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Cycloreversion of 4*H*-1,3-Thiazines and Selenazines Analogous: Theoretical Study by The Density Functional Theory (DFT) Method

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Abstract Experimental work has shown the possibility of cycloreversion of these heterocycles. In the case of 4*H*-1,3-thiazines, the possibilities of cycloreversion depend essentially on the nature of the substituent at the 4-position of the thiazine ring. Indeed, this reaction seems to be impossible with the methyl group in the 4-position but it is facilitated when the ethyl carboxylate group is at the same position. This difficulty does not occur with the selenium analogues. The density functional theory method at the level B3LYP/6-31G (d, p) was used to determine the influence of the heteroatom at position 1 on the cycloreversion reaction of these heterocycles. The thermodynamic and geometric parameters and the prediction of the reaction mechanism were developed in this work. The obtained results indicate a greater stability of the methylated thiazines in position 4. This would explain a difficulty of cycloreversion from these. These results also show a correlation between the reactivity of these heterocycles and their dipole moment.

Keywords: *cycloreversion, activation energy (Ea), Intrinsic Reaction Coordinate (IRC), 4H-1,3-thiazines, 4H-1,3-selenium*

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1. Introduction

Certain derivatives of 1,3-thiazines and selenazines analogous have been revealed to be anti-cancer, antibacterial or antioxidant agents [1,2,3]. Those possess various biological, geological and medical activities [4,5,6,7,8,9]. These heterocycles are generally obtained from the reaction of hetero Diels-Alder (4+2) [10,11,12,13]. Experimental work has shown that refluxing in toluene during the reaction can lead to cycloreversion of the cycloaddition heterocycle [14,15]. In the case of 4*H*-1,3-thiazines, the cycloreversion would depend essentially on the nature of the substituent at the 4-position of the thiazine ring. Indeed, this reaction seems to be impossible with the methyl group in this position but it is facilitated when an electron attractor group such as ethyl carboxylate in the same position. This difficulty is not encountered with their selenazines analogous [16]. Previous theoretical work in the gas phase has shown the influence of substituents on the cycloaddition and cycloreversion reactions of thiazine derivatives [17,18]. The present study aims to examine the influence of the heteroatom on the cycloreversion of 4*H*-1,3-thiazines and selenium analogues to understand experimental observations. In this sense, theoretical calculations are made in solution in toluene. The Density Functional Theory (DFT) calculations were performed with the B3LYP functional and 6-31G(d,p) basis set. The experimental difficulties evoked in the realization of the cycloreversion, leads us to consider theoretically the study of the reaction mechanism. The prediction of this mechanism is elucidated from the location of the transition state [19]. Frontier Molecular Orbital Theory (FMO) [20] is used to examine the reactivity and stability of these heterocycles. The thermodynamic parameters ($\Delta_r H$ and $\Delta_r G$) are determined. The influence of the heteroatom in position 1 on the geometrical parameters of these molecules is also analyzed.

2. Materials and Methods of Calculation

2.1. Calculation Level

Theoretical calculations are carried out with Gaussian software 03 [21]. The different molecular structures have been optimized using density functional theory (DFT). The calculation level used is B3LYP/6-31G (d, p). Earlier theoretical work on Diels-Alder reactions and similar reactions has shown that corrected gradient functional and hybrid functionals such as B3LYP using the 6-31G (d, p) base lead to potential energy gap which is in a good agreement with the experimental results [22,23,24,25,26].

This motivates the choice of the level of calculation implemented in this work. Calculations are made in solution containing toluene. In practice, toluene is used as solvent. This theoretical study in solution is carried out at the temperature of 400K. The Polarized Continuum Model (PCM), is taken as a solvation model [27]. The optimization of the molecular geometries is followed by calculations of vibration frequencies at the same level of theory in order to verify that the structures obtained are the expected ones (minima and transition states). On the potential energy surface, the minima and the first order stool points are determined. The geometry of these minima and those of the 1st order stool points were determined in order to establish the mechanism of the reaction. The determination of the reaction path was carried out by the application of the IRC (Intrinsic Reaction Coordinate) method [28,29].

