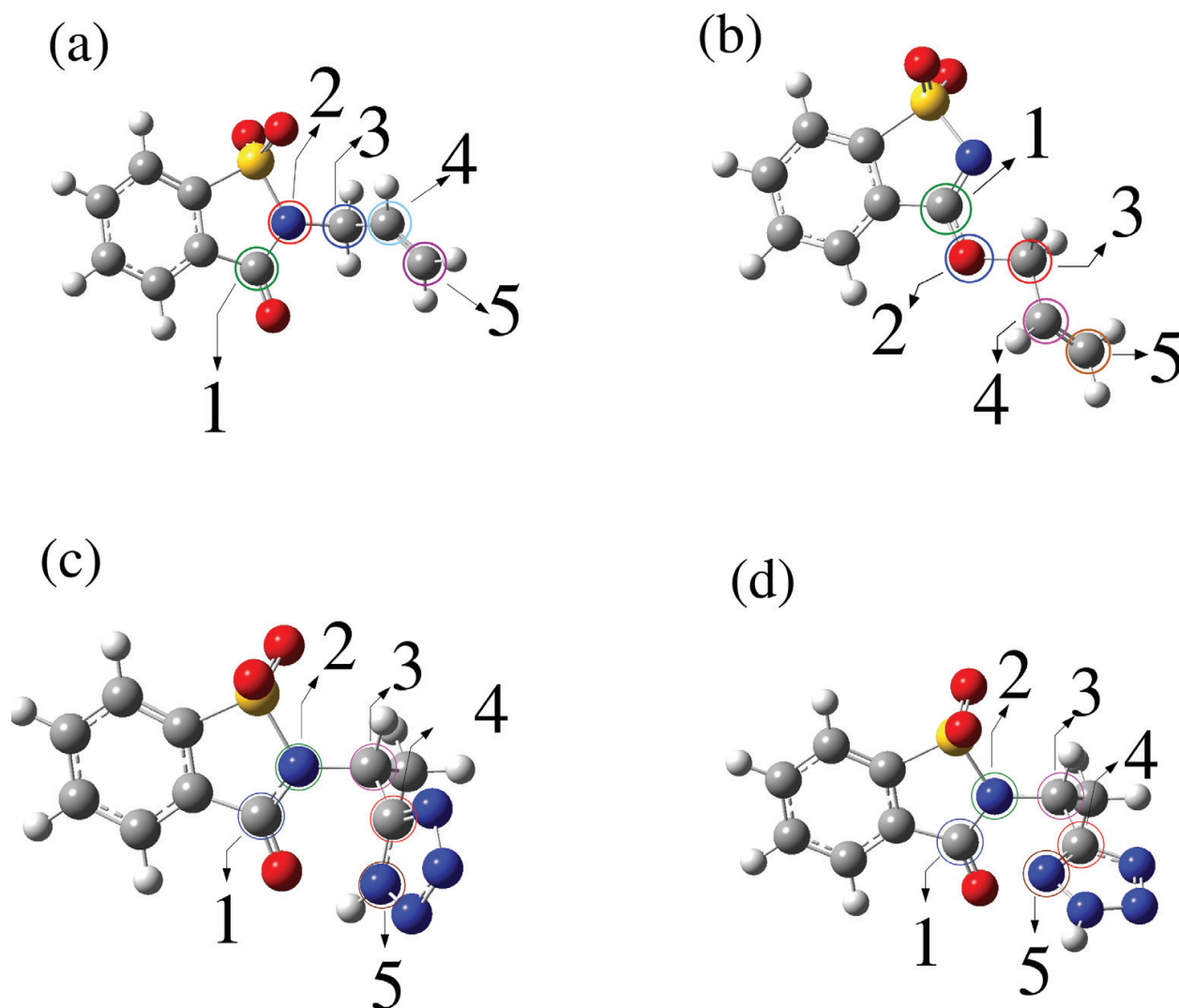
Figure 2. Pseudosaccharins studied in the present work. (a) ABIOD, (b) ABID, (c) and (d) tetrazole-saccharyl.

3.1. 2-allyl-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxide

The molecular structure of the ABIOD pseudosaccharin can be considered to be mainly formed by two components; a heterocyclic ring and a flexible allyl substituent. In ABIOD, the molecule can be rotated two dihedral angles and they give rise to different isomers (see **Figure 2(a)**), nevertheless, according to Ref. [4], the dihedral angle formed by atoms 1, 2, 3 and 4 is irrelevant in the formation of isomers because of the sterical hindrance between the allyl group and the rest of the molecule. Consequently, only the dihedral angle formed by atoms 2, 3, 4 and 5 originate different isomers. In the same study, there were found a total of three isomers of ABIOD in a minimum of the potential-energy surface (PES) and they were represented using the abbreviations $C = cis \approx 0°$, $Sk = skew \approx 120°$, $Sk' = skew' \approx -120°$.

In a first step, molecular optimization was performed through B3LYP functional; after that, reoptimizations were performed with M06-2X and PBE functionals.

The corrected zero-point relative energies of the three ABIOD isomers are presented in **Table 1**. For B3LYP XC-functional, it can be observed that the most stable isomer is *Sk*, however, it is important to note that energy differences with *Sk'* and *C* isomers are less than 1 kcal/mol, no matter the BS used. According to M06-2X XC-functional results, the BS that takes into account more polarization and diffuse functions located the *C* isomer as the most stable and the two BSs that do not possess the maximum increases in diffuse functions and polarization found the *Sk* structure as the most stable in a similar way as the B3LYP functional. Again, note that the energies between these isomers are small since they do not reach 1 kcal/mol. Unlike B3LYP and M06-2X, it was noticed that PBE outcame the *Sk'* isomer as the most stable at T = 0, nonetheless the energetic differences are very small since these do not reach 1 kcal/mol.

As can be observed from DFT calculations at T = 0, the analysis of isomerism is complicated, especially when small energy differences are presented between isomers. Since none of the three functionals (B3LYP, M06-2X and PBE) obtain the same most stable isomer, this quest appears to be quite dependent on the method used. However, it is also worth commenting that the energy difference between the three isomers is very small, regardless of the XC-functional used. Then, it could be considered that the energy differences are within the anticipated error of calculation and therefore, it would be expected that molar fractions as a function of temperature can provide relevant information.

