

Theoretical Analysis of the Regioselective Electrophilic Chlorination and Chemoselective Esterification of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid

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Abstract

The reaction between the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** and SOCl₂ has been studied within the Density Functional Theory (DFT) B3LYP/6-31G(d,p) computational level. Examination of the conceptual DFT reactivity indices permit the elucidation of the reactivity, and the regio- and chemoselectivity experimentally observed. The possible regioselective channels and chemoselective channels were explored and characterized. Analysis of the energies associated with the different reaction pathways shows that this reaction is completely chemoselective and regioselective, in conformity with the experimental results.

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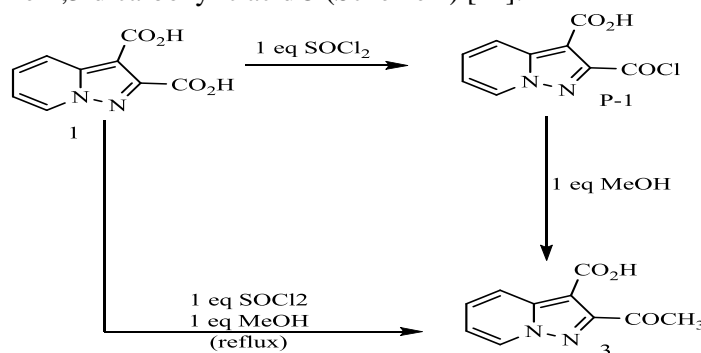
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1. Introduction

The improvement of environmentally friendly versatile and simple processes or methodologies for commonly utilized organic products starting easily accessible reagents is one of the main experiments for chemists in organic synthesis. Organic sulfur products are extensive in various natural compounds and generally used as different synthetic chemicals. Sulfonyl chlorides, specifically, are precursors with widespread uses in organic synthesis [1-3]. The mainly typical technique to prepare the sulfonyl chlorides is the oxidative chlorination of sulfur compounds, thiocarbamates, thioacetates, sulfides, thiols, and with aqueous chlorine [4-6]. While other techniques are obtainable to accomplish this transformation, [7-10] attention is moving to newer and choosier techniques for this aim. Thionyl chloride (SOCl_2) is a reactive chemical reagent. It is chiefly employed in the industrial fabrication of organochlorine products, which are frequently intermediates in agrichemicals and pharmaceuticals, in this In this context, the treatment of the acid pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** with one equivalent of SOCl_2 leads regioselectively to a single product 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid **2**, and then the product **2** is subjected to an esterification reaction with one equivalent of methanol in DMSO as a solvent which chemiospecifically gives the product pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **3** (Scheme 1) [11].



Scheme 1

Herein, we employed DFT calculation to investigate the reaction of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** with one equivalent of SOCl_2 experimentally studied by Ejjommany et al. [11] Our aim in this work is to explicate the regioselectivity and chemoselectivity experimentally observed.