2.2. Thermodynamic Reaction Parameters

The knowledge of the variations of energy contributions to the internal energy between the products and the reagents contributes to the energetic characterization of a chemical reaction [30,31]. For a given energy parameter X, its variation is determined according to the relation:

$$\Delta_r X = \sum X(products) - \sum X(reactants). \quad (1)$$

The determined thermodynamic quantities in this study are: enthalpy and free enthalpy of reagents and products. The reaction enthalpies (ΔrH) and the free enthalpies of reaction (ΔrG) are also calculated from the following relationships:

$$\Delta_r G = \sum \Delta_f G(products) - \sum \Delta_f G(reagents) \quad (2)$$

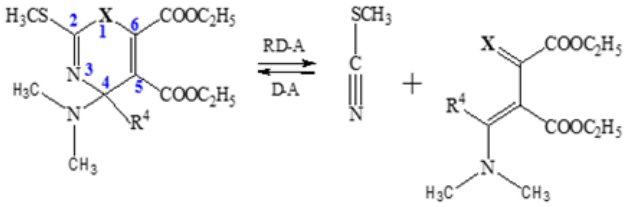
$$\Delta_r H = \sum \Delta_f H(products) - \sum \Delta_f H(reagents). \quad (3)$$

2.3. Conceptual DFT Reactivity Parameters

Frontier Molecular Orbital Theory (FMO) allows the understanding of chemical reactivity, that is to say the ease with which a molecule is transformed or reacted with other molecules. It gives a reasonable qualitative prediction of the excitation properties of a molecule. They therefore constitute quantum parameters for the determination of molecular reactivity [32,33]. The smaller the energy gap between the HOMO and LUMO orbitals, the easier the molecule can be excited. Similarly a large gap HOMO-LUMO indicates a high stability for the molecule which means that the reactivity in chemical reactions is low.

3. Results and Discussion

The analysis of the influence of the heteroatom on the cycloreversion of 4*H*-1.3-thiazines and selenazines analogous concerns the molecules **1a**, **2a**, **1b** and **2b** (Figure 1). The position 4 (**R^4**) of these molecules is substituted by two groups: CH_3 (electron donor) and $CO_2C_2H_5$ (electron attractor).



1a : X = S ; $R^4 = CH_3$; **1b** : X = S ; $R^4 = CO_2C_2H_5$
2a : X = Se ; $R^4 = CH_3$; **2b** : X = Se ; $R^4 = CO_2C_2H_5$

Figure 1. Diels-Alder retro reactions (R D-A) or cycloreversion of 4*H*-1,3-thiazines (X = S) and selenazines analogous (X = Se) and Diels-Alder (D-A)

3.1. Thermodynamic Parameters

Under the defined conditions in point **2** for our calculations, the results of the thermodynamic parameters of the compounds **1a**, **1b**, **2a** and **2b** are given in **Table 1**.

Table 1. Reaction enthalpy and reaction free enthalpy, activation energies and dipolar moments of heterocycles 1a, 1b, 2a and 2b, calculated at the level B3LYP/6-31G (d, p) at 400K in toluene

Hétérocycles	1a	2a	1b	2b
$\Delta_r H$ (kcal.mol^{-1})	6.582	0.825	5.586	5.212
$\Delta_r G$ (kcal.mol^{-1})	-3.508	-7.078	-3.366	-1.292
E_{a1} (kcal.mol^{-1})	25.134	17.565	19.130	10.907
E_{a2} (kcal.mol^{-1})	14.143	19.450	22.036	14.745
μ (debye)	2.313	4.154	3.607	4.797

The reaction enthalpies ($\Delta_r H$) are all positive (Table 1). These values indicate that the cycloreversion reaction is endothermic. These results are in agreement with experience. The procedure indicates that refluxing in toluene can favor cycloreversion of these compounds. The replacement of sulfur with selenium induces a decrease in this reaction energy of about 6 kcal.mol^{-1} (**1a** and **2a**). The variation of this reaction energy in the case of cycloadducts **1b** and **2b** is less important. Free reaction enthalpies ($\Delta_r G$) are all negative. They reflect the spontaneity of the cycloreversion of the studied molecules in the defined conditions. With methyl in position 4 (**1a** and **2a**), selenium decreases this energy. It increases with ethyl carboxylate at the same position (**1b** and **2b**). These results show that the influence of the heteroatom on these energy parameters is related to the nature of the substituent in position 4. The difference in thermodynamic reactivity of these molecules seems to be related to the conjugated effect of the heteroatom and the substituent in position 4 (**R^4**).