Considering the previous discussion, **Figure 3** shows the molar fractions as a function of temperature for the three isomers of ABIOD pseudosaccharine.

For B3LYP XC-functional it can be observed that the molar fractions do not vary significantly as the temperature increases, in fact, the line corresponding to the *Sk'* isomer is maintained

Isomer	6-311++G(3df,3pd)	6-31++G(3df,3pd)	6-311+G(d,p)	6-31+G(d,p)
B3LYP				
C	0.65	0.73	0.71	0.76
Sk	0	0	0	0
Sk'	0.15	0.16	0.09	0.04
M06-2X				
C	0	0	0.04	0.03
Sk	0.09	0.1	0	0
Sk'	0.59	0.58	0.05	0.43
PBE				
C	0.33	0.33	0.5	0.59
Sk	0.06	0.06	0.18	0.26
Sk'	0	0	0	0

Table 1. Corrected zero-point relative energies (kcal/mol) of ABIOD isomers.
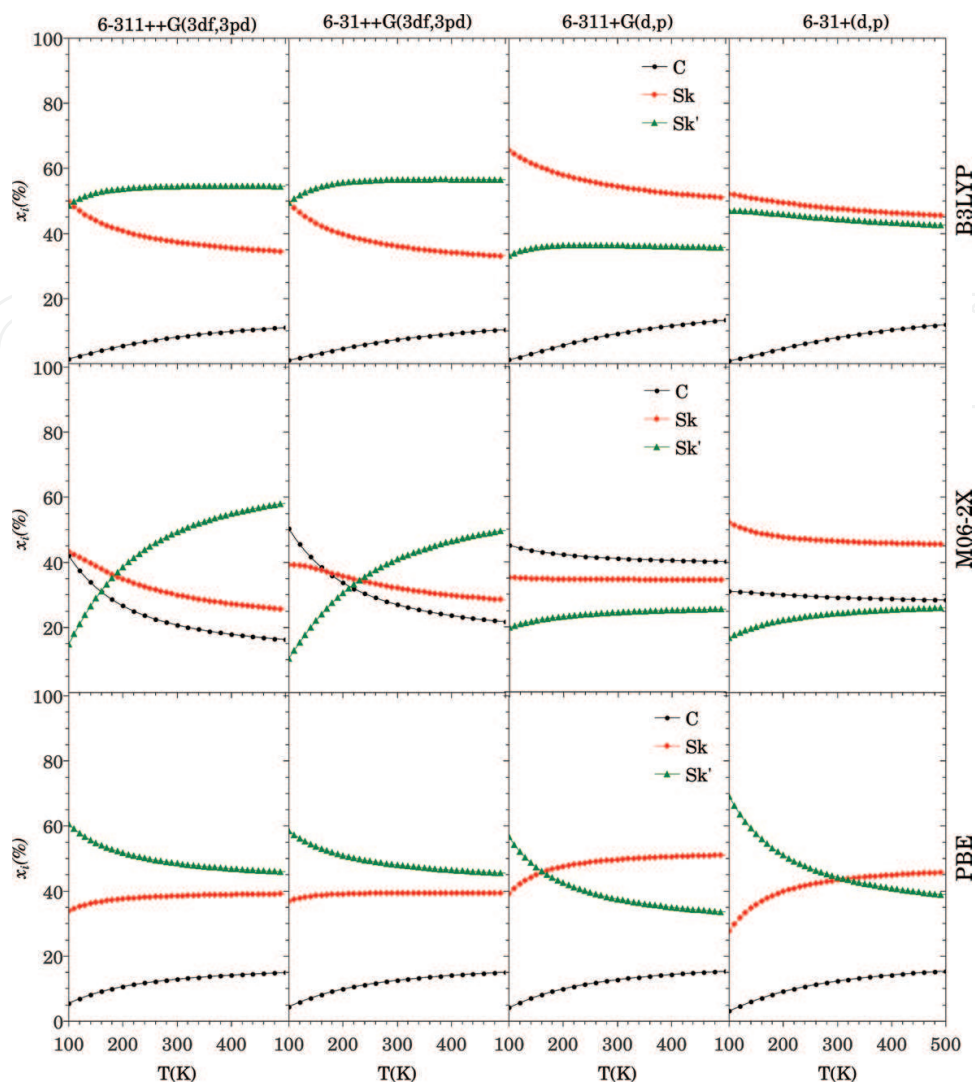
Figure 3. Molar fractions for ABIOD isomers taking into account three XC-functionals with a combination of four BSs.

almost at the same value in all the range of temperature studied. The same trends can be seen for the *Sk* isomer since beyond 200 K there is no significant change. The *C* isomer shows the same trend with a small population increase in the four graphs of B3LYP; that is, at the beginning of the studied range, its population is zero but it slowly grows while temperature increases.

For M06-2X functional, results show that for the first two BSs the graphs are similar and display the same trend in general; however, with 6-31++G(3df,3pd) it is observed that distribution of isomer populations are narrower than in 6-311++G(3df,3pd). Nonetheless, 6-311+G(d,p) and 6-31+G(d,p) present a different trend since the populations change, this behavior could be understood noticing that the energy difference between the three isomers obtained with these methodologies is very close (see **Table 1**), then, the vibrational frequencies, rotational constants and energy levels become important in the construction of the molar fractions. A deeper analysis on vibration frequencies, rotational constants and energy levels is presented below.

As mentioned in a previous paragraph, the relative energies obtained with PBE XC-functional place the *Sk'* isomer as the most stable, therefore, at the beginning of our range of calculation of molar fractions, this was the isomer with the largest population. As observed in (PBE) graphics for the first two BSs in **Figure 3**, the molar fraction plots of each isomer do not cross at any time, which means that the *Sk'* isomer is the most predominant over all the range of temperature studied here, even though the difference in energy with the second most stable isomer is at most 0.06 kcal/mol. For 6-311+G(d,p) and 6-31+G(d,p) a distinct trend can be observed in comparison with 6-311++G(3df,3pd) and 6-31++G(3df,3pd), since in 6-311 G(d,p) there is an exchange (before 200 K) of the most populated isomer which turns now to be *Sk*. Additionally, it can be noticed that the population of both *Sk* and *Sk'* isomers is around 45%. For 6-31+G(d,p), the intersection in the population of *Sk* and *Sk'* isomer is given approximately at 300 K.

