

On the importance of the novel RIRC technique to highlight the Hidden Intermediate of Reaction in the S_NAr Reaction of piperidine on 2-bromo-3,5-dinitrothiophene

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Abstract

DFT/M062X/6-311+G(2d,2p) theoretical calculations have been applied to the reaction mechanism of the S_NAr describing the action of the piperidine C₅H₁₀NH on the 2-bromo-3,5-dinitrothiophene. In a first predictive approach, the role of the ligand X in position 5 (X = NO₂, CN and H) of the 2-bromo-3-nitrothiophene motif has been studied. Our results show that the dinitro compound represents the best element playing the role of electrophile. In a second part focused on this latter compound, we elucidate the aromatic substitution of bromide by piperidine mechanism. To do this, we first use the traditional tools such as the energy, force and internal coordinate profiles based on the intrinsic reaction coordinate. Then, we strengthen our study by tracing the atomic charge and Wiberg bond indice profiles. All the results demonstrate that we were in the presence of a concerted but asynchronous reaction. This excluded the zwitterion to act as a reaction intermediate. However, by using our new technique, called Reactive Internal Reaction Coordinate (RIRC), which gives access to the reaction path according to the selected active internal coordinates, we were able to locate without ambiguity a singular point associated with the Hidden Reaction Intermediate (HRI), compatible with the zwitterion structure. The latter compound corresponded to a long-lived transient species.

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1. Introduction

Aromatic nucleophilic substitutions (S_NAr) have been investigated since the early 1870s¹. They are one of the most studied reactions in pharmaceutical and chemical research²⁻⁷ because of their relevance to both practical applications and mechanistic processes. An important part of the chemistry of heteroaromatic compounds concerned the nucleophilic substitution reactions^{2,8}. S_NAr reactions are often made on pyridines, pyrimidines and related heterocycles. Indeed these substitutions are common and of very high importance in medicinal chemistry and agrochemistry¹. Several experimental works on S_NAr reactions on five-membered heterocycles can be found in the literature^{2,8-14}. Indeed, the reaction of heterocycles with nucleophilic reagents is still extremely useful in many cases, in particular for five-membered heterocycles.

The chemistry of aromatic compounds was one of the first application of quantum mechanics to chemical problems. The reason was mainly the simplicity and the success of Hückel molecular orbital theory (HMO)¹⁵. The reactivity of the thiophene derivatives towards a nucleophilic attack has been the subject of various theoretical investigations^{14,16}. Recently, it has been shown that the study of the molecular systems under external disturbance can be considerably facilitated if reliable scales of electrophilicity and nucleophilicity are available. The usefulness of such global and local reactivity scales is of great importance for answering certain fundamental questions in chemistry such as the feasibility of the reaction (whether a given reaction takes place or not). An excellent source that illustrates this concept is the review work published by Mayr et al.¹⁷. The development of theoretical scales of electrophilicity and nucleophilicity is also desirable, since a validated theoretical scale can be used to project the global reactivity on particular regions of the molecule. There are different ways to model the concept of electrophilicity using the electronic structure of molecules. The best descriptors for studying local reactivity and regioselectivity will be local electrophilicity and local nucleophilicity¹⁸.

Usually, S_NAr reactions require the presence of one or more electron attracting groups (EWG) in the aromatic cycle able to stabilize any negative charge¹⁹. Indeed, the presence of one or two strong EWGs, such as the nitro group (NO_2), in the ortho and para positions, is generally considered as promoting a two-stage mechanism, characterized by addition/elimination through the formation of an anionic Meisenheimer intermediate²⁰.

However, in the absence of EWG, the reaction via a one-step mechanism in which the nucleophilic attack and the release of the leaving group take place in a single elementary step is more difficult to occur. Concerted nucleophilic substitutions were very rare⁷. Indeed, Ritter and Sanford postulated a concerted one-step mechanism⁵. For this, mechanistic proposals were supported by DFT calculations, which found no evidence of the existence of an intermediate. Presumably, the proximal location of the nucleophile (Nu) and the electrophile as well as a milder activation entropy helped these concerted substitution reactions, similarly to a number of related Newman-Kwart, Smiles, and Chapman rearrangements.