3.2. Reaction Mechanism

Two approaches are used in order to study the prediction of the reaction's mechanism which are the Transition State Theory (TST) [19] and the determination of the reaction path by the application of the IRC method [28,29].

3.2.1. Transition State Theory (TST)

According to the theory of transition state, the passage from reagents to products requires a transition state; that is

the crossing over of an activation energy barrier ***Ea*** which is calculated from the following relation:

$$E_a = E_{(TS)} - E_{(reagents)}. \quad (4)$$

The activation energies (***Ea***) and dipole moments of the compounds **1a**, 1**b**, **2a** and **2b**, calculated at the level B3LYP/6-31G (d, p) at 400K in toluene are shown in Table 1.

Each chemical reaction is linked to a characteristic duration, determined from the length of the energy barrier **Ea** to be crossed. The higher the barrier, the longer this characteristic duration is, the slower the chemical system transformation is. The energies Ea_1 and Ea_2 are respectively the barriers to be crossed in order to open the cycle (cycloreversion) and for the formation of the cycle from the products resulting from the cycloreversion. The data mentioned in Table 1 show that the activation energies Ea_1 of the sulfur compounds (**1a** and **1b**) are greater than those obtained with the selenium analogues (**2a** and **2b**). It is very clear that the cycloreversion reaction of a *thiazine* would be more energetic than analogous one selenazine. The substitution of sulfur with selenium induces a significant decrease of the activation energy Ea_1 for the cycloreversion of these heterocycles. This decrease is estimated about 7.6 kcal.mol^{-1} between the heterocycles **1a** and **2a** and about 8.2 kcal.mol^{-1} between **1b** and **2b.** The highest energy barrier Ea_1 to be crossed is obtained with thiazine **1a**. This energy is greater than the energy Ea_2 about 11 Kcal.mol^{-1}. In the case of the heterocycles **2a**, **1b** and **2b**, the energy Ea_1 is lower than the energy barrier Ea_2. These values indicate almost impossible cycloreversion with thiazine **1a**.

The dipole moment (μ) indicates the stability of a molecule in water, in particular an aqueous solution. Work has shown that the higher the dipole moment of a molecule, the more reactive it is [34,36]. The dipole moment values show that for two similar heterocycles, selenazine is more polar than thiazine. This difference in polarity is very significant (2.4 D) between compounds **1a** and **2a**. For these two compounds, the dipole moment value at least doubled from thiazine to selenazine (2.31 D at 4.70 D). This difference in polarity is less important between the compounds **1b** and **2b** (1.19 D). The ethyl carboxylate substituent increases the polarity of these heterocycles. The data in Table 1 show that the energy barrier Ea_1 of the heterocycles decreases as their dipole moment increases. Which leads us to say that the ease of cycloreversion of these heterocycles can be linked to the increase of their polarity. If the selenazines are more polar than the analogous thiazines, the electron donor or attractor character of the substituent R^4 seems to be at the origin of the difference of polarity between these heterocycles. We are also led to think that substituents on the cycle of 4*H*-1,3-selenazines in order to decrease its polarity, can prevent the realization of the cycloreversion of these heterocycles.

3.2.2. Determination of the Reaction Path (Intrinsic Reaction Coordinate)

The determination of a transition state can be followed by an Intrinsic Reaction Coordinate (IRC) calculation [28,29]. The reaction path of the reaction is determined and the transition state is connected to both minima (reagent and product). For the sulfur compounds **1a** and **1b**, the reaction paths reveal the difficulty of opening the thiazine ring. This reaction is easier with the selenium compounds **2a** and **2b**. Particularly with 4*H*-1,3-thiazine (**1a**), the product resulting from the cycloreversion is significantly less stable than the cycloadduct. A Diels-Alder bringing cyclorversion products to cycloadduct is therefore very probable. This would explain the impossibility of the opening the thiazine ring at the experimental level when the substituent R^4 is methyl (**1a**).