From **Figure 3**, it can be observed that B3LYP and PBE XC-functionals obtain the same trends: the less stable structure (*C* isomer) has the lowest population, while the two most stable isomers (*Sk* and *Sk'*) are maintained with the largest population. In fact, it can be seen how for the first two BSs in B3LYP, that even though the *Sk* isomer is the most stable, *Sk'* is the most populated since an exchange in population appears at very low temperatures, which is in agreement with PBE. Additionally, in the last two BSs of the PBE functional, although *Sk'* is the most stable isomer at T = 0, it is not maintained as the isomer with the largest population when the temperature increases. So far, at least it is stated that the two most stable isomers are the ones with the largest population regardless of the methodology (functional and BS) used. On the other hand, M06-2X/6-311++G(3df,3pd) and M06-2X/6-31++G(3df,3pd) are consistent showing that *Sk'* has the largest population at room temperature, however, the last two BSs are not in agreement with these results since 6-311+G(d,p) presents the *C* isomer as the most populated, while 6-31+G(d,p) presents *Sk* isomers as the most populated. Therefore, a deeper analysis must be performed, that is why the peculiar case of M06-2X/6-311+G(d,p) results will be analyzed below.

Due to the complicated comparison between the different results obtained, mainly with M06-2X, both at T = 0 and varying temperature, it was decided to refine the electronic energy through the MP2 method. As a first step, a comparison of energies of the three isomers MP2 optimized and non-optimized was performed.

Firstly, the molecular structures of the three isomers were optimized with MP2/6-311++G(3df,3pd) methodology resulting in the following relative energies: *Sk* = 0, *Sk'* = 0.74 and *C* = 1.09 kcal/mol. The isomer with the lowest energy is taken as 0 kcal/mol. After that, a single point calculation with MP2/6-311++G(3df,3pd) methodology on the previously optimized structure through B3LYP/6-311++G(3df,3pd) methodology was performed, getting the following relative energies: *Sk* = 0, *Sk'* = 0.7 and *C* = 1.2 kcal/mol. These outcomes clarify that optimization of the three isomers, not only result in the same order of stability, but also do not represent a great variation in the relative stability. This can give us confidence in performing only single point calculations with MP2 on structures optimized with different methodologies.

In a second step and according to the results discussed in the previous paragraph, single point calculations were performed with MP2 along with 6-311++G(3df,3pd) and 6-31+G(d,p) BSs on

previously relaxed structures with B3LYP, M06-2X and PBE in order to obtain relative stabilities. For B3LYP optimization and single point calculations through MP2, the relative energies were $Sk = 0$, $Sk' = 0.7$ and $C = 1.2$ kcal/mol using 6-311++G(3df,3pd), on the other hand, $Sk = 0$, $Sk' = 0.68$ and $C = 1.39$ kcal/mol using 6-31+G(d,p). For optimization with M06-2X the results were $Sk = 0$, $Sk' = 0.38$ and $C = 1.21$, additionally, $Sk = 0$, $Sk' = 0.74$ and $C = 1.24$ kcal/mol, when 6-311++G(3df,3pd) and 6-31+G(d,p) were, respectively, used. Finally, for PBE optimization, the results were $Sk = 0$, $Sk' = 0.84$ and $C = 1.31$ with 6-311++G(3df,3pd), and $Sk = 0$, $Sk' = 0.76$ and $C = 1.54$ kcal/mol for 6-31+G(d,p).

As it can be seen, the Sk isomer results as the most stable, as B3LYP functional, however, the energy differences are magnified compared to B3LYP. On the other hand, the narrowest energy difference between the Sk and Sk' isomers is given by MP2/6-311++G(3df,3pd)//M06-2X/6-311++G(3df,3pd) methodology and the largest energy difference is obtained by MP2/6-31G(d,p)//PBE/6-31G(d,p) methodology. It is worth to mention that, regardless of the functional and BS used to relax the molecular structure, the energy obtained through MP2 resulted in the same order of stability ($Sk > Sk' > C$). Therefore, it seems to be that MP2 energy treatment could help to homogenize results at T = 0, additionally, these results are in agreement with the previously reported by Gómez-Zavaglia et al. [4], since they predicted the same most stable isomer with B3LYP functional. In consonance with these results, Sk can be expected to be the isomer with the largest population.

Molar fractions as a function of temperature were re-built using the electronic energy data from MP2 calculations on optimized structures with B3LYP, M06-2X and PBE (see **Figure 4**). As expected, the most populated isomer in all the range of temperature was Sk, however, M06-2X with 6-311++G(3df,3pd) maintained the Sk' isomer as the most populated. From a previous paragraph, it is known that M06-2X got the lowest energy difference between the Sk and Sk' isomers, and it could be the reason of the exchange in population, however, there could be something else inducing that exchange. In order to find a possible reason of this induced exchange, several things were tested, for example, knowing that the Sk' isomer is the one that presents a different behavior in the M06-2X/6-311++G(3df,3pd) methodology (**Figure 4(b)**) in comparison with the other methodologies, rotational constants obtained with M06-2X/6-311++G(d,p) were inserted instead of those obtained with M06-2X/6-311++G(3df,3pd), however, there was no great modification in the graph (see **Figure 5(b)**). Subsequently, the same exchange was made with the electronic transitions, without finding again great modifications in the graph (see **Figure 5(c)**). But, when the same exchange was made with the vibrational frequencies, it was observed that the graphs of the populations changed(see **Figure 5(a)**), obtaining the same trends as the other methodologies of **Figure 4**, where Sk is the most populated isomer followed by Sk' and C.