2. Computational methods

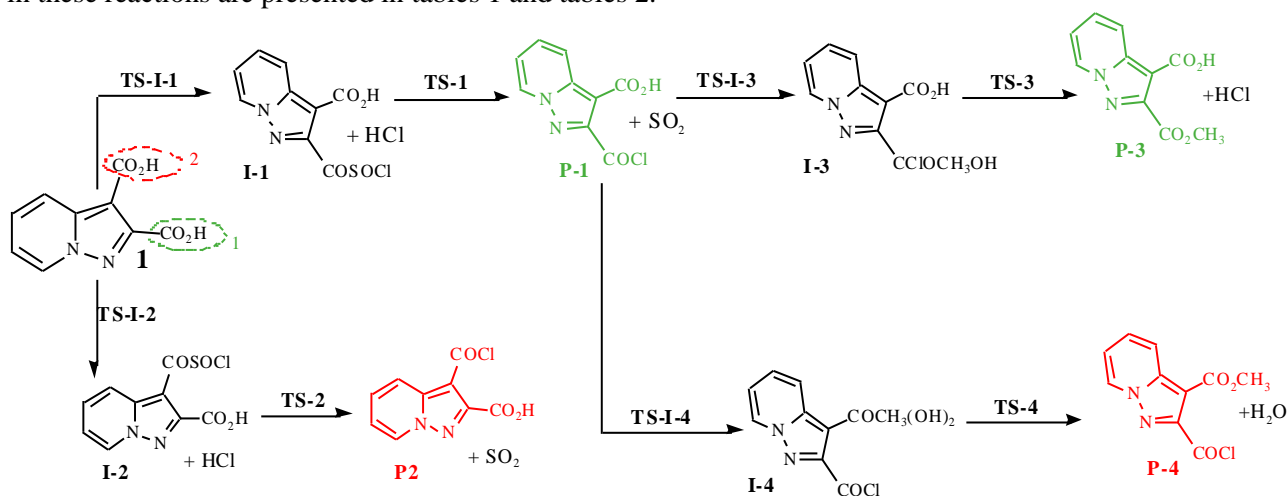
DFT computations were carried out using the B3LYP functional [12], together with the standard 6-31G(d,p) basis set. The optimizations have been realized using the Berny analytical gradient optimization method [13]. All computations have been shown with the Gaussian 09 suite of programs [14]. The global electrophilicity index [15] ω , was given by the following expression, $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η . Both quantities could be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L , as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively [16]. The empirical (relative) nucleophilicity index N [17], based on the HOMO energies obtained within the Kohn–Sham scheme [18], and defined as $N = E_{\text{HOMO}}(\text{Nu}) - E_{\text{HOMO}}(\text{TCE})$. The nucleophilicity was referred to tetracyanoethylene (TCE). This choice allowed us to handle conveniently a nucleophilicity scale of positive values. Electrophilic P_k^+ and nucleophilic P_k^- Parr functions [19-25], were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radical cation of the reagents. The local electrophilicity indices were evaluated using the following expressions: $N_k = N \cdot P_k^-$ [26]. The stationary points were characterised by frequency computations in order to verify that TSs have one and only one imaginary frequency. Intrinsic reaction coordinates (IRC) [27] pathways were traced to verify the connectivity between minima and associated TSs.

3. Results and Discussions

The present theoretical study has been divided in three parts: (1) the potential energy surface (PES) associated with the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** with one equivalent of SOCl_2 are explored and characterized, (2) next, an analysis of the conceptual DFT indices of the reagents involved in the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** with one equivalent of SOCl_2 . (3) Finally transition states geometries are analyzed.

3.1. Analysis of the PESs of the chloration reactions of **1** by thionyl chloride and esterification of **P-1** with methanol.

Analysis of the stationary points involved in the reaction between **1** and thionyl chloride SOCl_2 indicates that this chloration reaction takes place through a two-step mechanism. Consequently, the reagents, **1** and thionyl chloride SOCl_2 , two TS, **TS-I-1**, **TS-1**, intermediate **I-1** and **P-1** were located and characterized. Examination of the stationary points concerned in the reaction between **P-1** and methanol show that this esterification reaction takes place through a two-step mechanism. Therefore, the reagents, **P-1** and methanol, two TS, **TS-I-3**, **TS-3**, intermediate **I-3** and **P-3** were sited and described (see Scheme 2). Gas phase total and relative electronic energies of the stationary points elaborate in these reactions are presented in tables 1 and tables 2.



Scheme 2. Chloration of **1** by thionyl chloride SOCl_2 and esterification reaction between **P-1** and methanol

Table 1. Energetic values in (a. u) of isolated species in gas phase and relative energy in (kcal/mol) involved in the chloration reaction of **1** by thionyl chloride SOCl_2 .

system	E	ΔE
1 + SOCl_2	-2150.70081625	-----
TS-I-1	-2150.65432412	29.17
I-1 + HCl	-2150.66267534	23.93
TS-1 + HCl	-2150.69743547	2.12
P-1 + SO_2 + HCl	-2150.73336200	-20.42
TS-I-2	-2150.63407396	41.88
I-2 + HCl	-2150.69098720	6.16
TS-2 + HCl	-2150.43439748	41.67
P-2 + SO_2 + HCl	-2150.73300323	-20.19

Table 2. Energetic values in (a. u) of isolated species in gas phase and relative energy in (kcal/mol) involved in the esterification reaction between P-1 and methanol

system	E	ΔE
P-1+MeOH	-1257.06908480	-----
TS-I-3	-1257.01358557	34.82
I-3	-1257.03248608	22.96
TS-3	-1257.06471472	2.74
P-3+HCl	-1257.08425226	-20.98
TS-I-4	-1256.99154531	48.65
I-4	-1257.03569191	20.95
TS-4	-1257.00583782	39.68
P-4+H ₂ O	-1257.05653440	-10.94

