



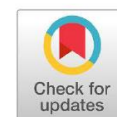
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Original Research article

Conformational Analysis of 2-halo-1,3,2-dioxaphosphinanes: A Density Functional Theory (DFT) Investigation



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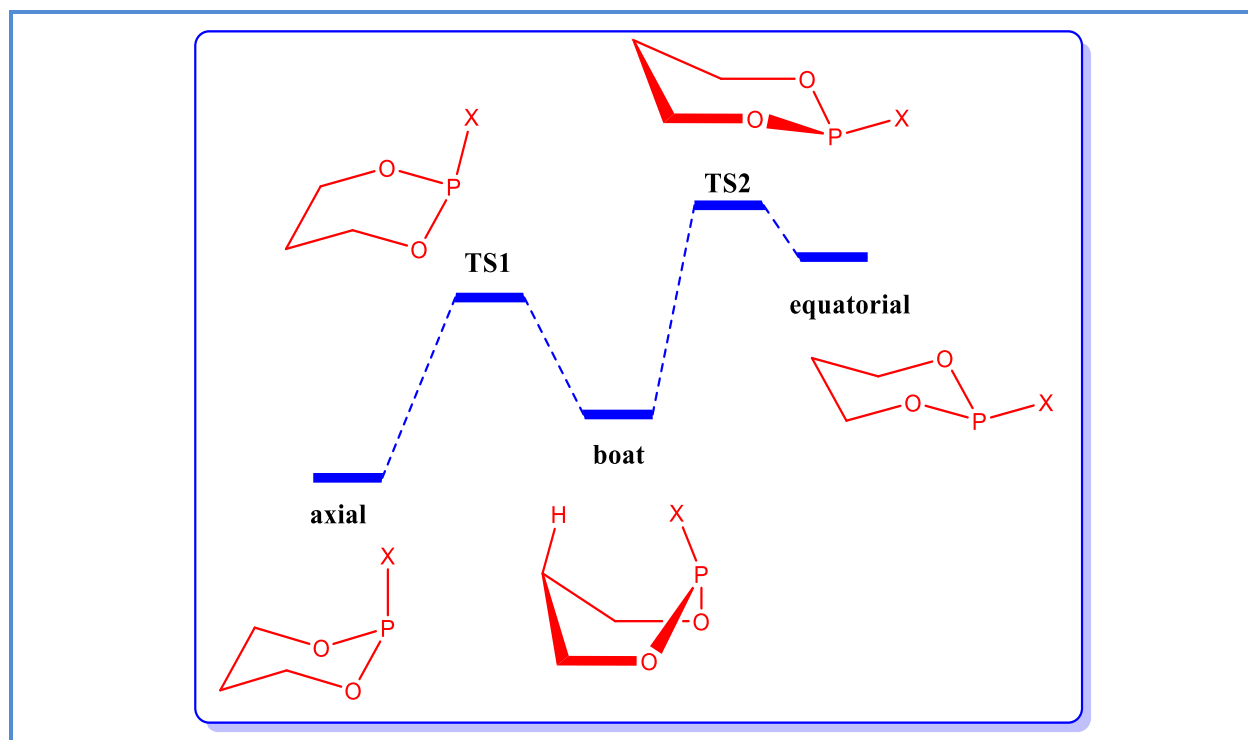
Natural bond orbital analysis

