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Research Article

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Understanding the Regioselective and Molecular Mechanism of the TCE in Cycloaddtion Reaction (TCE+Cp) and Addition Reaction (TCE+HCl) using DFT calculation

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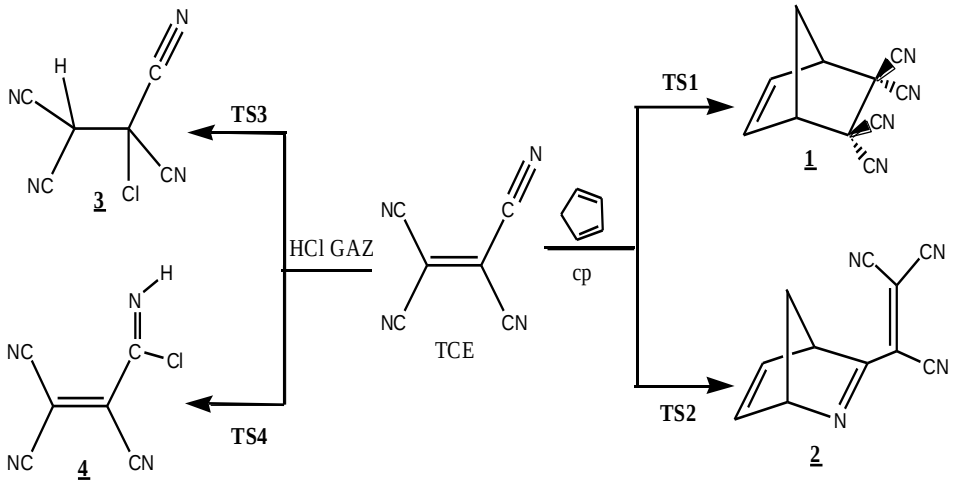
Abstract: The polar Diels–Alder (P-DA) reaction of TCE (*2,3-Dicyano-but-2-enedinitrile*), diene Cp, toward Bicyclo[2. 2. 1]hept-5-ene-2, 2, 3, 3-tetracarbonitrile , was theoretically studied using DFT methods at the B3LYP/ 6-31G(d) level and 6-31G(d,p) in the presence of water. Calculated relative enthalpy associated with the two feasible reactive channels indicate that this P-DA cycloaddition takes place via C2–C3 regioselectivity, furnishing a formal [4+2] P_1 in excellent agreement with experimental outcomes. In the considered P-DA reaction, while C2–C3 regioselectivity can be explained using calculated Parr functions at the interacting sites of reagents. In addition, Hydrochloric acid does not react with the TCE (*2,3-Dicyano-but-2-enedinitrile*) due to the high activation energy of this reaction.

Keywords: TCE, DFT, B3LYP/ 6-31(d), Regioselectivity, P-DA. [4+2], Parr functions

1. INTRODUCTION

Cyclic compounds are important pharmacophores in several pharmaceutical compounds [1-3]. They are also useful intermediates for synthesis of natural products and biologically active compounds [4-10]. A variety of synthetic methods has been developed for preparation of cyclic compounds, of which the most convenient and attractive route is probably the cycloaddition of diene or dipole to alkenes [10-11]. The Diels-Alder reactions an organic chemical reaction (specifically, a [4+2] cycloaddition) between a conjugated diene end a substituted alkene, commonly termed the dienophile. From the discovery of the DA reaction in the 1920s by Otto Diels and Kurt Alder [12], the new methods developed to give highly variable yields. Having low toxicity, ready availability, easy handling like iodine compounds, Iodobenzene (PhI) is the most utilized iodoarene, and m-chloroperbenzoic acid (mCPBA) and oxone are usually used as the terminal oxidants [13-16]. the lot of theoretical work has been devoted to the study of the mechanism and the selectivity of these cycloaddition reactions. FMO analysis has also been used to explain the regioselectivity patterns observed in Diels–Alder reactions of substituted systems [17, 18], the transition state theory (TST) [19, 20], and more recently static reactivity indexes defined within the

conceptual density functional theory (DFT) [21]. Aim in this work is to present a theoretical study of the reactivity of tetracyanoethelene with Cyclopentadiene (Cycloadditions Reactions) and reactivity of tetracyanoethelene with Hydrochloric acid (additions Reactions) (Scheme 1) and compared the results of our calculations with experimental results available in the literature [22, 23].