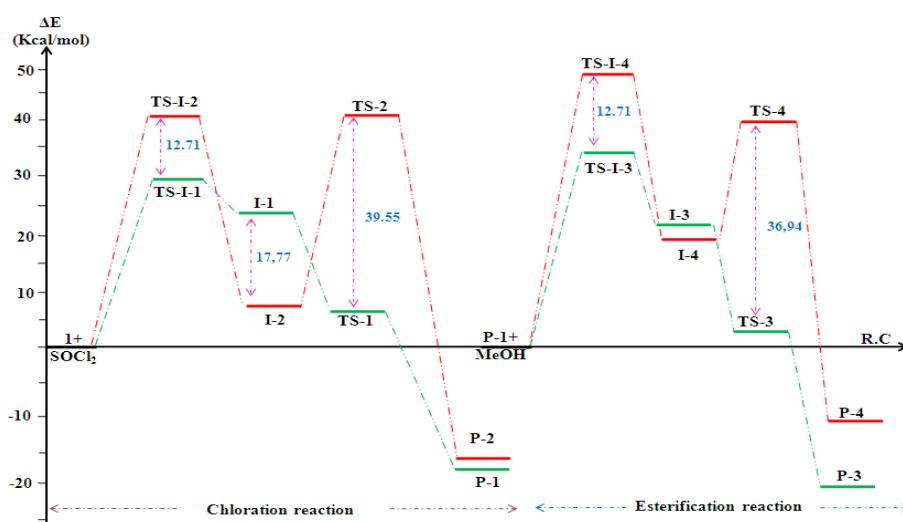


Figure 1. Energy profile (ΔE , in kcal mol⁻¹) of the chlorination reaction 1 by thionyl chloride SOCl₂ and the esterification reaction between P-1 and methanol

The B3LYP/6-31G(d,p) gas phase activation energies associated with the two reactive channels of chlorination reaction between 1 and thionyl chloride are 29.17 (TS-I-1), and 41.88 (TS-I-2) kcal mol⁻¹. Additionally, these chlorination reactions are being exothermic between 20.19 and 20.42 kcal mol⁻¹. Therefore, this chlorination reaction presents for the most favored channels average activation energy about (29.17 kcal mol⁻¹) corresponding to (TS-I-1). A comparison between the energies of the two intermediates I-1+HCl (23.93) and I-2+HCl (6.16) indicates that intermediate I-2 is the most stable than intermediate I-1 and activation energies of the intermediates are 2.12 (TS-1), and 41.67 (TS-2) kcal mol⁻¹. Therefore, the position COOH (1) regioisomeric approach mode is more favorable than the position COOH (2) one, alike to those of the experimental findings. Conversely, the exothermic character of these chlorination reactions accounts that these chlorination pathways are irreversible and, thereby, this process is only under kinetic control.

A distinguishing between the energies of the two intermediates I-3 (22.96) and I-4 (20.95) designates that intermediate I-3 is the largely stable than intermediate I-4 and activation energies of the intermediates are 2.74 (TS-1), and 39.68 (TS-2) kcal mol⁻¹. In addition, these esterification reactions are being exothermic between 20.98 and 10.94 kcal mol⁻¹. Hence, these esterification reactions present average activation energy (29.17 kcal mol⁻¹) for the most favored

channels (TS-I-3). Therefore, the position COCl chemio-isomeric approach mode is more favorable than the position COOH (2) one, similarly to those of the experimental result. Conversely, the exothermic character of these chloration reactions accounts that these chloration pathways are irreversible and, thereby, this process is under thermodynamic and kinetic control.

3.2 Geometrical parameters

The Figures 2 summarize all the structures optimized of the transition states in gas phase which are involved in the studied chloration and esterefication reactions.