ABSTRACT

This research aimed at evaluating the stability of the 2-halo-1,3,2-dioxaphosphinanes conformers at the LC-BLYP/aug-cc-pVTZ level of theory. The estimation of the total energy and the dipole moments of the axial and equatorial conformations were first done for the aforementioned molecules. Intermediate states of the transformations of the axial to equatorial conformer were determined. In the basis of the calculations, the axial conformer was found to be more stable than the equatorial conformer in these molecules. Transition states of these transformations were studied, as well. IN addition, the energetic and thermodynamics parameters of these transformations were investigated. Change of the P=O bond distances were illustrated with *endo* and *exo*-anomeric effects. The comparison of the P-O bond distances indicated the shorter bonds in the axial conformer compared to the equatorial conformer. These changes attributed to a dominant LP (2)O \rightarrow σ^* (P-X) negative hyperconjugation interaction between a pair of non-bonded electrons on oxygen and the adjacent P-X bond in axial conformer. The partitioning of the total electronic energy E_{tot} into Lewis E_{L} and non-Lewis E_{NL} parts was performed using the concept of the natural bond orbital (NBO) analysis. Then, the natural coulomb electrostatic (NCE) potential energies, total energies into Lewis components, and total steric exchange energies were estimated. Calculations revealed that axial conformer was more stable than the equatorial conformer in the studied molecules. In addition, the barrier energy values of the transformations of axial \rightarrow boat \rightarrow equatorial conformers enhanced with decreasing the electronegativity of halogen.

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Graphical Abstract



Introduction

The 1,3,2-dioxaphosphorinane derivatives are an interesting group of organophosphorus heterocycles. Various researches focused on evaluating their biological activities, particularly in reference to the design of enzyme inhibitors [1-8]. 1,3,2-dioxaphosphorinanes have attracted a great deal of attention from medicinal and pesticide scientists due to their inclusive stereochemistry and biological activities [9]. In this regard, 1,3,2-dioxaphosphorinanes and 1,3,2-oxazaphosphorinanes adopt chair conformations [10, 11]. Though, numerous instances of related molecules with the boat and twist-boat conformation have been reported. Stereoelectronic effects were recognized in 1,3,2-dioxaphosphorinanes [12-15] bearing an alkoxy group on phosphorus. The axial disposition of both the *tert*-butyl and methoxy groups studied by X-ray diffraction analysis in 4-*tert*-butyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane, and this conformation was illustrated by anomeric. Also, the kinetics and thermodynamics of the anionic and cationic polymerization of 2-methoxy-2-oxo-1,3,2-dioxaphosphorinane have been reported [16, 17].

The anomeric effect indicated the significant influence in organic chemistry by affecting the conformation of cyclic molecules [18]. The anomeric effect is occurred when two

electronegative substituents are attached to a sp^3 -hybridized carbon atom. Many theoretical investigations have assessed the anomeric effect [19-28].

In this research, conformational preference in the 2-halo-1,3,2-dioxaphosphanes conformers was investigated at the LC-BLYP/aug-cc-pVTZ level. NBO analysis was employed to illustrate the responsible interactions in the conformational preference.

Experimental

Computational methods

All the computations were carried out using the Gaussian 09 software package [29]. The geometry was optimized using aug-cc-pVTZ basis set [30] and the hybrid functional of the LC-BLYP method. This method is a combination of the Becke exchange functional (B) and the LYP correlation functional. The correlation functional of Lee, Yang, and Parr includes both local and non-local terms [31, 32]. The prefix LC- may be added to any pure functional to apply the long correction of the Hirao and coworkers [33].

Frequency analysis was used to confirm the stationary points as minima. The NBO 6.0 population analysis [34] compiled in the Gaussian 09 package, was performed at the LC-BLYP/aug-cc-pVTZ level of theory. Visualization of the NBOs was plotted with Multiwfn 3.5 software package [35].

Results and discussion

Energetic aspects

The structures of the axial and equatorial conformers in chair form the boat form and transition states of the conversion between chair and boat forms of 2-halo-1,3,2-dioxaphosphanes are presented in Figure 1. Absolute energy and relative energy values of these structures are summarized in Table 1. These values reveal that, the axial conformer of the chair form has the most stable structure. The transformations of axial→boat→equatorial conformers enhanced with decreasing the electronegativity of the halogen.