Having noticed that the vibrational partition function influences in an important way, the vibration frequencies obtained through M06-2X/6-311++G(3df,3pd), were observed for each isomer. Interestingly, it was found that the first frequencies for each isomer are 32, 35 and 14 cm⁻¹, for C, Sk and Sk', respectively. As it can be seen, Sk' has the first frequency of less than half compared to the first frequency of the other two isomers, which could be one reason why the Sk' isomer becomes the one with the highest population at very low temperature
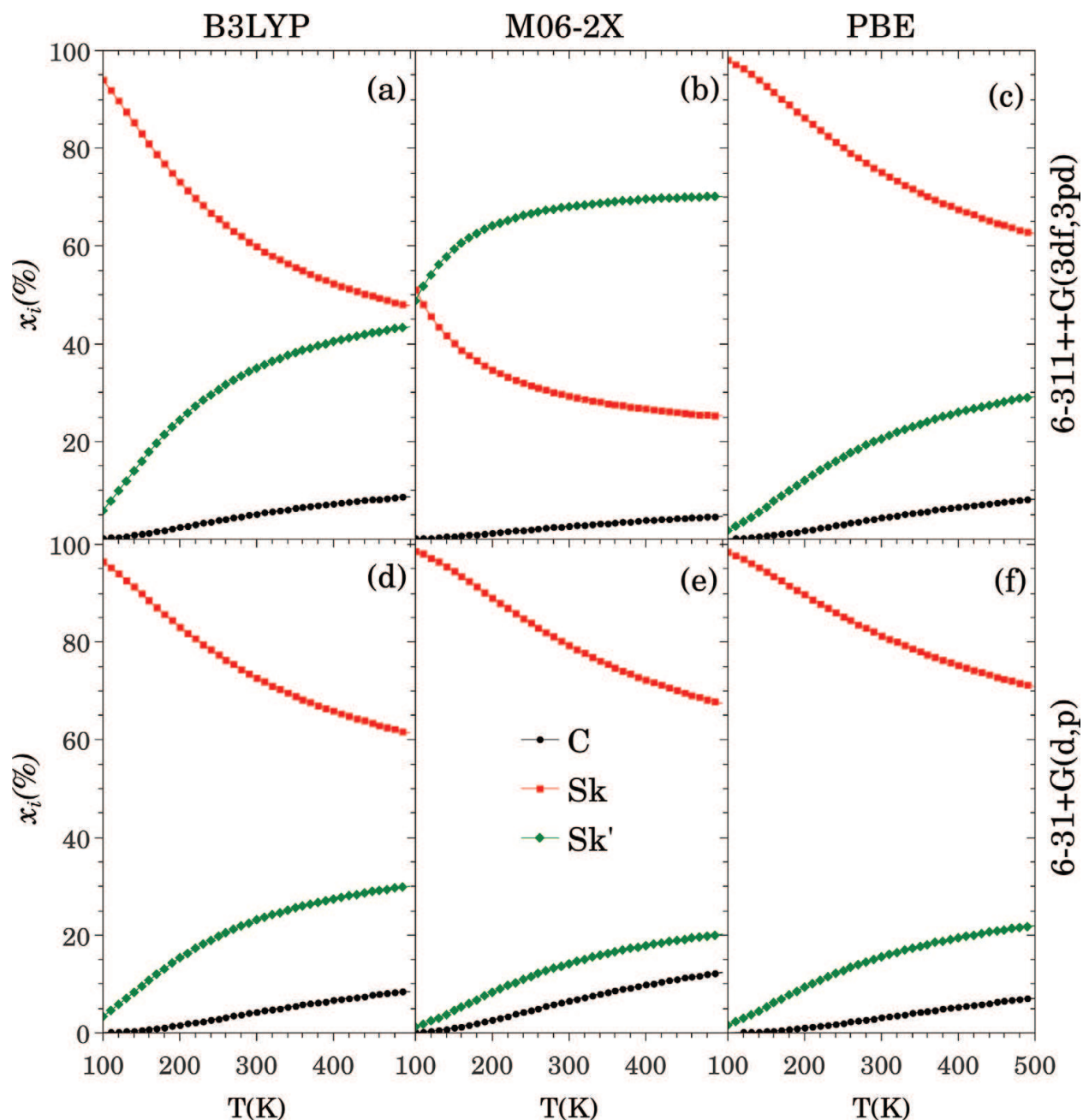
Figure 4. Molar fractions with MP2 energy.

(**Figure 4(b)**), even though the *Sk* isomer had the lowest energy at T = 0. In order to verify if the low value of the first frequency in the isomers result in a larger population when the temperature increases, several variations were made in the vibration frequencies trying to observe an effect. For example, the 66 frequencies of *Sk'*, (with first frequency at 14 cm^{-1}), were changed by the 66 frequencies of *Sk*, (first frequency at 35 cm^{-1}), obtaining the graph of the molar fractions such as those obtained with the other methodologies; that is, when the *Sk'* isomer has similar frequencies to those of the other isomers, this promotes the *Sk* isomer with the largest population due to its lower energy at T = 0. Given this interesting result, a simple test was then proposed by changing only the first frequency of the *Sk'* isomer (14 cm^{-1}), by a
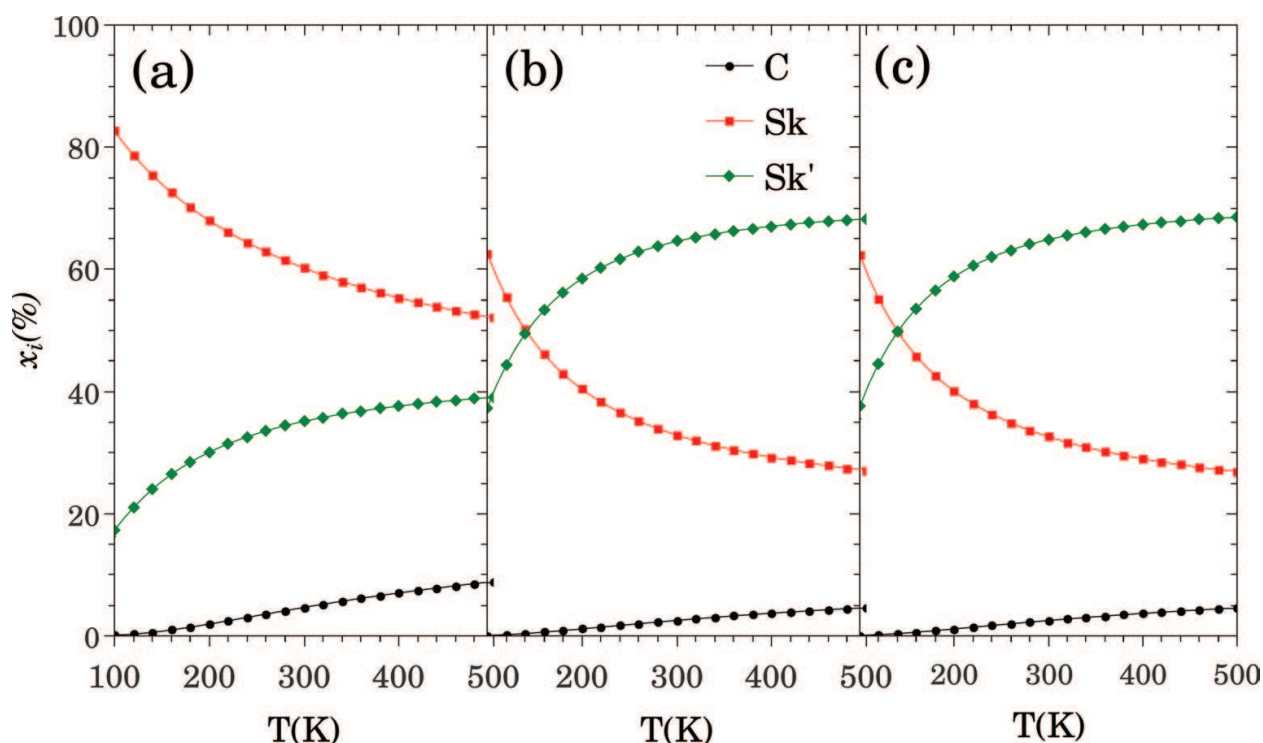
Figure 5. Comparison of molar fractions varying (a) vibrational frequencies, (b) rotational constants and (c) electronic transitions.