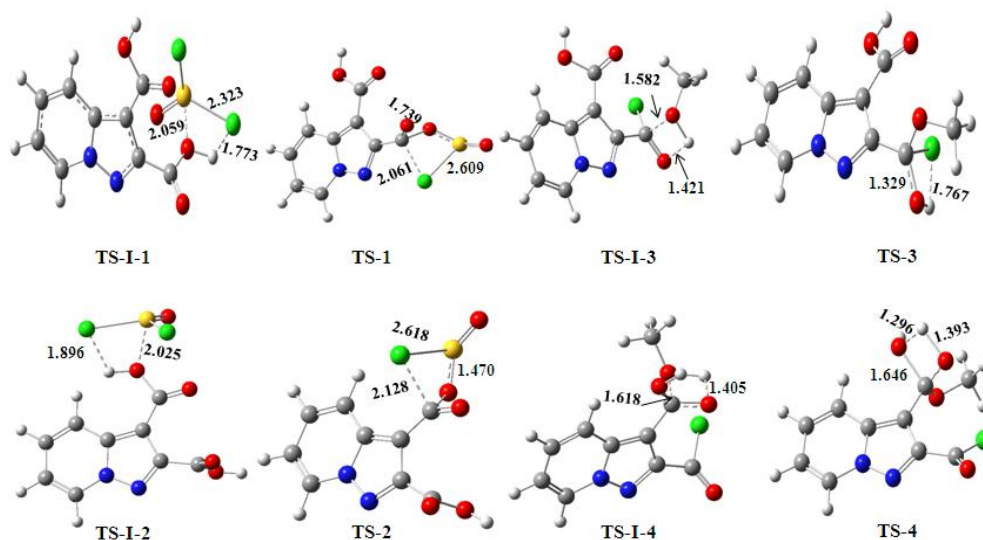


Figure 2. Structures of the transition states gas phase calculated by B3LYP/6-31G (d). Distances are given in Angstroms.

At **TS-I-1**, the lengths of the two forming bonds are 2.059 Å (S-O) and 1.773 Å (Cl-H), while at the **TS-I-2** these lengths are 2.025 Å (S-O) and 1.896 Å (Cl-H). From these geometrical parameters some significant behaviours should be remarked: *i*) these large S-O distances indicate that these TSs are earlier; *ii*) the difference between the two forming bonds shows that they correspond with asynchronous TSs. The most favourable **TS-I-1** is more asynchronous than **TS-I-2**.

At **TS-I-3**, the lengths of the two forming bonds are 2.059 Å (C-O) and 1.421 Å (O-H), even as at the **TS-I-4** these lengths are 1.618 Å (C-O) and 1.405 Å (O-H). From these geometrical parameters some significant behaviours should be *observed*: *i*) these large H-O distances indicate that these TSs are previously; *ii*) the variation between the two forming bonds shows that they relate with asynchronous TSs. The most favourable **TS-I-3** is more asynchronous than **TS-I-4**.

3.3. The analysis of the conceptual DFT indices of the reagents

The global DFT indices, namely the electronic chemical potential μ , chemical hardness η , electrophilicity ω and nucleophilicity N , are given in table 1. The electronic chemical potential of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic **1**, $\mu = -3.96$ eV, is higher than that of SOCl_2 , $\mu = -7.24$ eV, thereby indicating that along a polar reaction the global electron density transfer [22] (GEDT) will go from the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic **1** towards SOCl_2 . The values of the electrophilicity ω indices of the two reagents are: 1.69 (**1**) and 2.82 (**2**) eV. On the other

hand, the nucleophilicity N indices of the reagents, 2.82 (**1**), 0.80 SOCl_2 eV, indicate that the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic **1** will participate as nucleophile and SOCl_2 will participate as electrophile.

Table 1. B3LYP/6-31G(d,p) electronic chemical potential, chemical hardness, electrophilicity and nucleophilicity in eV, of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid of SOCl_2 , 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid and methanol.

