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A Theoretical Study on Applying Conformational Analysis of 2-Halo-2-Oxo-1,3,2-Dioxaphosphorinanes

Fatemeh Azarakhshi[1*], Nazanin Farhadyar[1], Mehrnoosh Khaleghian[2]
[1]Department of Chemistry, Varamin-Pishva Branch, Islamic Azad University, Varamin, Iran
[2]Department of Chemistry, Islamshahr Branch, Islamic Azad University, Islamshahr, Iran
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Abstract

The quantum-chemical calculations on the conformational properties of 2-flouro-2-oxo-1,3,2-dioxaphosphorinane (1), 2-choloro-2-oxo-1,3,2-dioxaphosphorinane (**2**) and 2-bromo-2-oxo-1,3,2-dioxaphosphorinane (**3**) have been investigated by means of ab initio molecular orbital (HF/6-311+G**) and hybrid density functional theory (B3LYP/6-311+G**) based methods and Natural Bond Orbital (NBO) interpretation in solid state was performed. Geometrical analysis supports clearly the participation of hyperconjugative endo-anomeric (LPO→σ*P-X) effect in the stabilization of axial series of compounds and the participation of exo-anomeric (LPX→σ*P-O) effect in the stabilization of the equatorial phosphinanes in chair conformations. The stereoelectronic effects associated with bonding-anticoding delocalization electron are more significant for the explanation of the conformational behavior of compounds **1-3** than the dipole-dipole interaction effects.

Keywords: *Ab initio, Dioxaphosphorinanes, Natural Bond Orbital, Density Functional Theory, Generalized Anomeric Effects, Stereoelectronic effects.*

Introduction

Conformations of phosphorinanes and 1,3,2-diheterophosphorinanes have been widely studied [1]. 1,3,2-dioxaphosphorinanes and 1,3,2 oxazaphosphorinanes have received most interest since examples of these system are found in physiologically active molecules. Interestingly, there are considerable interests due to their stereochemical features and biological applications and some of their derivatives are clinical antitumor agents [2, 3]. Three types of conformations as chair, boat

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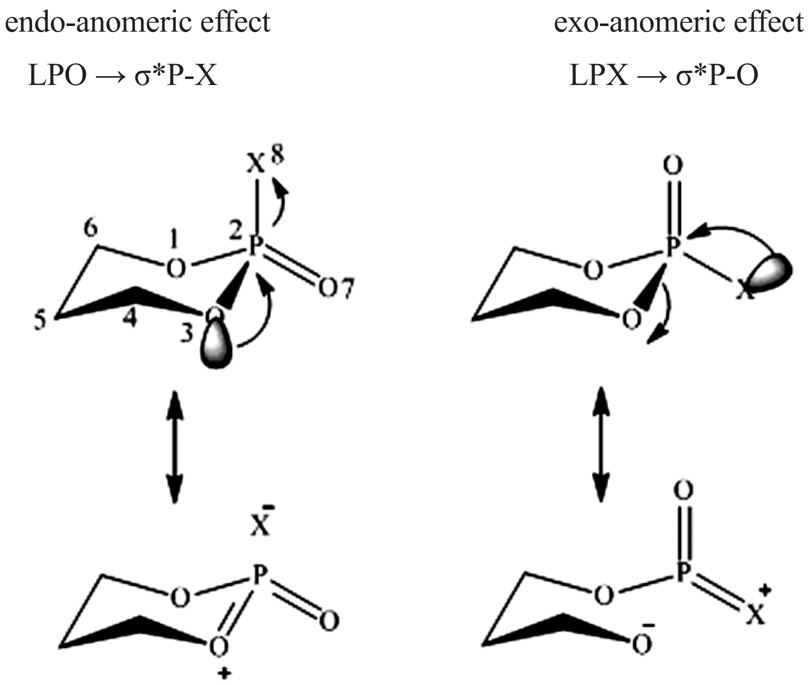
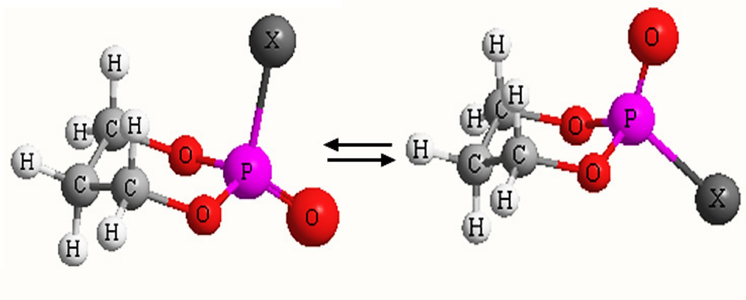
***Corresponding author:** *Fatemeh Azarakhshi, Department of Chemistry, Varamin-Pishva Branch, Islamic Azad University, Varamin, Iran. E-mail: Fa_azarakhshi@iauvaramin.ac.ir, Tel/fax: +982136724767.*