value of 34 cm^{-1}, which is a value around the first frequency of the other two isomers. With this modification, it was observed that the molar fractions return to those obtained by the other methodologies; that is, resulting *Sk* as the most populated. According to this analysis, it can be concluded that the vibrational part is very important for the calculation of the molar fractions. In fact, a similar analysis was performed for the molar fractions obtained in **Figure 3** with M06-2X/6-311+G(d,p) results, which showed a different behavior in comparison with the other methodologies. It was observed that the *C* isomer had a frequency of 23 cm^{-1}, whereas the *Sk* and *Sk'* isomers had their first frequencies at 37 and 39 cm^{-1}. A change was then made in the first frequency of the *C* isomer to a value of 38 cm^{-1}, which is close to those of the other two isomers, resulting in a graph of molar fractions where the *Sk* isomer is the most populated for the entire temperature range shown. In summary, when all isomers have very similar first frequency values, enthalpy predicts the isomer with the largest population; however, if one of the isomers presents its first frequency with a very low value in comparison with the correspondent frequency for the other isomers, it is very likely that such isomer presents a larger population when T is increased. From the present analysis, it can be concluded that the choice of a functional that correctly describes the vibration modes of a molecule is of utmost importance for obtaining the predominant zones through molar fractions.

3.2. Pseudosaccharyl allyl ether 3-(allyloxy)-1,2-benzisothiazole1,1-dioxide

The pseudosaccharyl allyl ether 3-(allyloxy)-1,2-benzisothiazole1,1-dioxide (ABID) is a system that has been studied from an experimental and theoretical point of view [13]. In that

study, five structures were found in a minimum in the PES and whose energetic differences are small. The differences between the five isomers are particularly due to the values of two dihedral angles in the structure. In **Figure 2(b)** atoms that conform these angles are shown, the first of them is formed by the atoms numbered as 1, 2, 3, 4 and the second by the atoms 2, 3, 4, 5. From Ref. [13] the five isomers were named according to the values of the dihedral angles in question, the value of the angle formed by the atoms 1, 2, 3, 4 was represented using the abbreviations $T = trans \approx 180°$, $G = gauge \approx 60°$, $G' = gauge' \approx -60°$, for dihedral angle formed by 2, 3, 4, 5 its value was represented by the abbreviations $C = cis \approx 0°$, $Sk = skew \approx 120°$, $Sk' = skew' \approx -120°$. Four of the five isomers belong to the C_1 point group of symmetry with the exception of the TC isomer whose point group is C_s.

Molar fractions as a function of temperature of the five isomers with the XC-functionals and the four BSs used in previous subsection were obtained. For each level of theory, the necessary frequency vibrations were obtained in order to obtain, on one hand, the molar fractions and, on the other hand, to corroborate that molecular structure is in a minimum of PES; rotational constants for building the rotational partition function; and 10 excited states for obtaining the electronic partition function. In **Table 2**, the relative energies obtained with B3LYP, M06-2X

Isomer	6-311++G(3df,3pd)	6-31++G(3df,3pd)	6-311+G(d,p)	6-31+G(d,p)
B3LYP				
GC	1.46	1.51	1.49	1.67
GSk	0.47	0.51	0.38	0.44
GSk'	0.91	0.93	0.8	0.89
TC	0.5	0.59	0.52	0.67
TSk	0	0	0	0
M06-2X				
GC	0.4	0.32	0.41	0.5
GSk	0.18	0.12	0.001	0.004
GSk'	0.39	0.34	0.19	0.24
TC	0	0	0	0
TSk	0.1	0.05	0.05	0.004
PBE				
GC	1.1	1.18	1.18	1.38
GSk	0.13	0.33	0.14	0.27
GSk'	0.64	0.8	0.64	0.77
TC	0.37	0.43	0.36	0.5
TSk	0	0	0	0

Table 2. Corrected zero-point relative energies (kcal/mol) of ABID isomers.

and PBE XC-functional and the proposed BS for the five isomers are shown. It can be observed that B3LYP and PBE got the same order of stability (*TSk* > *GSk* > *TC* > *GSk'* > *GC*) independently of the BS. Although the energy difference between the isomers is not maintained at the same rate, the order of stability is not compromised by varying the BS.