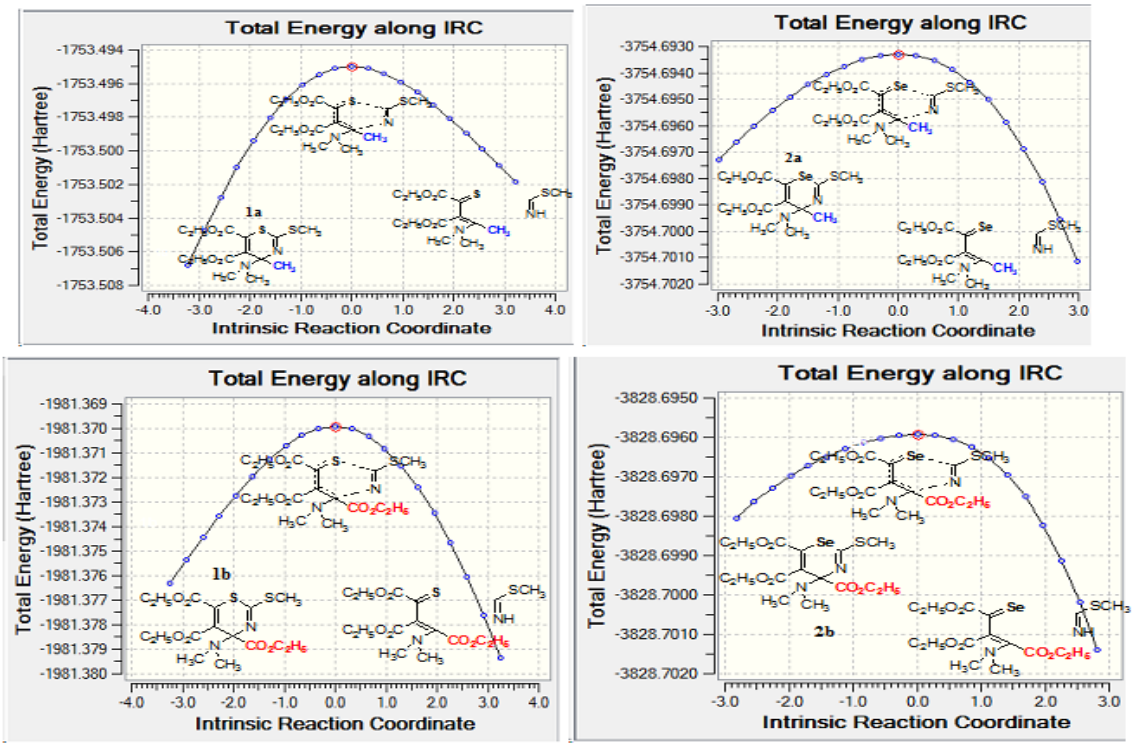


Figure 2. Global IRC of the cycloreversion reaction of heterocycles and their formations, calculated at the level B3LYP/6-31G (d, p)

From these different reaction paths, the complete optimization of the two extreme structures leads either to the products issued from of the opening of the ring or to the starting product as the case may be. This result indicates the nonexistence of an intermediate reaction product. These reactions therefore follow concerted and asynchronous mechanisms. Which is in agreement with the experimental data.

3.3. Frontier Molecular Orbital Theory (FMO)

The energies of the HOMO and LUMO boundary molecular orbitals were calculated at the DFT/B3LYP level. The gap $\Delta E = \varepsilon_{LUMO} - \varepsilon_{HOMO}$ is also estimated from these energies. The results are summarized in Table 2.

Table 2. Energies of the HOMO and LUMO boundary orbitals in atomic units, molecules 1a, 1b, 2a and 2b, calculated at the B3LYP/6-31G(d, p) level

Adducts	1a	2a	1b	2b
ε_{HOMO}	-0.223	-0.207	-0.218	-0.214
ε_{LUMO}	-0.061	-0.062	-0.066	-0.066
ΔE	0.162	0.145	0.151	0.148

The variation of LUMO energies when sulfur is replaced by selenium is negligible. The heteroatom has very little influence on this energy. Compared to the sulfur analogues (**1a** and **1b**), the seleniated heterocycles (**2a** and **2b**) have their HOMOs higher in energy. These possess the smaller energy gaps (Table 1). The selenium compounds are therefore more reactive than the sulfur compounds. Sulfur heterocycles have the smallest energy gaps. These would be more stable than the selenium analogues. From the point of view of reactivity, the greater stability of sulfur compounds could explain why their cycloreversion is so difficult.