Scheme 1: Reaction paths involved in the reactions of TCE with Cp and TCE with HCl.

2. COMPUTATIONAL METHODS

DFT computations were carried out using the B3LYP functional [24], together with the standard 6-31G′ basis set [25]. The optimizations were carried out using the Berny analytical gradient optimization method [26]. The stationary points were characterized by frequency computations in order to verify that TSs have one and only one imaginary frequency. The IRC paths [27] were traced in order to check the energy profiles connecting each TS to the two associated minima of the proposed mechanism using the second order González–Schlegel integration method [28]. The electronic structures of stationary points were analyzed by the natural bond orbital (NBO) method [29]. All computations were carried out with the Gaussian 09 suite of programs [30]. The global electrophilicity index [31] ω, is 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 may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, eH and eL, as μ= (eH - eL)/2 and η= (eL - eH), respectively [32]. Recently, we introduced an empirical (relative) nucleophilicity index N [33], based on the HOMO energies obtained within the Kohn–Sham scheme [34], and defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. This choice allows us to handle conveniently a nucleophilicity scale of positive values. Electrophylic P_k^+ and nucleophilic P_k^- Parr functions [35] were obtained through the analysis of the Mulliken atomic spin density (ASD) of the radical anion and radial cation of the reagents. The local electrophilicity indices and local nucleophilicity indices [36], were evaluated using the following expressions: $\omega_k = \omega . P_k^+$, $N_k = N . P_k^-$ [35].

3. RESULTS AND DISCUSSIONS

3.1. Analysis of the reactivity indices of the reactants.

The static global properties, namely electronic chemical potential μ, chemical hardness η, global electrophilicity index ω and global nucleophilicity index N of tetracyanoethylene (TCE), cyclopentadiene (Cp) and hydrochloric acid (HCl) are the chemical properties which we used to analyse reactivity at the various sites in the reactants (Table1).

Table 1: DFT/B3LYP/6-31G(d) Electronic chemical potential, μ, chemical hardness, η, electrophilicity ω, and nucleophilicity N values, in eV.

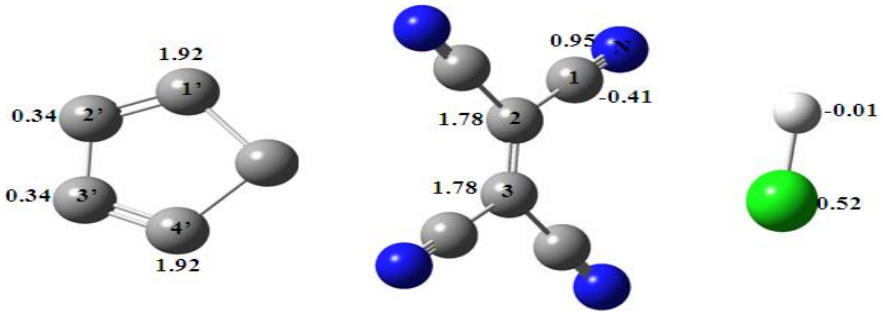
	η	μ	Ω	N
TCE	4.16	-7.03	5.95	0.40
Cp	5.32	-3.01	0.85	3.84
HCl	9.29	-4.37	1.02	0.51

We can deduce from table 1 that:

- The electronic chemical potential of cyclopentadiene (Cp) and hydrochloric acid (HCl) are greater than that of the tetracyanoethylene (TCE), which implies that electron transfer takes place from cyclopentadiene (Cp) and hydrochloric acid (HCl) to the tetracyanoethylene (TCE).
- The nucleophilicity index of the cyclopentadiene (Cp) and hydrochloric acid (HCl) (3.84, 0.51 eV) are greater than that of the tetracyanoethylene (TCE) (0.40 eV), implying that in these reactions cyclopentadiene (Cp) and hydrochloric acid behaves as a nucleophile while the tetracyanoethylene behave as electrophiles.