Several other theoretical studies have previously revealed that Meisenheimer complexes are not always energetically easily accessible^{21,22} and that a concerted pathway with a single energy barrier can better explain the nucleophilic attack, the disruption of aromaticity and the loss of the leaving group. However, to date, conclusive experimental data for a single-step pathway have not been reported. Recently, Jacobsen and colleagues indicated that is intended to redefine the way S_NAr is taught to undergraduate⁴. By using experiments to verify their calculations, the authors predict that most of the S_NAr reactions such as the intermolecular substitutions of substrates occurring in pharmaceutical syntheses, will in fact take place by a concerted route: 99 reactions out of 120 (83%) had to be concerted. In addition, a progressive pathway should only work with substrates containing the highest level of anionic resonance stabilization and a poor leaving group, such as nitro and fluoride.

The key concept used to differentiate the concerted mechanisms and those operating by steps is based on the comparison of the kinetic isotopic effects (KIE) for different S_NAr reactions. Substitution of an atom with a heavier isotope naturally leads to a slower rate of bond breakage (or bond formation) due to the higher activation energy. The KIE is the ratio of these rates and, most importantly, provides information on bonds in the transition state (TS). Higher KIEs are observed for concerted pathways with a more symmetrical TS and weaker interactions with the entering nucleophile and the electrophile. The progressive mechanisms modify one bond at a time and the TS is closer to the reagent or product, so that the difference in the activation energy between isotope compounds is smaller, thus leading to lower KIEs. ¹²C / ¹³C KIEs should be the most informative kinetic probe for S_NAr reactions, and can be measured by a natural abundance ¹³C NMR method introduced by Singleton and Thomas²³. This method was verified by comparing the KIEs measured for a simple S_N2 reaction with other methods. Then it was applied to three different S_NAr reactions that were chosen according to intuitive predictions of the reaction mechanisms step by step (A), concerted (B) and borderline situation (C) (Figure 1).

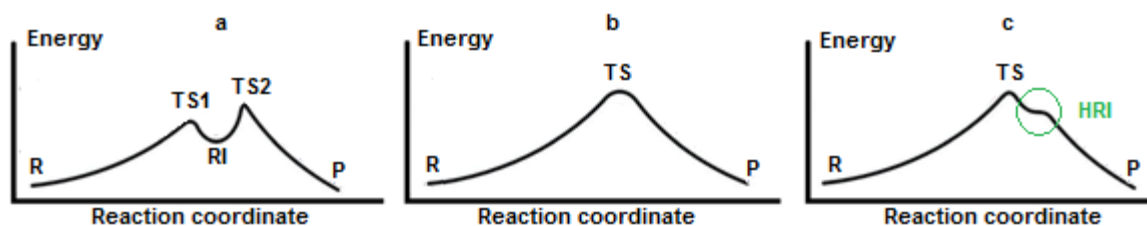


Figure 1: a) Progressive reactions, b) Concerted reactions, c) Borderline situation. R, TS, RI, HRI and P design reacts, transition state, reaction intermediate, hidden reaction intermediate and products respectively.

The calculations of the potential energy surface were in agreement with the experiment, since an intermediate was clearly revealed in reaction (A), while no proof of this was found for reaction (B). In addition, the quasi-classical dynamics was used to model 200 trajectories initiated from TS-(B) which were almost all productive and proceeded to the product. Binding in TS-(B) is described as essentially a delocalized, but not aromatic anion generated by two simultaneous but asynchronous processes, and has been rightly named "Meisenheimer transition state". The Meisenheimer anionic complex in reaction (C) is stabilized but has a better leaving group (Cl^- versus F^-), and the KIE measured with respect to the maximum theoretical KIE has indeed been found to be of intermediate value between reactions (A) and (B). The quasi-classical dynamic trajectories initiated from TS-(C) detected a clustering of points in a shallow region in which a hidden reaction intermediate(HRI) lingered for multiple vibrations before heading towards the product. Reaction (C) can therefore be described occurring step by step with a short-lived intermediate which can also be called long-lived transient species (Figure 1).

Theoretical calculations of our paper concerned the reaction mechanism of the SnAr , describing the action of the piperidine $\text{C}_5\text{H}_{10}\text{NH}$ on the 2-bromo-3,5-dinitrothiophene. The presented work is divided into two distinct and complementary parts. The first part concerned 3 compounds having in common the 2-bromo-3-nitrothiophene motif differentiated by the ligand X ($\text{X} = \text{NO}_2$, CN and H) in position 5. All the results converge to classify the dinitro compound as the best one for playing the role of electrophile. The second part, focused on this latter compound, aims at elucidating the mechanism of aromatic substitution of bromide by piperidine.