3.4. Geometric Parameters

The geometrical parameters of the optimized geometries of the cycloadducts **1a**, **2a**, **1b** and **2b** are listed in Table 3. This analysis relates to the distances between the bonded atoms, the valence angles formed by three bonded atoms and the dihedral angles formed by four atoms of the cycle. The numbers of the different atoms are given in Figure 1.

Only the two bonds formed between the heteroatom X1 (S or Se) and the neighboring carbons (C2 and C6) in the ring change significantly after substitution. The X1-C2 bond is estimated to be longer than X1-C6. This could be explained by the fact that the C2 carbon is surrounded by 2 heteroatoms. These bonds are shorter in the sulfur compounds than in the selenium compounds. The highest size of selenium could explain these results. Concerning N3-C2, N3-C4, C4-C5 and C5-C6 bonds, their small variations do not clearly show a dependence on the size or the electronegativity of the heteroatoms (Table 3).

The smallest valence angle in the cycle is those centered on the X heteroatom. Expectedly, this angle increases with the size of the heteroatom. The influence of heteroatoms on the other valence angles is less important. The evolution of these angles (C5C6X1, X1C2N3, N3C4C6 and C4C5C6) does not correlate with the size or electronegativity of heteroatoms.

The dihedral angle Φ1 (C2N3C5C6) is practically zero in these heterocycles. This indicates that the atoms C2, N3, C5 and C6 are in the same plane. The dihedral angles Φ2 (C2N3C4C5) and Φ3 (N3C2X1C6) become larger with selenium. The same observation is made with compound **1b**. The replacement of sulfur by selenium leads to an increase in these angles and therefore a greater deformation of the six-membered ring. The same observation is made when methyl is replaced by carbonyl in thiazine.

Table 3. Link lengths (Å), valence angles and dihedral angles calculated at the level B3LYP/6-31G (d, p).

	Link lengths (Å)					
	X1-C2	**C2-N3**	**N3-C4**	**C4-C5**	**C5-C6**	**X1-C6**
1a	1.801	1.262	1.476	1.539	1.345	1.784
1b	1.792	1.270	1.463	1.533	1.348	1.779
2a	1.934	1.267	1.480	1.551	1.346	1.907
2b	1.932	1.268	1.465	1.535	1.346	1.909
	Valence angles (°)					
	X1C2N3	**C2N3C4**	**N3C4C5**	**C4C5C6**	**C5C6X1**	**C6X1C2**
1a	127.5	123.8	113.5	123.6	123.3	98.1
1b	126.1	121.6	111.4	119.7	122.6	96.6
2a	125.5	120.3	109.3	121.1	121.3	92.3
2b	125.0	120.3	111.6	120.1	121.9	92.3
	Dihedral angles (°)					
	Φ1	**Φ2**	**Φ3**			
1a	1.4	-29.5	-16.5			
1b	-1.4	-47.0	-26.2			
2a	-0.2	-52.0	-28.8			
2b	-1.6	-52.4	-28.8			

Φ1: angle defined by the atoms C2, N3, C5 and C6
Φ2: angle defined by the atoms C2, N3, C4 and C5
Φ3: angle defined by the atoms N3, C2, X1 and C6.

4. Conclusion

The results of this theoretical study have shown that the cycloreversion of 4*H*-1,3-thiazines and their selenium analogues is a concerted and asynchronous reaction. Selenium reduces the energy barrier to be overcome for its realization. This heteroatom causes an increase in the dipole moment of these heterocycles. The ethyl carboxylate group at the position 4 also increases the dipole moment in thiazine. The difference in reactivity of the selenium compounds and those of the sulfur analogous having the methyl substituent at the position 4 in the cycloreversion reaction could be due to the increase of the dipole moment. The analysis of the HOMO-LUMO energy gaps revealed a greater stability of the sulfur compounds. This would explain a difficulty of cycloreversion from these. The replacement of sulfur by selenium causes an increase in the values of dihedral angles. These structural modifications could explain the more or less easy realization of the cycloreversion of the heterocycles studied.

A study of the cycloreversion of these heterocycles with different solvents is envisaged in order to analyze the influence of the solvent on this reaction.

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