3.2. Prediction of the regioselectivity of the reaction using local electrophilicity and local nucleophilicity indices.

According to Chattaraj's polar model, the local philicity indices (ω_k and N_k) can be used to reliably predict the most favoured interaction between two polar centers [37, 38]. The most favourable attack is that which is associated with the highest local electrophilicity index ω_k of the electrophile and the highest local nucleophilicity index N_k of the nucleophile. We calculated the values N_k for the cyclopentadiene (Cp) and hydrochloric acid (HCl) and ω_k for tetracyanoethylene in order to predict the most likely electrophile/nucleophile interaction throughout the reaction pathway and so explain the regioselectivity of the reaction.



Scheme 2: Local nucleophilicity N_k (eV) of Cp and HCl, local electrophilicity ω_k (eV) of TCE.

Considering the Parr functions presented in scheme 2, the local electrophilicity indexes (ω_k) for the N, C_1, C_2 and C_3 carbon atoms of TCE are 0.95, -0.41, 1.78 and 1.78 eV, respectively. On the other hand, the local nucleophilicity indexes (N_k) for the C'_1, C'_2, C'_3 and C'_4 carbon atoms of Cp are 1.92, 0.34, 0.34 and 1.92 eV, respectively. The most electrophilic activation found on the C_2 and C_3 carbon atoms of TCE, and the most nucleophilic activation found on the C'_1 and C'_4 carbon atoms of Cp are responsible for the four-center C'_1–C_2 and C'_4–C_3 interaction found at the most favorable TS1, leading to the predominant C2–C3 regioisomeric attack during the corresponding P-DA cycloaddition. In other words, the regioselectivity predicted according to the calculated local reactivity indexes is in excellent agreement with the regioselectivity observed experimentally.

3.3. Kinetic study of the reactions.

Due to the symmetry of both reagents and the Planar structure of TCE, two regioisomeric reactive channels are feasible along the nucleophilic attack of Cp on TCE; depending on the relative position of the C≡N bond of the TCE with respect to the C2=C3 bond of the TCE, the regioisomeric channels were named P1, P2, P3 and P4.

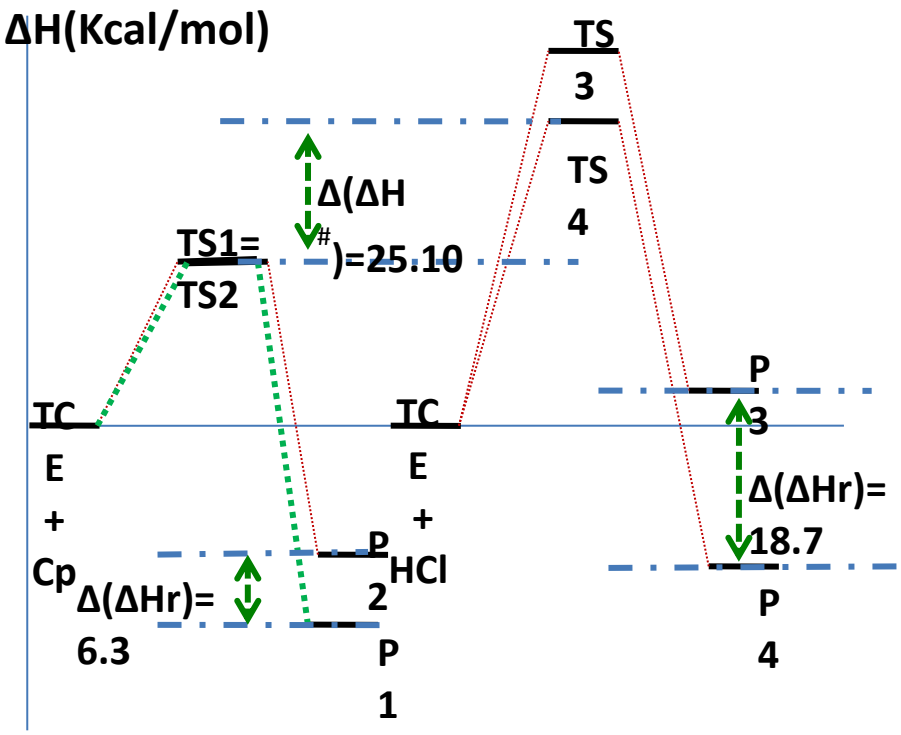
Relative enthalpies (ΔH), entropies (ΔS), and Gibbs free energies (ΔG) for the species involved in the P-DA reaction between TCE and Cp (Addition reacction between TCE and HCl) are displayed in Table 2.