2. Methods

DFT calculations were performed using the functionnal M062X^{24} with the basic set 6-311G+(2d, 2p). Transition states were characterized by frequency calculations, taking into

account that they had a single imaginary frequency. Intrinsic reaction coordinate paths (IRC)²⁵ were determined using the second order González-Schlegel integration method^{26,27}. All calculations were performed using the Gaussian 09 revision D.01 program²⁸.

3. Results and discussion

3.1. Reactivity study of 2-bromo-3-nitro-5X-thiophene (X=NO₂, CN, H)

Chemical reactivity is an important concept in organic chemistry. For this, several quantum theories have been developed to find an interpretation allowing to explain the transformation of interacting molecules. The most used methods are : i) Theory of the frontier molecular orbitals (FMO)^{29,30}, ii) Chemical concepts and reactivity indices derived from DFT^{31,32}, iii) HSAB principle (Hard and Soft Acids and Bases)^{33,34} and iv) Transition state theory (TST)^{35,36}.

3.1.1. FMO approach

The comparison of the lowest unoccupied molecular orbitals (LUMO) energies of the compounds derived from the thiophene and the 2-bromo-3-nitro-5X-thiophene (X=NO₂,CN,H) makes it possible to classify their electrophilic character. Indeed, the lower the energy of LUMO, the more electrophile the thiophene is. The optimization of the reagents geometry carried out at DFT/M062X/6311+G(2d, 2p) level of calculations allowed us to obtain the energies of LUMO and HOMO (High Occupied Molecular Orbital). Table 1 gathers the energies of the frontier molecular orbitals and the gaps defined as difference between the LUMO and the HOMO energies of the compounds (ΔE). We also compute the crossed terms energies defined as the gap energies between two different compounds (i.e. $\Delta E_a = E_{\text{LUMO}}(\text{Thiophene}) - E_{\text{HOMO}}(\text{Piperidine})$ and $\Delta E_b = E_{\text{LUMO}}(\text{Piperidine}) - E_{\text{HOMO}}(\text{Thiophene})$, respectively). Figure 2a summarizes the results from Table 1.

Table1: HOMO / LUMO and gap energies ΔE (eV) of thiophene compounds and piperidine calculated at DFT/M062X/6311+G (2d, 2p) level. k (mol⁻¹ sec⁻¹) designs the rate constant¹³.

	X	E _{HOMO}	E _{LUMO}	ΔE	ΔE_a	ΔE_b	10 ³ . k
Thiophene	1 NO ₂	-9.421	-2.620	6.801	5.192	9.792	2950
	2 CN	-9.144	-2.234	6.910	5.578	9.516	187
	3 H	-8.655	-1.670	6.986	6.142	9.027	0.151
Piperidine		-7.812	0.371	8.183	-	-	

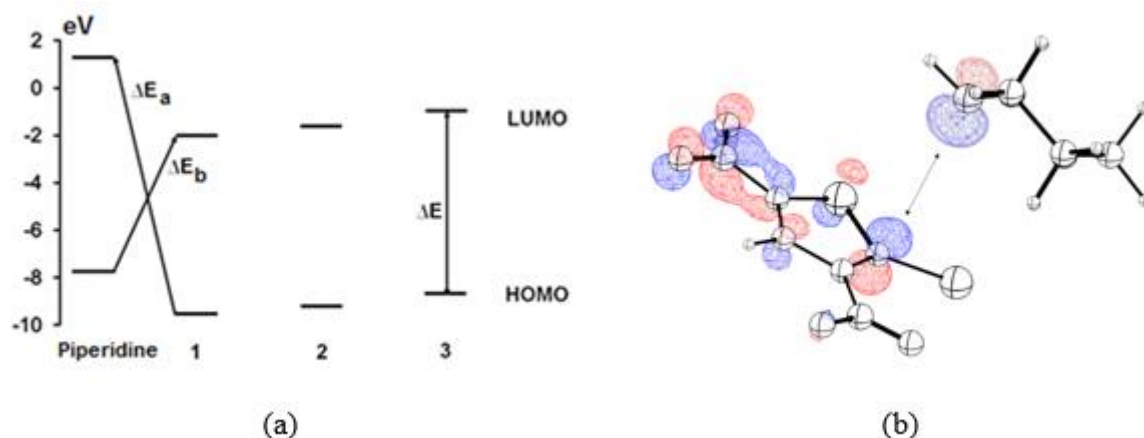


Figure 2: a) FMO (eV) energy diagram of 2-bromo-3-nitro-5X-thiophene (X=NO₂, CN, H) **1**, **2** and **3** and piperidine, calculated at DFT/M062X/6-311+ G(2d, 2p) level, b) Interaction of the HOMO (iso = 0.015) of piperidine with the LUMO (iso = 0.08) of **1**.