One imaginary frequency is observed for each of the transition states. These values are -134.38 (X=F), -242.17 (X=Cl) and -233.19 (X=Br) cm^{-1} for **TS1**, and -92.88 (X=F), -99.79 (X=Cl) and -90.65 (X=Br) cm^{-1} for **TS2**. The vibrational mode of these frequencies is shown in Figure 2.

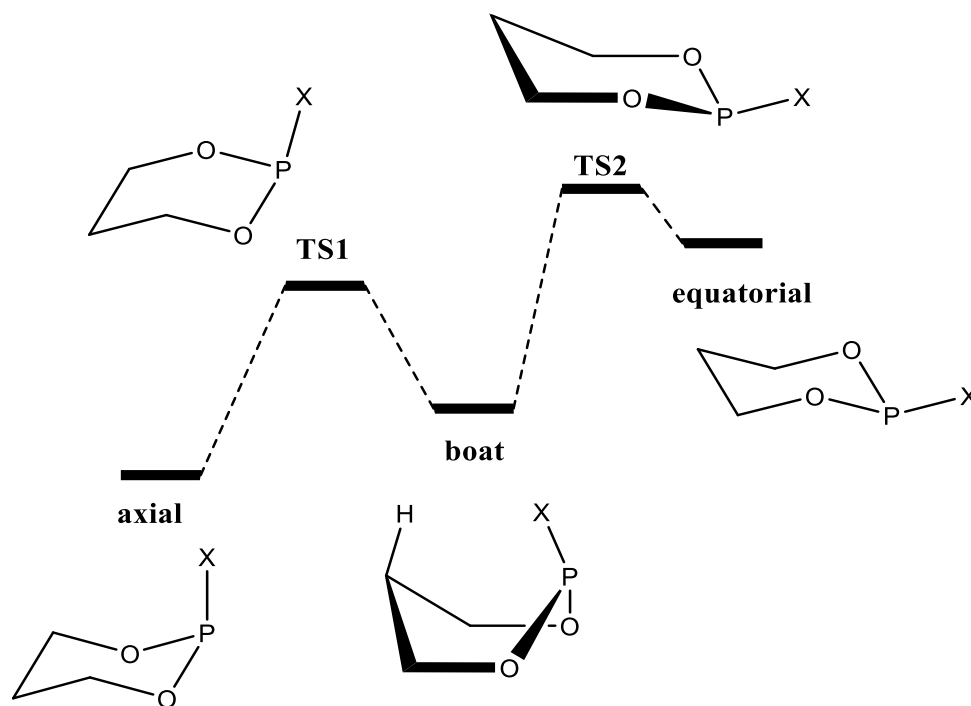


Figure 1. The structures of the axial and equatorial conformers in chair form, boat form and transition states of the conversion between chair and boat forms of 2-halo-1,3,2-dioxaphosphinanes (X= F, Cl , Br)

Table 1. Energy (a.u), relative energy (ΔE , kcal/mol), free energy (G, a.u), enthalpy (H, a.u), relative free energy (ΔG , kcal/mol), relative enthalpy (ΔH , kcal/mol), dipole moment (μ , Debye) and P-O bond distances (r(P-O), Å) of the axial, boat, equatorial conformers of 2-halo-1,3,2-dioxaphosphinanes (X=F, Cl, Br) and their transition states at the LC-BLYP/aug-cc-pvtz theory level