With M06-2X functional a change in order of stability is shown, in contrast to B3LYP and PBE functional, *TC* isomer is the most stable. In spite of the order of stability changes, it is also possible to observe that the energy differences are narrower than B3LYP and PBE, since with this functional the largest difference of energy between the distinct isomers and taking into account the four BSs is at most of 0.5 kcal/mol. From M06-2X, it is difficult to propose an isomer to work in a theoretical study. Then, considering that energy differences are very small, it would be worthwhile to observe the effects of temperature on populations of the five isomers.

The temperature of interest is around 350 K, since these compounds are synthesized at this temperature. Remember that for B3LYP XC-functional and the four BSs, the *TSk* isomer is the most stable and the energy difference with the second and third most stable isomers is small. In **Figure 6**, molar fractions as a function of temperature obtained with B3LYP and the utilized BSs are shown. The results display that all used BSs are consistent, it is observed that the isomer of greatest population for all BSs at the temperature of interest is *TSk*, although it is the predominant isomer, its population at 350 K does not exceed 60%, the second is around 17% and the rest is lower than 12%. As it can be observed in **Figure 6**, populations obtained through PBE functional have the same trends as B3LYP functional, and despite there is only a small difference, it is shown that the second most stable isomer (*GSk*) has a higher population (at around T = 300 K) compared to its population with B3LYP functional.

Regarding M06-2X, there is an interesting event with the lowest potential-energy species, in spite of *TC* isomer having actually the lowest energy at absolute zero (see **Table 2**), the most populated is the second lowest potential-energy isomer. Therefore, the molar fraction calculations showed the *TSk* isomer as the most predominant at the temperature of interest and the rest of them with very similar populations no matter the BS used, in fact, from the theoretical point of view, it is worth mentioning that two well-defined horizontal lines begin to form in **Figure 6**, the first one with the population of the most stable isomer and the other one with the populations of the rest of the isomers. The molar fractions determine that the consideration of statistical physics, in order to introduce thermal effects in the isomerization of molecular structures with small energy differences, becomes important, since, as we can see in **Figure 6**, regardless of the greater stability of the *TC* isomer, *TSk* is obtained as the most abundant, even at very low temperatures as the ones used in the present analysis. Based on these results, the importance of performing an analysis of this nature must be considered.

From these results, it can be concluded that, in one hand, both B3LYP and PBE XC-functional remark the same trends and, on the other hand, in spite than M06-2X obtained a more complicated distribution of relative energies at T = 0, when thermal effects are taken into account, the same trends in populations of the five isomers compared to B3LYP and PBE functionals are obtained.
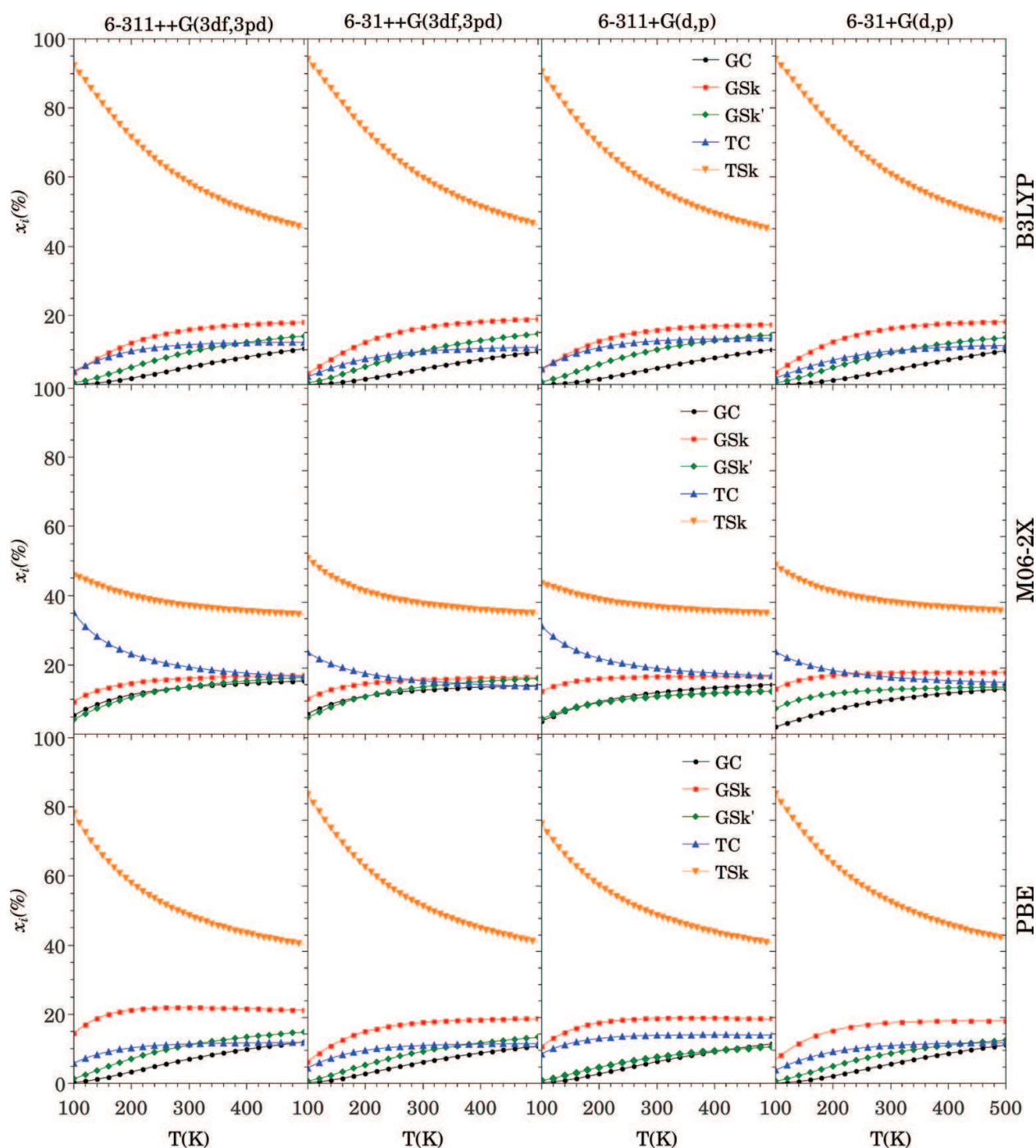
Figure 6. Molar fractions for ABID isomers.