Analysis of the results recorded in Table 1 shows that piperidine has the highest HOMO energy compared to the thiophene series. Therefore, piperidine plays the role of electron donor. The LUMO energy values of the different thiophene compounds are always lower than the piperidine one. The studied thiophene series are therefore good electron acceptors. The results also show that thiophene **1** (X=NO₂) has the lowest gap energy ($\Delta E = 6.801\text{eV}$) compared to thiophene compounds **2** (X=CN) and **3** (X=H). We can thus conclude that thiophene **1** is the most reactive element towards piperidine. In addition, the gaps ΔE_b are always greater than ΔE_a . This result confirms that the thiophene systems play the role of electron acceptors and piperidine behaves like an electron donor.

According to the kinetic constants k measured experimentally¹³, the addition reactions are more favored when the thiophene derivatives carry electron-withdrawing groups as CN or NO₂. So, the reactivity of the studied thiophene series is in decreasing order **1** > **2** > **3** since the bimolecular rate constant $k(\mathbf{1}) > k(\mathbf{2}) > k(\mathbf{3})$ accordingly to our calculation results $\Delta E_a(\mathbf{1}) < \Delta E_a(\mathbf{2}) < \Delta E_a(\mathbf{3})$. We show that the FMO approach provides the exact order of thiophene compounds reactivity. We can also conclude that the reactivity of the thiophene derivatives is stronger with respect to piperidine when the group in position 5 is an attractor. Indeed, this configuration leads to the weaker ΔE_a in the electron-attracting groups in position 3 and 5 series.

The knowledge of the shape of border molecular orbitals improves the presented reactivity analysis³⁷. Indeed, we note from Figure 2b that the involved HOMO/LUMO interaction takes place between the carbon atom C2 of the 2-bromo-3,5-dinitrothiophene,

representing the largest coefficient of LUMO, and the nitrogen atom piperidine, representing the largest coefficient of the HOMO.

3.1.2. Conceptual DFT descriptors

In order to evaluate the electrophilic character of the studied thiophene series (**1**, **2** and **3**) and the nucleophilicity of the piperidine, we calculated the values of the global indices: chemical potential μ , electrophilicity ω , nucleophilicity N , hardness η and softness S of the reagents expressed in (eV) at the M062X level using the base 6-311+G (2d, 2p). These values are reported in Table 2 and lead to the following observations:

-The electronic chemical potential of piperidine (-3.720 eV) is higher than that of thiophene series **1**, **2** and **3**. This means that the transfer of electrons will take place from piperidine to thiophene.

-The values of the global electrophilic indices ω of the different thiophene compounds are higher than that of piperidine (1.692 eV). Therefore, thiophene behaves like electrophiles and piperidine acts like a nucleophile.

- Thiophene **1** has an overall electrophilicity value ω (5.330 eV) which is the highest one compared to the other thiophenic compounds **2** (4.684eV) and **3** (3.815eV). Consequently, thiophene **1** is the most electrophilic and the most reactive towards piperidine.

We will now focus on local indices. It was shown³⁸ that for reactions controlled by frontier molecular orbitals, the higher the value of the Fukui indice is, the more reactive the site is. In Figure 3a, we give the isodensity maps of the Fukui indice on the C2 carbon atom of the thiophene series. The results were obtained using the electronic densities of LUMO³⁹.

Table2: Chemical potential μ , electrophilicity ω , nucleophilicity N , hardness η and softness S of the reagents expressed in (eV).

	X	μ	ω	N	η	S
Thiophene	1 NO ₂	-6.020	5.330	1.491	3.400	0.147
	2 CN	-5.689	4.684	1.768	3.455	0.145
	3 H	-5.162	3.815	2.257	3.492	0.143
Piperidine		-3.720	1.692	3.100	4.091	0.122