	E	ΔE	G	ΔG	H	ΔH	μ	R (P-O)
X=F								
Axial	-708.8006	0.00	-708.7304	0.00	-708.6926	0.00	3.41	1.606
TS1	-708.7891	7.21	-708.7195	6.85	-708.6820	6.66	3.68	1.616
Boat	-708.7957	3.08	-708.7254	3.14	-708.6887	2.46	3.67	1.604
TS2	-708.7869	8.58	-708.7178	7.94	-708.6803	7.75	4.25	1.616
Equatorial	-708.7874	8.30	-708.7183	7.60	-708.6797	8.08	4.14	1.620
X=Cl								
Axial	-1069.0126	0.00	-1068.9443	0.00	-1068.9053	0.00	3.75	1.604
TS1	-1068.9965	10.07	-1068.9293	9.39	-1068.8897	9.79	3.51	1.594
Boat	-1069.0051	4.72	-1068.9369	4.60	-1068.8988	4.08	4.17	1.600
TS2	-1068.9956	10.62	-1068.9289	9.67	-1068.8899	9.69	4.65	1.618
Equatorial	-1068.9970	9.79	-1068.9299	9.02	-1068.8903	9.45	4.21	1.625
X=Br								
Axial	-3182.8621	0.00	-3182.7953	0.00	-3182.7550	0.00	3.94	1.602
TS1	-3182.8460	10.07	-3182.7801	9.55	-3182.7394	9.81	3.68	1.593
Boat	-3182.8542	4.92	-3182.7876	4.83	-3182.7482	4.30	4.43	1.598
TS2	-3182.8445	11.03	-3182.7792	10.12	-3182.7390	10.09	4.86	1.617
Equatorial	-3182.8456	10.37	-3182.7802	9.51	-3182.7391	9.99	4.33	1.626

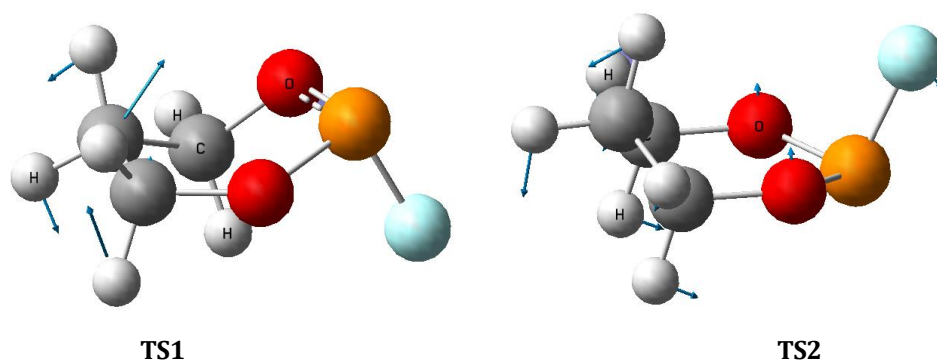


Figure 2. The vibrational modes of imaginary frequencies of transition states

Dipole moment

Generally, it has been accepted that there is a preference for the conformation with the smallest resultant dipole moment [36]. In the gas phase or in the nonpolar media, the conformations with the larger dipole moment may have a greater electrostatic energy. Therefore, we may expect that the conformation with the larger dipole moment may have a greater overall energy.

The calculated dipole moments for the axial and equatorial conformers in chair form and boat form of 2-halo-1,3,2-dioxaphosphinanes compounds are given in Tables 1. These results depicted that, the dipole moments for the axial conformer of the studied compounds are smaller compared with those in boat form and equatorial conformer.

Thermodynamic parameters

The thermodynamic parameters of the conversion between the studied conformers are listed in Table 1. As observed, the activation free energy and activation enthalpy values enhanced with decreasing the electronegativity of halogen. Also, the difference between the free energy and activation enthalpy values of the axial and equatorial conformers (ΔG and ΔH , respectively) increased with raising the electronegativity of halogen. The positive values of ΔG and ΔH revealed that, the conversion between these conformers are non-spontaneous and endothermic.

P-O bond distances

P-O bond distances of the studied molecules are listed in Table 1. The comparison of the P-O bond distances showed that the shorter bonds belonged to the axial conformer.