and twist-boat are showed for the saturated phosphorinane rings. The phosphorinane rings are somewhat flattened at the phosphorus atom because of the relatively long PO bonds. Considering the chair conformation, two situations can be distinguished, in which rapid chair-chair interconversions between the axial and equatorial conformations of the 2-substituted 1,3,2-dioxaphosphorinane rings take place and the ones highly biased towards one conformer [4]. The 1,3-diaxial repulsions between the substituent and syn-axial protons and carbons play a dominant role on the conformational preference of a monosubstituted 1,3,2-dioxaphosphorinane, while for 2-substituted 1,3,2-dioxaphosphorinane, such interactions still are important, but the donor-acceptor electronic delocalizations and dipole-dipole interactions are considerable for conformational analysis of heterocycles [5, 6]. Information about the conformation in 2-oxo-1,3,2-dioxaphosphorinanes has been obtained by a number of different techniques. Such as X-ray crystallography, dipole moment studies, IR spectroscopy, NMR chemical shifts and coupling constants [7]. It has been noted that, the available data justified a chair conformation with the substituent on phosphorus at the axial position [8]. In contrast to the role of the steric effects in the prediction of the conformational behavior of substituents, in monosubstituted cyclohexanes [9], the stereoelectronic effects are more important to explain the conformational preference of 1,3,2-dioxaphosphinanes [10]. The electronic features of the substituents (X) at the ring as electron donating groups or electron withdrawing groups play a great role in the interpretation of the conformational equilibrium of monosubstituted heterocyclic compounds. In the case of the 2-substituted 1,3,2-dioxaphosphorinane, the conformational equilibrium is shifted to the right when X is an electron donating group (X), or to the left when X is an electron withdrawing group (X) [11]. The stabilizing stereoelectronic effects (*endo*-, *exo*-anomeric effects) have been used to describe the axial or equatorial conformational preference (Scheme 1) [12, 13]. The conformational preference of 2-substituted 1,3,2-dioxaphosphorinane importantly has been ascribed to the stereoelectronic effects.



Scheme 1. The stabilizing stereoelectronic effect has been used to describe the axial and the equatorial preference.

The stabilizing interaction (*endo*-anomeric effect nπO→σ*P-X) is related to interaction between the lone pair of heteroatom and one of the antibonding orbitals of phosphorus [14]. On the other hand, with the (*exo*-anomeric effect LPX→σ*P-O), the equatorial preference of a substituent (X) at the four-coordinated phosphorus atom of a heterocyclic ring has been attributed to the repulsive 1,3-syn axial interaction between the axial hydrogen atoms at the 4 and 6 positions of the ring and the substituent (X). Theoretical studies on phosphorus heterocyclic compounds have provided evidence the participation of antibonding orbitals even in molecules with low acceptor orbitals such as PO and PS groups [15, 16]. These results reveal that the features of the substituent may alter the orientation of the substituent groups to occupy the equatorial or axial position; an equatorial orientation tendency perceived in hindered thiophosphoramidates [17]. In this work, the stereoelectronic interaction effects, dipole-dipole interactions and also the conformational behaviors of two series of anomeric 2-halo 1,3,2-dioxaphosphorinane (Scheme 2) in solid stat have been studied computationally using both ab initio MO and DFT methods and NBO analysis. Kohn–Sham DFT calculations [18] were carried out to indicate the participation of n–σ* anomeric stabilization the geometry of the optimized structures.



Scheme 2. Numbering used for compounds 1-3 as 1: X=F, 2: X=Cl, 3: X=Br.

Computational Details

Ab initio calculations were carried out using Hartree-Fock method (HF/6-311+G**) and density functional theory (B3LYP/6-311+G**) with the GAUSSIAN 09 package of programs [19]. NBO analysis was performed for the axial and equatorial conformations of compounds **1-3** by the NBO 5.G program [20]. The bonding and antibonding orbital occupancies and energies and HOMO-LUMO energy gaps in the axial and equatorial conformations of compounds **1-3**, the resonance energy, the generalized anomeric effect (*GAE*) associated with electron delocalizations [$GAE = \Sigma (GAE_{eq}) - \Sigma (GAE_{ax})$] and bond orders were calculated using NBO analysis [21, 22].