3.3. Tetrazole-saccharyl

The third system of the pseudosaccharine family studied in this work is tetrazole-saccharyl (see **Figure 2(c) and (d)**). This system, as well as the previous ones, has been studied from an experimental and theoretical approach, for this molecule there are two tautomers and for each one of them several isomers can be generated by the rotation of two dihedral angles. In **Figure 2(c) and (d)** the involved atoms in the dihedral angles are shown, again the structures

were named according to the letters G = *gauge* ≈ 60°, Sk = *Skew* ≈ 120°, G' = *gauge'* ≈ −60°, Sk' = *Skew'* ≈ −120°, the angle formed by the atoms numbered as 1, 2, 3 and 4 was used to assign the first letter, while the angle formed by the atoms numbered as 2, 3, 4 and 5 were taken as reference for the second letter [14].

Tautomers are called as 1H tautomer and 2H tautomer, the first one is obtained when H is bonded to atom number 5 (**Figure 2(c)**) and the second one is obtained when H is bonded to the nitrogen atom beside to atom number 5 (**Figure 2(d)**) [14]. Relative energies were obtained for the same levels of theory as previous subsections.

In **Table 3**, corrected zero-point relative energies are shown. As it can be seen, B3LYP and PBE are consistent in the sense that they present the $G'Sk'$ isomer as the most stable, with the exception of the B3LYP/6-311+G(d,p) methodology, since this gives GSk' as the most stable, although it should be noted that, in this case, the energy difference between $G'Sk'$ and GSk'

Isomer	6-311++G(3df,3pd)	6-31++G(3df,3pd)	6-311+G(d,p)	6-31+G(d,p)
B3LYP				
$G'Sk'$	0	0	0.06	0
GSk'	0.51	0.55	0	0.25
$G'Sk$	1	1.12	0.65	0.9
GSk	1.96	2	1.94	1.85
$G'G'$	1.64	1.8	1.37	1.65
GG'	1.97	2.17	1.49	1.74
M06-2X				
$G'Sk'$	0.48	0.37	1.2	0.78
GSk'	0	0	0	0
$G'Sk$	0.47	0.47	0.57	0.46
GSk	1.18	1.22	1.93	1.49
$G'G'$	1.75	1.81	1.92	1.73
GG'	1.23	1.33	1.09	1.06
PBE				
$G'Sk'$	0	0	0	0
GSk'	0.64	0.67	0.16	0.44
$G'Sk$	1.23	1.34	0.89	1.18
GSk	1.75	1.77	1.65	1.62
$G'G'$	1.63	1.78	1.31	1.64
GG'	1.71	1.91	1.19	1.48

Table 3. Corrected zero-point relative energies (kcal/mol) of the six isomers of tetrazole-saccharyl.

is only 0.06 kcal/mol. On the other hand, M06-2X states the *GSk'* isomer as the most stable for all used BSs. As a summary, all methodologies showed the *G'Sk'* and *GSk'* isomers as the most stables at T = 0 K, with the exceptions of M06-2X/6-311+G(d,p) and M06-2X/6-31+G(d,p).

Here it is worth to mention that in ABIOD and ABID molecules, M06-2X reduced the energy differences, while tetrazole-saccharyl M06-2X does not reduce the energy differences in comparison with the results of B3LYP and PBE. The molar fractions as a function of temperature are analyzed below.

Observing **Figure 7**, it can be seen that the trend of B3LYP and PBE with the four BSs is maintained, there are two predominant isomers in all the graphs at room temperature, with the first two BSs the isomer of greatest abundance is the *G'Sk'* and the second is the *GSk'*, with populations of almost 50 and 20%, respectively. For the last two BSs the difference between the isomers of largest population is reduced, even in the case of B3LYP and the third BS, the *GSk'* isomer has the greatest population, although it is important to note that at room temperature the difference is not very significant, in general the same behavior is kept with PBE, however, in the third BS, *G'Sk'* has the largest population but with a small difference in population with *GSk'*, since it is approximately 33 and 30% for *G'Sk'* and *GSk'*, respectively.

Analyzing the molar fractions as a function of temperature for M06-2X functional, it can be observed that the first two BSs found three isomers with significant populations and the rest remained with a very low population, therefore, it is possible to say that the three isomers whose populations are considered important are the same ones that are predicted as the most stable. For the third and fourth BSs, we can observe that the *GSk'* and *G'Sk* isomers maintained a large population; however, the *G'Sk'* isomer, which had the largest population with B3LYP and PBE, disappears from the isomers of greater population. From this, it can be indicated that M06-2X describes in a different way the most populated isomer in comparison to B3LYP and PBE, however, we can also see that for the two BSs with more diffuse BS and greater freedom in the polarization also obtain *G'Sk'* and *GSk'* as the largest population isomers, indicating then, that M06-2X could be used with a large BS.

An important difference between the results obtained by B3LYP and M06-2X is the change of the order in stability of isomers since M06-2X always brought the *GSk'* isomer as the one with the lowest energy and greatest abundance. On the other hand, it is interesting to observe that in the work of Ismael et al. [14], they compared the experimental infra-red spectrum with the theoretical one at B3LYP/6-311++G(3df,3pd) level of theory and although they found *G'Sk'* isomer is the most favored energetically (as this work showed through B3LYP), they took the infra-red spectrum of *GSk'* as the representative one because its theoretical spectrum agreed better with the experimental spectrum, for this reason, it is important to remark that the M06-2X presents the *GSk'* isomer as the most stable at T = 0 K, even for all BSs.