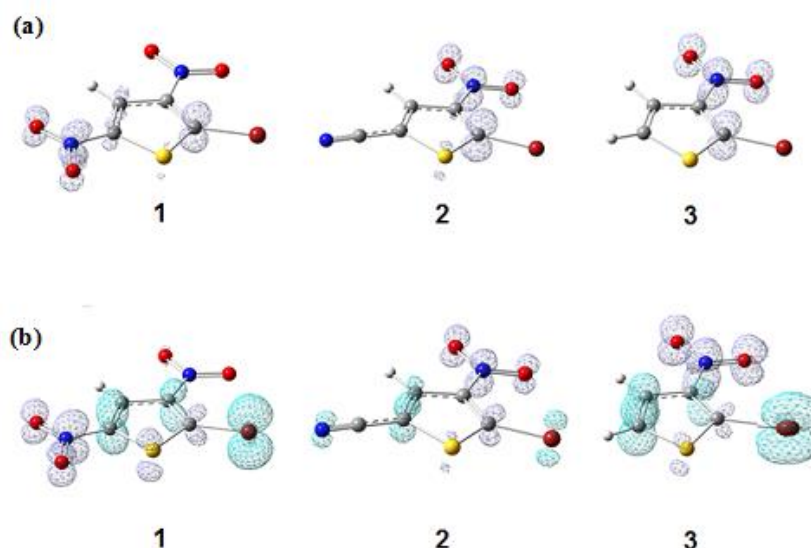


Figure 3: a) Isodensity map of Fukui indice f^+ (iso = 0.01 a.u) b) Isodensity map of the dual descriptor Δf (iso = 0.01 a.u) of 2-bromo-3-nitro-5X-thiophene (X = NO₂, CN, H) **1**, **2** and **3** calculated at DFT/M062X /6-311+G(2d, 2p) level.

Figure 3a clearly shows the electrophilic nature of the C2 atom. It confirms also that S_NAr will take place between the piperidine nitrogen and the C2 atom of the thiophene. The use of the dual Δf descriptor, equal to the difference ($f^{+}-f^{-}$), allows the prediction of the most reactive site in an electrophilic (or nucleophilic) attack in the context of orbital interactions. Indeed, Figure 3b indicates that the carbon C2 has a positive Δf symbolized by the dark blue lobes. This descriptor confirms that the carbon C2 will act preferentially with the nucleophile site of the piperidine (nitrogen atom). In the following of this work, we will especially focus on the compound **1** and the 2-bromo-3,5-dinitrothiophene.

3.2. Reaction mechanism

3.2.1. Energy profile

Determining the structure of the transition state is the first step in studying the reaction mechanism. Despite all our efforts, we were only been able to optimize one transition state. This excludes the 2-steps mechanism. To confirm that the obtained transition state (TS) well describes the substitution of bromine from reagent **1** by piperidine, we calculated the energy profiles (Fig. 4a), the force (Fig. 4b) and the internuclear distance (Fig. 4c) of this S_NAr reaction versus the intrinsic reaction coordinate (IRC). The structures of the two energy profile limits correspond to the reactants and the products.

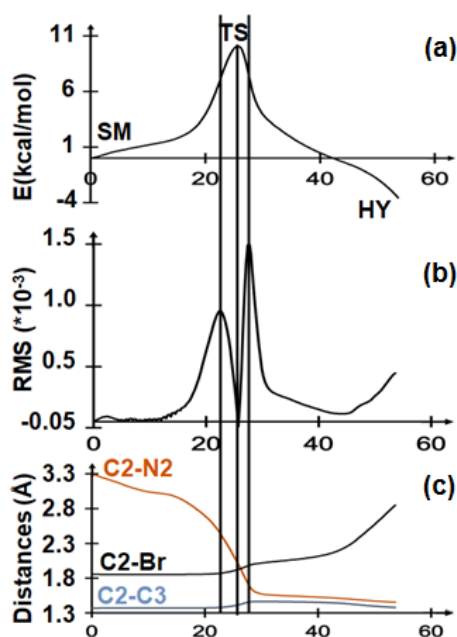


Figure 4: a)Energy, b)force and c) internal coordinate profiles of 2-bromo-3,5-dinitrothiophene **1** and piperidine at the DFT/M062X/6-311+G(2d,2p) calculation level.

We can state that the studied reaction is concerted since there is only one transition state. Such a reaction must have a simple force profile presenting 3 zones delimited by extrema and which represent: i) the approach of the reactants, ii) the transition state zone of influence and iii) the formation of the final compounds. However, Figure 4b shows an abrupt change in the direction from the energy derivative at abscissa 40 a.u. This is translated by a change in concavity at the same abscissa of the energy profile of Figure 4a.

To better understand the origin of this evolution in the studied reaction, the profile of the relevant and active internal coordinates have been plotted in Figure 4c. We have chosen the distance of the breaking C2-Br bond leading to the formation of the bond and distance of the bond C2-C3 changing from single to double bond. The analysis of these curves shows that, until the end of the TS zone of influence, the distance C2-N2 decreases to a bond length slightly greater than 1.5Å while the length of the bond C2- C3 increases to a value close to 1.44Å. At the same time, the length of the C2-Br bond increased from 1.86Å to 2.19Å while the N2-H2 length remained practically unchanged.