These variations in P-O bond distances are explained in terms of *endo*-anomeric and *exo*-anomeric effects [12-15]. The *endo*-anomeric effect is a dominant LP (2)O \rightarrow σ^* (P-X) negative hyperconjugation interaction between a pair of non-bonded electrons on oxygen and the adjacent

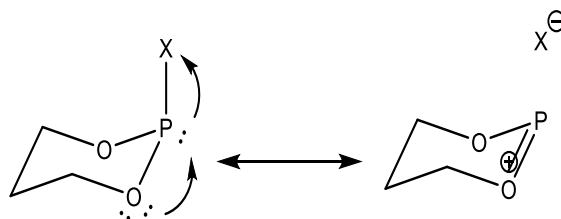
P-X bond in axial conformer (Figure 3). This interaction is the donation of electron density from a filled p -orbital of oxygen to a neighboring σ^* -orbital of the P-X bond. Other *endo*-anomeric effect is a dominant LP (1)P $\rightarrow \sigma^*$ (C-O) negative hyperconjugation interaction between a pair of non-bonded electrons on phosphorous and the adjacent C-O bond in axial conformer (Figure 3). This interaction is the donation of electron density from a filled p -orbital of oxygen to a neighboring σ^* -orbital of the P-X bond.

The *exo*-anomeric effects are due to LP (2)X $\rightarrow \sigma^*$ (P-O), LP (3)X $\rightarrow \sigma^*$ (P-O) and σ (P-X) $\rightarrow \sigma^*$ (C-O) interactions. LP (2)X $\rightarrow \sigma^*$ (P-O) and LP (3)X $\rightarrow \sigma^*$ (P-O) interactions are occurred between a pair of non-bonded electrons on halogen and the adjacent P-O bond (Figure 2). Σ (P-X) $\rightarrow \sigma^*$ (C-O) interaction is the donation of electron density from a σ (P-X) to a neighboring σ^* -orbital of the C-O bond.

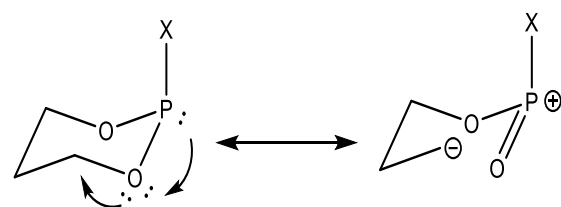
The second order perturbation theory of Fock matrix in NBO basis of the responsible interactions in the axial and equatorial conformers of the studied molecules are listed in Table 2. There is a stronger *endo*-anomeric effect in axial conformer compared with the equatorial conformer. In contrast, *exo*-anomeric effects are stronger in equatorial conformer compare to the axial conformer.

(i) *endo*-anomeric effect

LP (2)O $\rightarrow \sigma^*$ (P-X)



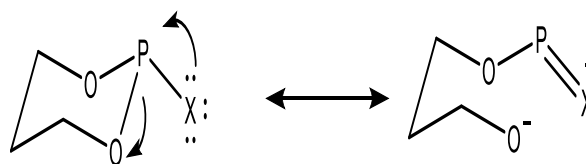
LP (1)P $\rightarrow \sigma^*$ (C-O)



(ii) *exo*-anomeric effect

LP (2)X $\rightarrow \sigma^*$ (P-O)

LP (3)X $\rightarrow \sigma^*$ (P-O)



(a)