As it can be observed, M06-2X predicts a different isomer as the most populated compared with B3LYP and PBE, however, it seems to be that the *GSk'* isomer is the one present in the experiment according to the explanation in the previous paragraph, if this is the case, then the question arises as to why M06-2X is the one that better describes this pseudosaccharin. In order to answer the question, let us note that in **Figure 2**, it can be seen that
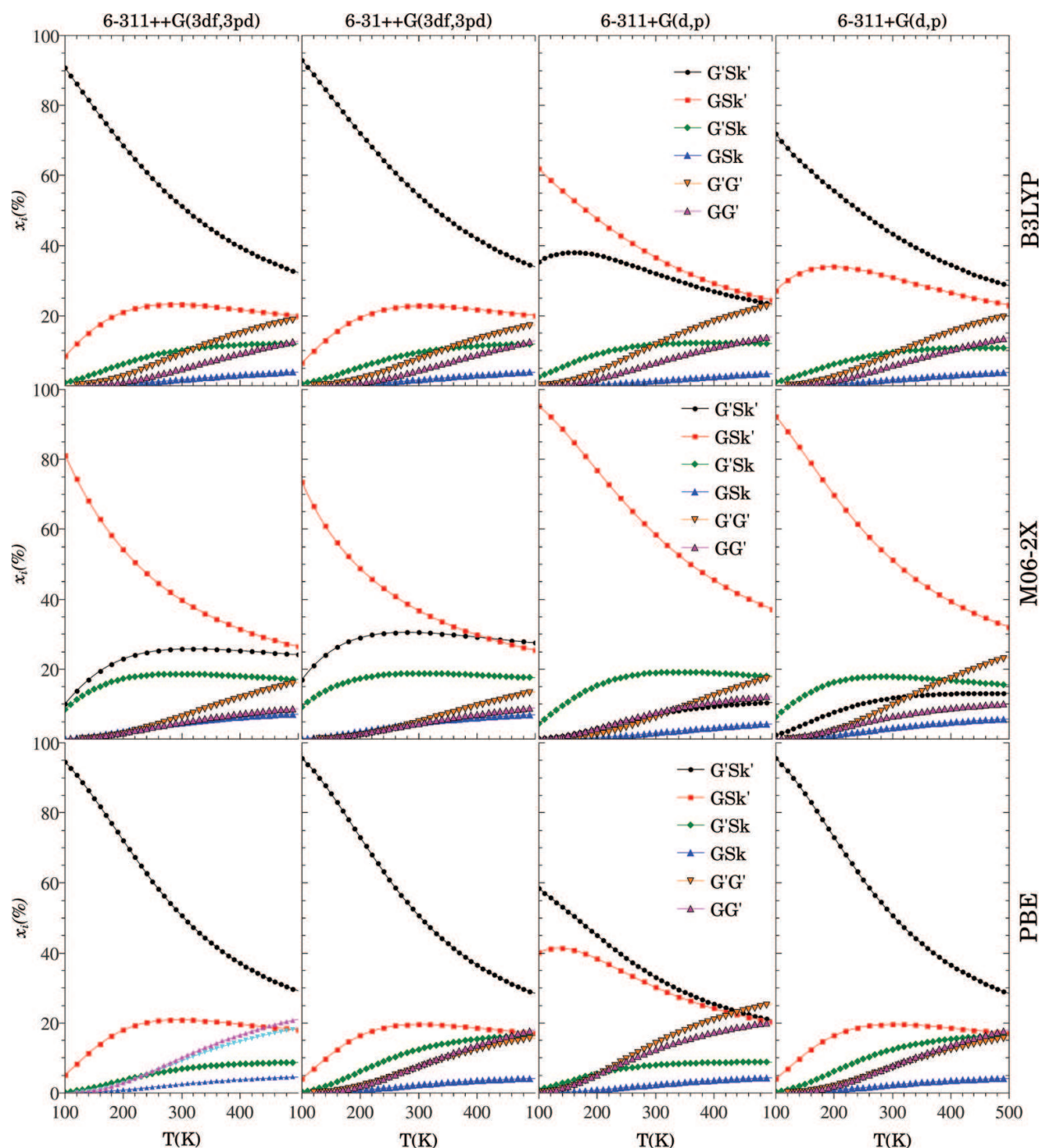
Figure 7. Molar fractions of tetrazole-saccharyl.

tetrazole-saccharyl is bigger (in size) than ABIOD and ABID molecules, in fact, the tetrazole group could interact with the saccharyl group through noncovalent interactions, moreover, it is well-known that the M06-2X functional has shown promising performance for noncovalent interactions [23, 24], thus, it is the reason why M06-2X describes tetrazole-saccharyl molecule in a better way. This once again proves the importance of testing several methodologies.

4. Conclusions

In this work, an analysis of molar fractions as a function of temperature on three pseudosaccharyl systems (ABIOD, ABID and tetrazole-saccharyl) was performed with three XC-functionals and four BSs. In general, for ABIOD and ABID systems, M06-2X functional reduces the energy differences between the isomers, while B3LYP and PBE are in agreement with each other, but different from M06-2X. It is important to observe that in ABID pseudosaccharine, even if the order of stability changes with the M06-2X functional, the molar fractions maintain the same trend, placing the *TSk* isomer as the one with the largest population, in spite of not being the most stable from DFT calculations at T = 0 K. Additionally, considering the results that are shown in **Table 2**, a minimal effect of the BS is evident considering that the same trend is conserved and the results do not vary significantly in ABID. For tetrazole-saccharyl, it seems that M06-2X describes correctly the predominant isomer found experimentally, contrary to B3LYP and PBE results. Although, this could be understood since it is well-known that M06-2X correctly describes systems with noncovalent interactions as can be inferred in the tetrazole-saccharyl system showed in **Figure 2(c)** and **(d)**.

Even though the molar fractions show a dependence on the enthalpies of the isomers, the most stable structure is not necessarily the one with the greatest population. By taking into account the vibrational, rotational and electronic partition functions in the calculation of the molar fractions, several aspects are involved to obtain the most predominant isomers at T ≠ 0. It was found that vibrational contribution is the most important factor in obtaining the predominant isomer. Therefore, the use of methodologies that correctly describe the vibrational spectra in order to obtain molar fractions is recommended. Additionally, when a theoretical-experimental spectra comparison is carried out, calculated spectra could be weighted by molar fractions at the temperature of interest.

One of the main differences between the results obtained with the different methodologies is that herein calculations can predict a different order of stability and modify the relative energies. However, in order to be able to assume that an isomer will predominate, it is important to consider the contributions of the different partition functions instead of only considering the relative potential energies.

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