We have grouped together in Table 3 pertinent bond lengths and angles as well as dihedral angles of the compounds involved in this reaction. We can notice that we do not observe the departure of H-Br but that the final compound is more like a complex where hydrogen H2 is shared between nitrogen N2 and bromine. It is for this reason that we noted it HY.

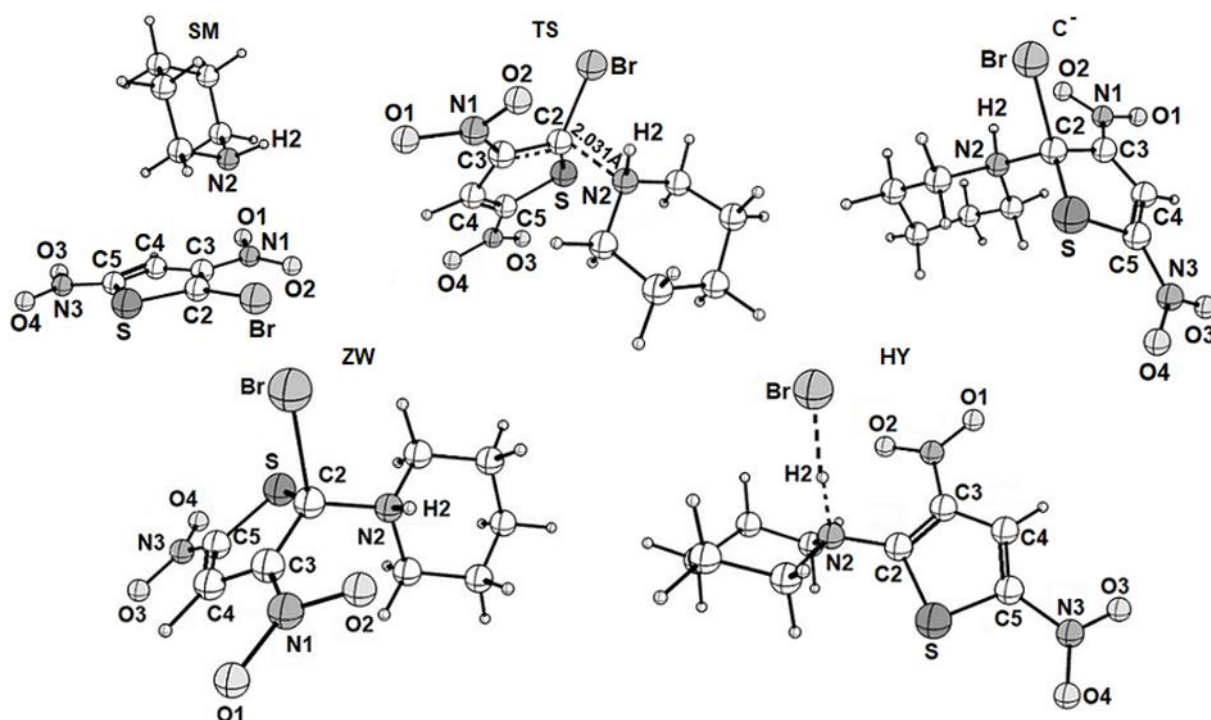


Figure 5: Geometry of involved compounds in the reaction of 2-bromo-3,5-dinitrothiophene **1** and piperidine.

On the other hand, we detect far from the TS zone of influence a sudden and significant change in the C2-Br internuclear distance. We can conclude that the studied reaction, although concerted, does not involve structural modifications synchronously. We present in Figure 5 the obtained structures: the supermolecule (SM) grouping the two separate reagents, the transition state (TS) and the final product (HY). We are therefore in the case of a "borderline case" or "type C" reaction. In the case of concerted and asynchronous mechanisms, it is usual to search for a hidden reactive intermediate (HRI). This species is assumed to play the role of a reaction intermediate, while never experimentally detected and never theoretically located as a singular point.

3.2.2. RIRC

To circumvent the usual theoretical chemistry methods which are unable to locate the hidden reaction intermediate and to better elucidate the reaction mechanism, we have implemented a new tool called « Reactive Internal Reaction Coordinate » (RIRC). This new method allows us to plot the complete reaction path showing the evolution of the reaction energy versus the active pertinent internuclear distances called active form or break during the reaction. This new RIRC representation allows by a simple reading, to describe the course of the reaction from the supermolecule to the final products.