System	μ	η	N	ω
1	-3.96	4.65	2.82	1.69
SOCl_2	-7.24	2.15	0.80	2.82
P-1	-5.769	8.36	-0.82	1.98
MeOH	-2.55	9.30	1.91	0.35

The electronic chemical potential of the methanol, $\mu = -2.55\text{eV}$, is higher than that of 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid **P-1**, $\mu = -5.76\text{ eV}$, thus demonstrating that along a polar reaction the global electron density transfer (GEDT) will go from the methanol towards 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid **P-1**. The values of the global electrophilic indices ω indicate that the 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid **P-1** is more electrophilic than the methanol. In fact, the calculated value of ω is 1.98 eV for **P-1** and 0.35 eV for methanol. Thus, the **P-1** would act as an acceptor of electrons; Similarly, the analysis of the values of the global nucleophilic indices N shows that the methanol has a higher value of 1.98 eV than that of the **P-1** which is -0.82 eV, hence the compound methanol acts as an electron donor; It has been established that along a polar reaction with non-symmetric reagents the most favourable reactive channel is that where the two-centre interaction is developed between the most electrophilic centre of the electrophile and the most nucleophilic centre of the nucleophile. The electrophilic P_k^+ and the nucleophilic P_k^- Parr functions have been reported as derived from the changes of spin electron density attained by a GEDT process developed from the nucleophile towards the electrophile. According to the Parr functions, the most favourable single bond formation arises between the most electrophilic and nucleophilic centers of the reagents. The electrophilic and nucleophilic Parr functions of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid(**1**), 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid (**P-1**), SOCl_2 , and methanol are displayed in figure 3.

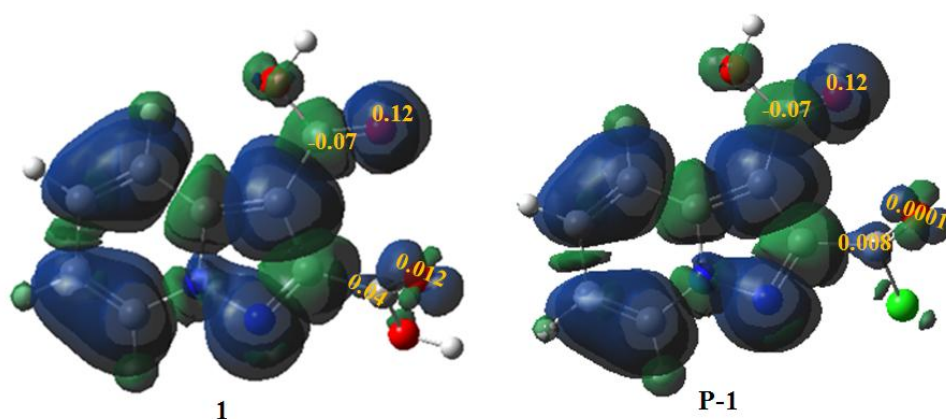


Figure 3. The ASD of the radical anion and the radical cations as well as the electrophilic and nucleophilic Parr functions of the pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid(**1**), 2-(chlorocarbonyl)pyrazolo[1,5-a]pyridine-3-carboxylic acid (**P-1**), SOCl_2 , and methanol.

Analysis of the nucleophilic P_k^- Parr functions for pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** indicates that the carbons of the carboxylic acid COOH (1) is more nucleophilically activated, $P_k^- = 0.04$, than this of the carboxylic acid COOH (2), $P_k^- = -0.07$. Consequently, as expected, the carboxylic acid COOH (1) is the more reactive one of the two carboxylic acid COOH of pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1**, in excellent agreement with experimental outcomes.

4. Conclusion

The chloration reaction of the carboxylic acid COOH (1) with SOCl_2 has been studied within the DFT method at the B3LYP/6-31G(d,p) computational level. The chemo- and regioisomeric reaction paths associated with the chloration and esterification of pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1**, and the regioisomeric reaction paths associated with the chloration reaction and chemosomeric reaction paths associated with the esterification reaction have been investigated and illustrated. Scrutiny of the CDFT indices report for the reactivity of pyrazolo[1,5-a]pyridine-2,3-dicarboxylic acid **1** is organize as a strong electrophile and a moderate nucleophile. Analysis of the nucleophilic P_k^- Parr functions indicates that the carboxylic acid COOH (1) is more nucleophilically activated of the carboxylic acid COOH (1) is more nucleophilically activated. The chloration and esterification reactions take place through a one-step mechanism, in which the formation of the two new single bonds is somewhat asynchronous. Examination of the energy profiles associated with the chloration reaction show that this reaction presents a high regioselectivity and examination of the energy profiles associated with the esterification reaction indicates that this reaction presents a high regioselectivity.

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