Table 2: enthalpies, ΔH in kcal mol^{-1}, entropies, ΔS in cal mol^{-1} K^{-1} and Gibbs free energies, ΔG in kcal mol^{-1}, for the species involved in the P-DA cycloaddition between TCE and Cp, (TCE and HCl). relative [a]

	B3LYP/6-31G(d) in gas phase			B3LYP/6-31G(p,d) in water		
	ΔH	**ΔS**	**ΔG**	**ΔH**	**ΔS**	**ΔG**
TS1	**18.8**	44.4	25.1	18.1	46.1	26.3
TS2	**18.8**	43.1	25.1	18.8	42.6	30.7
P1	-18.8	51.9	0	-12.5	52.3	-10.0
P2	-12.5	48.5	6.2	-8.7	50.4	-7.5
TS3	**50.2**	34.7	56.4	55.2	34.1	65.2
TS4	**43.9**	32.7	50.2	33.8	30.3	42.6
P3	6.2	41.2	18.8	16.9	36.2	28.2
P4	-12.5	35.1	-2.5	4.3	35.7	14.4

a: relative to TCE + Cp and TCE + HCl

As can be observed, while activation enthalpies are 18.8 (TS1), 18.8 (TS2), 50.2 (TS3) and 43.9 (TS4) kcal mol^{-1}, reaction enthalpies imply that formation of the corresponding formal [4+2] is highly exothermic; -18.8 (P_1), -12.5 (P_2). These values clearly indicate that product P_1 is thermodynamically preferred than P_2. Due to the bimolecular nature of the DA cycloaddition, both activation and reaction entropies are very positive, acting as a favorable factor in the formation of TSs. In the case under investigation, while activation entropies vary in the range of 32.7 to 44.4 kcal mol^{-1} K^{-1}, reaction entropies are located in a narrow range between -50.9 and -35.1 kcal mol^{-1} K^{-1} (see the third column of Table 2). While the values of the relative Gibbs free energies for the species involved in the P-DA reaction between TCE and Cp are given in the last column of Table 2, the corresponding relative enthalpy diagram is depicted in Scheme 3.



Scheme 3: 6-31G(d) relative enthalpie energy diagram for the reaction of TCE witn Cp and TCE

with HCl (see Scheme 1 for details).

Scheme 3 comprises some appealing points as follows:
While product P1 is thermodynamically more stable than P2, the preference of one regioisomeric pathway over another should be controlled by the kinetic aspects of the reaction ($\Delta\Delta Hr$ = 6.3 kcal mol^{-1}).