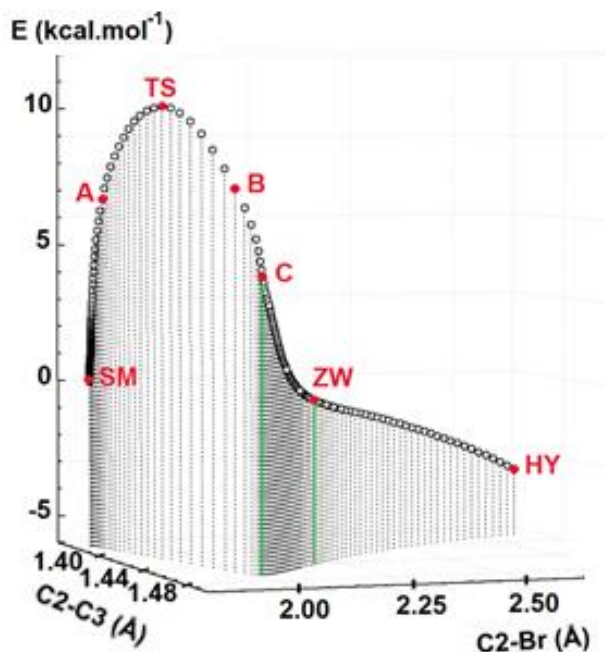


Figure 6: RIRC-pathway of the piperidine action on 2-bromo-3,5-dinitrothiophene calculated by the DFT / M062X / 6-311+G (2d, 2p) method. SM, TS, C, ZW and HY design the supermolecule, the transition state, the carbanion, the zwitterion and the product, respectively. A and B delimit the TS zone of influence.

Indeed, the curve in Figure 6 depicts the 3D reaction energy path under two constraints representing the two active internal coordinates. We used here, as in the 3.2.1 part, the C2-C3 bond length which evolves during the reaction from a double to a single bond and the C2-Br bond which breaks during the reaction. The reaction energy will increase until reaching its maximum which represents the transition state TS. Then, it will decrease to reach the final product HY. Although the reaction path of Figure 6 seems identical to the energy profile of Figure 3a, we detect an important difference in this 3D representation. Indeed, it reveals the presence of two inflexion points of the reaction coordinate which are the projection of the reaction path on the horizontal plane. The first one, denoted by C positioned at 1.464Å, 2.013Å and 4.257 kcal mol⁻¹, represents the situation where the C2-C3 bond length is maximum. From C, the C2-C3 bond length begins to shrink. The NBO analysis of the structure associated to C is a C3 carbanion where the negative charge is carried by a pure p orbital. The second inflexion point is localized at (1.441Å, 2.194Å and -0.250 kcal mol⁻¹). The values of the internuclear distances are compatible with the length of single C-C and C-Br bonds leading to the corresponding zwitterion denoted ZW. This structure is considered as the hidden reaction intermediate. Although most experimenters consider zwitterion as a reaction intermediate, our study does not confirm this hypothesis.

Tableau 3: Selected internuclear distances expressed in Å (Wiberg indice) and atomic charge variation calculated by DFT/M062X/6-311+G(2d,2p) method of the supermolecule (SM), transition state (TS), carbanion (C), zwitterion (ZW) and final product (HY). All those compounds are involved in the reaction of 2-bromo-3,5-dinitrothiophene **1** and piperidine.

Designation		SM	TS	C	ZW	HY
Internuclear distance	C2-N2	3.296(0.0)	2.031(0.4)	1.581(0.8)	1.511(0.9)	1.424(1.0)
	C2-Br	1.856(1.1)	1.920(1.0)	2.013(0.9)	2.194(0.7)	3.524(0.0)
	H2-N2	1.015(0.8)	1.018(0.8)	1.028(0.7)	1.031(0.7)	1.251(0.3)
	H2-Br	3.848(0.0)	2.838(0.0)	2.731(0.0)	2.729(0.0)	1.743(0.5)
	C2-C3	1.369(1.5)	1.412(1.3)	1.464(1.1)	1.441(1.2)	1.375(1.5)
Charge variation	C2	0	0.12	0.2	0.30	0.37
	C3	0	-0.12	-0.11	-0.11	0.02
	N2	0	-0.15	-0.20	-0.19	0.10
	Br	0	-0.08	-0.19	-0.42	-0.80

However, we can locate the most representative atomic structure of the zwitterion by the RIRC (Figure 6). The reaction path shows that the zwitterion is not a local minimum. However, this entity could be called "long-lived transient species"^{40,41}. The C2-Br bond length increased to 2.194Å while C2-N2 internuclear distance decreases to 1.511Å. The C2-N2 bond is thus well established and the distance C2-C3 lengthens to reach the value of 1.441Å.