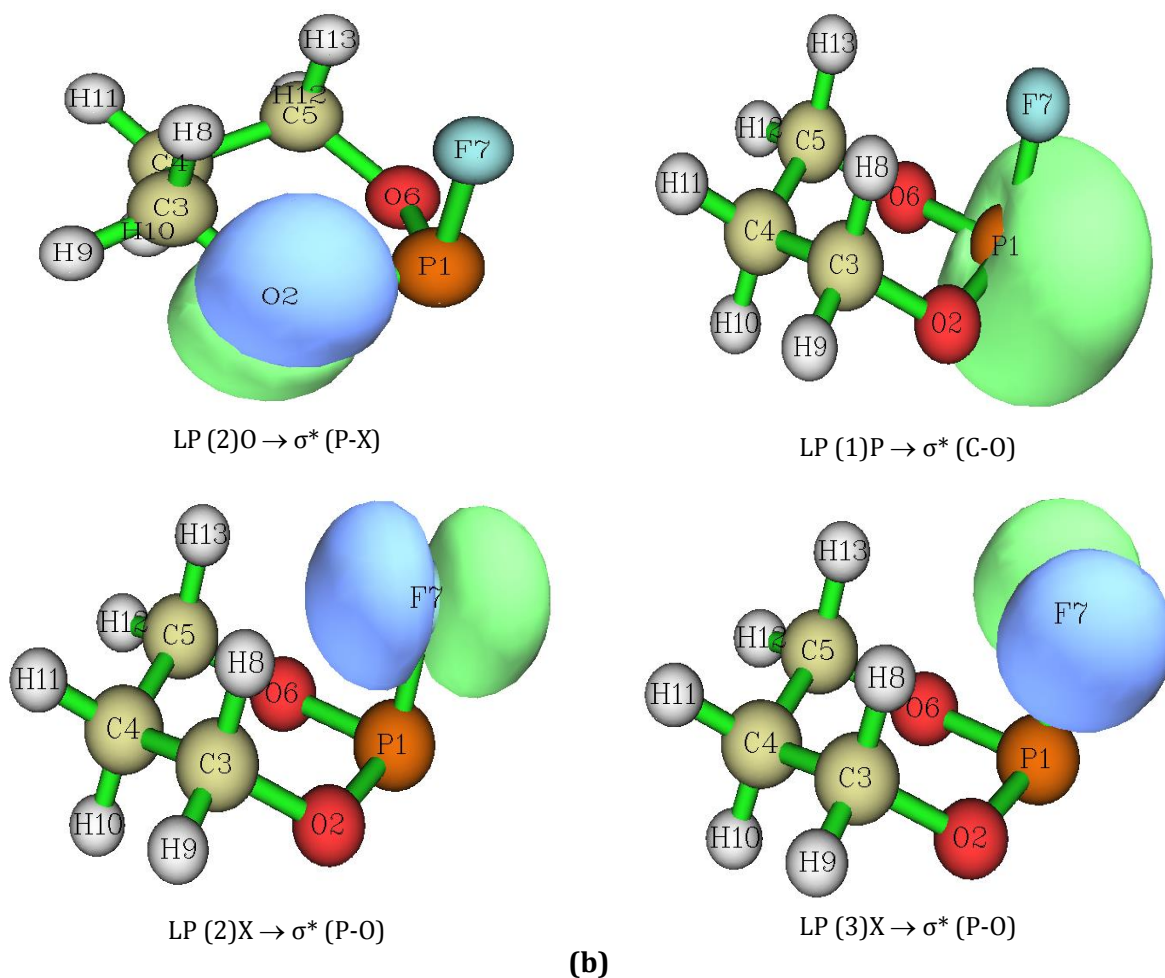


Figure 3. (a) The canonical resonance structures representing the mentioned negative hyperconjugation interactions and (b) visualizations of the corresponding NBOs in the 2-halo-1,3,2-dioxaphosphinanes

Table 2. The second order perturbation theory analyses of Fock matrix ($E^{(2)}$, kcal/mol) in NBO basis of the responsible interactions in the axial and equatorial conformers of the 2-halo-1,3,2-dioxaphosphinanes (X=F, Cl, Br) and their transition states at the LC-BLYP/aug-cc-pvtz theory level

X	F		Cl		Br	
	Axial	Equatorial	Axial	Equatorial	Axial	Equatorial
<i>endo</i> -anomeric						
$LP(2)O \rightarrow \sigma^*(P-X)$	15.25	2.76	17.01	1.12	2.78	1.32
$LP(1)P \rightarrow \sigma^*(C-O)$	5.49	1.88	5.39	1.64	5.37	1.70
Σ	41.48	9.28	44.8	5.52	16.3	6.04
<i>exo</i> -anomeric						
$LP(2)X \rightarrow \sigma^*(P-O)$	4.79	5.25	3.29	4.21	2.71	3.55
$LP(3)X \rightarrow \sigma^*(P-O)$	6.81	7.72	4.74	6.12	3.90	5.08
$\Sigma(P-X) \rightarrow \sigma^*(C-O)$	-	-	-	1.01	-	1.17
Σ	23.2	25.94	16.06	22.68	13.22	19.6