In other words, as shown in Scheme 3, the difference between the relative enthalpy associated with TS1 and TS4 is $\Delta\Delta H^{\#}$ = 25.1 kcal mol^{-1}. This apparently big value has a noticeable effect on the rate of formation of products P3 and P4. According to transition state theory (TST), the second order rate constant (k_{TST}) at a given temperature (T) can be determined using the following equation [39]:

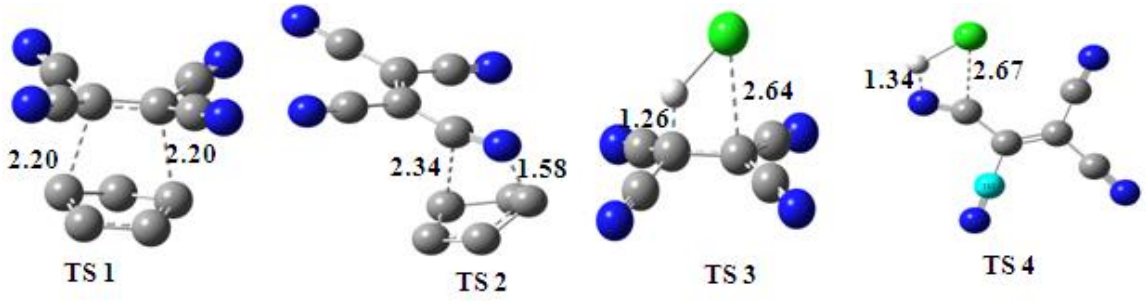
$$\mathbf{K_{TST} = \frac{k_B T}{hC_0} e^{\frac{-\Delta G^{\#}}{RT}} \quad (1)}$$

Where k_B, h, C_0, and R denote Boltzmann's constant, Planck's constant, standard concentration (1 mol L^{-1}), and the universal gas constant, respectively. Using eqn (1), the generation rate ratio of product P1 and product P4 becomes as follows

$$\mathbf{: \frac{K1}{K3} = e^{\frac{\Delta\Delta G^{\#}}{RT}} \approx e^{18.7} \approx 10^8.}$$

That is, P1 is formed 10^8 times faster than P4, in complete agreement with experimental outcomes [23, 24].

Optimized geometries of TSs involved in these reactions, including some selected bond distances and the corresponding unique imaginary frequencies, are given in Scheme 4



Scheme 4: Optimized structures of the TSs of the reaction of the TCE with cyclopentene and TCE with HCl, the values of the bond lengths directly involved in the processes are given in Å.

As shown in Scheme 4, the lengths of the C2–C'1 and C3–C'4 forming bonds are 2.20 A at TS1 and the lengths of the C1–C'1 and N–C'4 forming bonds are 2.34 and 1.58 A at TS2, respectively. On the other hand, the lengths of the C2–Cl and C3–H forming bonds are 2.64 and 1.26 A at TS3 and 2.67 and 1.34 A at TS4, respectively. The extent of the asynchronicity can be measured from the difference between the distances, d1 and d2, of the two new single bonds, which are being formed at the TSs, Δd = d1 - d2. [40, 41] The values of Δd for TS1, TS2, TS3 and TS4 are 0, 1.70, 1.38 and 1.33 A, respectively. Considering the calculated Δd values, it is obvious that the most favorable TS1 displays the highest degree of asynchronicity. On the other hand, in spite of the relatively larger asynchronicity found in TS1, analysis of the corresponding IRC profile obviously rules out the existence of any stable intermediate.

4. CONCLUSION

The energetic, regioselectivity as well as the molecular mechanism of the polar Diels–Alder (P-DA) reaction of TCE with Cp and reaction of TCE and HCl were theoretically studied using DFT methods at the B3LYP/6-31G(d) level. The calculated relative enthalpy indicate that the transition state TS1, leading to the formal [4+2] product P1 observed experimentally, is the most favorable TS among the two feasible TSs located on the potential energy surface (PES) of the investigated P-DA reaction along the regioisomeric pathways of C'1–C2 and C'1–C1. Analysis of the nucleophilic P_k^- Parr functions in Cp and the electrophilic P_k^+ Parr functions in TCE offers an explanation of the C2–C3 regioselectivity found in this P-DA reaction. While the C'1 and C'4 carbon atoms of Cp are the most nucleophilic centers of the diene, the C2 and C3 carbon atoms of TCE are the most electrophilic center of the dienophile, is experimentally formed as the major product of this reaction. In addition the hydrochloric don't react with TCE, because the activation energy of this reaction is very high.

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The authors declare no conflict of interest

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