3.2.3. Charge distribution

Analysis of the charge distribution in a molecular system can be obtained using Mulliken population or natural bond orbital analysis⁴² (NBO). This technique uses the second order energy perturbation E2 in order to understand the donor – acceptor interactions. The NBO calculation is performed at the same level of theory than before. Figure 8 shows the charge profile indicating the variation of the atomic charges of the atoms involved in the S_NAr reaction versus the intrinsic reaction coordinate while each value of interest are given in Table 4. The C2 and N2 atoms recover positive charge until the formation of ZW. The atomic charge continues to decrease for C2 until the formation of HY but stabilizes for N2. Conversely, the bromine atom will acquire a partial negative charge until the zwitterion forms, then its charge will further decrease to the value -1 indicating the formation of a bromide group.

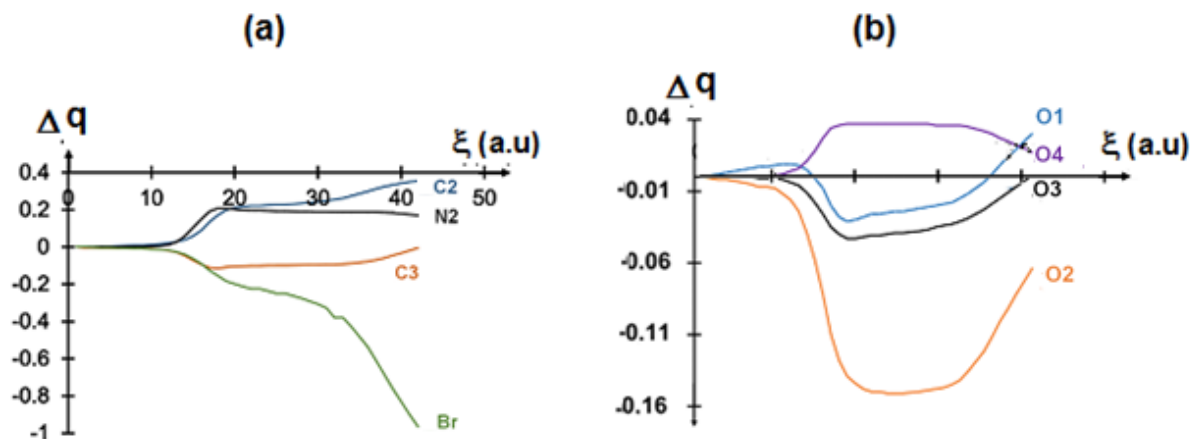


Figure 7: Atomic charge and Wiberg indice profiles of the reaction between 2-bromo-3,5-dinitrothiophene **1** and piperidine calculated by DFT/M062X/6-311+(2d,2p) method.

We note also that the charge variations of the atoms O1, O2, O3 and C3 evolve in the transition state zone of influence (Figure 7). This evolution continues until the formation of the zwitterion. This polarization is temporary since it will eventually cancel out at the end of the reaction. For the zwitterion, according to the analysis of NBO calculations, the O2 and O4 atoms store the negative charge. They can be considered as anions since NBO calculations have assigned them 3 electron lone pairs.

3.2.4. Solvent effects

We performed now calculations with the SCRF option to simulate the solvation effect of water as a polar solvent capable of stabilizing the charged entities. Unfortunately, the zwitterion still keeps its hidden reaction intermediate status. The only modification was the evolution of the final product towards the structure of ammonium bromide.

4. CONCLUSION

The work presented in this article is divided into two distinct and complementary parts. The first, predictive in nature, concerned 3 compounds having in common the 2-bromo-3-nitrothiophene motif and differentiating by the ligand X in position 5 (X = NO₂, CN, H). All the results converge to classify the dinitro compound as the best electrophile element. The second part, focused on this latter compound, allows to elucidate the mechanism of the aromatic substitution of bromide by piperidine. We first used the traditional tools such as the energy,

force and internal coordinate profiles as a function of the intrinsic coordinate of the reaction, together with the Fukui indices. All the results aim at concluding on a concerted but asynchronous reaction. This excludes the zwitterion as a reaction intermediate. However, the use of our new technique which gives access to the reaction path according to the active internal coordinates makes it possible to locate without ambiguity a singular point associated with the zwitterion. This shows that the latter is a transient species with a long lifetime.

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