Natural bond orbital (NBO) analysis

In the current study, natural bond orbital (NBO) analysis was performed to partition the total electronic energy E (tot) into Lewis E (L) (orbital population=2.0) and non-Lewis E (NL) components (Table 3). The localized Lewis E (L) component provided a good approximation of all the steric and classical electrostatic effects since corresponding to over 99.5% of the full electron density, while all the conjugation types could be described by the Non-Lewis E (NL) component [37]. Table 3 shows that the greater preference of the equatorial conformer when only considering the conjugation effects.

Natural coulomb electrostatic potential energy (NCE)

An explicit depiction of the long-range electrostatic interactions can be provided on the conception of effective atomic point charges Q_A that interact similar to the traditional law of Coulomb electrostatics:

$$E_{Coulomb} = \sum_{A,B} \frac{Q_A Q_B}{R_{AB}}$$

Where R_{AB} is the interatomic distance between the nuclei A, B. If this equation is calculated according to the natural atomic charges, the formula describes what may be called the “Natural Coulomb Electrostatics” (ENCE) potential energy for the investigated molecules [37]. The E (NCE) of the studied conformers are listed in Table 3. The results show more stability of axial conformer than equatorial conformer based on E (NCE) values.

Table 3. Results of the NBO analysis and energy decomposition of total electronic energy E (total) into Lewis E (L), non-Lewis E (NL), total steric E (steric) and electrostatic E (NCE) energies (in kcal/mol) of the axial and equatorial conformers of 2-halo-1,3,2-dioxaphosphinanes (X= F, Cl, Br) at LC-BLYP/aug-cc-pvtz level of theory

	E (NCE)	ΔE (NCE)	E (ST)	ΔE (ST)	E (NL)	ΔE (NL)
X=F						
Axial	-673.06	0.00	188.97	0.00	306.715	12.136
Equatorial	-650.658	22.40	189.90	0.93	294.579	0.00
X=Cl						
Axial	-540.022	0.00	189.93	0.00	295.345	17.172
Equatorial	-496.887	43.14	192.54	2.61	278.173	0.00
X=Br						
Axial	-517.821	0.00	189.90	2.5	291.828	18.052
Equatorial	-472.176	45.65	187.40	0.00	273.776	0.00

Total steric exchange energy values

Calculation of the total steric energy (E_{ST}) was done through the NBO analysis. Table 3 displays the more pronounced steric interactions occurring in the equatorial conformer compared to the axial conformer in the presence of X=F, Cl. In contrast, E (ST) value in the equatorial conformations of X=Br compound was lower compared with those in their axial conformation.

Conclusion

The obtained stability results of 2-halo-1,3,2-dioxaphosphinanes (Halogen=F, Cl, Br) conformers at the LC-BLYP/aug-cc-pVTZ theory level were as follows.

1. The axial conformer was more stable than the *equatorial* conformer in the studied molecules.
2. The barrier energy values of the transformations of axial→boat→equatorial conformers enhanced with decreasing the electronegativity of halogen.
3. Dipole moments for the *axial* conformer are smaller than those in the boat form and equatorial conformer.
4. The comparison of the P-O bond distances indicated the shorter bonds in *axial* conformer compared to *equatorial* conformer. This was attributed to the dominant LP (2)O → σ^* (P-X) negative hyperconjugation interaction between the pair of non-bonded electrons on oxygen and the adjacent P-X bond in the axial conformer.
5. In the basis of the NBO results, it was observed the greater preference of the equatorial conformer when only considering the conjugation effects.

Conflict of Interest

We have no conflicts of interest to disclose.

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