Results and discussion

The values of relative energies ΔE_0 and thermodynamic ΔG, ΔS and ΔH parameters at 25ºC and 1 atm pressure for the most stable axial and equatorial conformations of compounds **1-3**, was calculated at the B3LYP/6-311+G** and HF/6-311+G** levels of theory (Table 1). All of the methods used showed that in these compounds the values of calculated Gibbs free energies in axial conformations are lower than the equatorial conformations. The B3LYP/6-311+G** results gave the Gibbs free energy difference between the axial and equatorial conformations ($\Delta G_{eq\text{-}ax}$) of compounds 1-3 as 2.21, 2.96 and 3.13 (kcal.mol^{-1}) while the HF/6-311+G** level of theory results gave 1.91, 2.14 and 2.29 (kcal.mol^{-1}). The calculated ($\Delta G_{eq\text{-}ax}$) values for compounds 1-3 at the B3LYP/6-311+G** level of theory are close to those obtained at the HF/6-311+G** level (Figure 1). Based on these results, there is a strong axial preference for compounds 2-flouro (**1**), 2-choloro (**2**), and 2-bromo (**3**) -2-oxo-1,3,2-dioxaphosphorinanes. This fact is in agreement with the reported experimental based data [9].

Table 1. The calculated thermodynamic parameters *ΔH* & *ΔG* / (kcal.mol^{-1}), *ΔS* / (cal.mol^{-1}K^{-1}) and relative energies E_0 / (kcal.mol^{-1}) for the axial and equatorial conformations of compounds **1-3**.

Method	HF/6-311+G**//HF/6-311+G**			B3LYP/6-311+G**//B3LYP/6-311+G**			
Geometry	H^a	S^a	G^a	H^a	S^a	G^a	E_0^a
1-Eq	2.42	0.68	2.21	2.06	0.49	1.91	2.36
1-Ax	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2-Eq	3.22	0.88	2.96	2.41	0.91	2.14	3.16
2-Ax	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3-Eq	3.50	1.23	3.13	2.60	1.04	2.29	3.40
3-Ax	0.00	0.00	0.00	0.00	0.00	0.00	0.00

[a] Relative to the ground state.

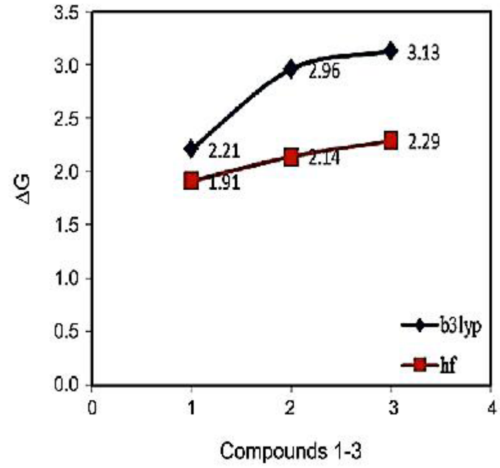


Figure 1. The calculated Gibbs free energy difference between the axial and equatorial conformations ($\Delta G_{eq\text{-}ax}$) of compounds **1-3**.

The NBO analysis of donor–acceptor (bonding–antibonding) interactions at the B3LYP/6–311+G** level of theory showed that the most stabilization energies (resonances energies) (*E2*) are associated with LPaxY→σ*P-X electron delocalizations for the axial conformations of compounds **1–3**. The values of resonances energies associated with LPaxY→σ*P-X electron delocalizations for the axial conformations of compounds **1-3** are 11.64, 10 and 24.38 (kcal.mol^{-1}), respectively. This stereoelectronic orbital interaction for the axial forms is more effective to indicate the axial conformations preference of compounds 1-3. The *GAE* (Generalized Anomeric Effects) values that calculated based on Eq. (1), for compounds 1–3 are -8.76, -9.44 and -16.72 (kcal.mol^{-1}) respectively. The results showed the *GAE* value increases from compound **1** to compound **3** (Table 2).

$$GAE = \Sigma\,(endo\text{-}GAE_{eq} + exo\text{-}GAE_{eq}) - \Sigma\,(endo\text{-}GAE_{ax} + exo\text{-}GAE_{ax}) \qquad Eq.\ (1)$$

The increase of the resonance energy values could be justified by increase of the Gibbs free energy difference between the axial and equatorial conformations ($\Delta G_{eq\text{-}ax}$) and the relative energies ($\Delta E_{0eq\text{-}ax}$) from compound 1 to compound 2 and from compound 2 to compound 3. The obtained results reveal that the calculated *GAE* values are more significant for interpretation of the conformational preferences of these compounds than the electrostatic effects. It is notable that, the increase of dipole-dipole interactions can increase the stability of the equatorial conformations and also decrease the stability of the corresponding axial conformations.

It is considerable that, the calculated dipole moments differences $\Delta(\mu_{ax}\text{-}\mu_{eq})$ values μ / Debye between the axial and equatorial conformations of compounds 1-3 as calculated by the B3LYP/6-311+G** method increase from compound **1** to compound 2 and from compound **2** to compound 3 and this trend is accordance with the variation of (*GAEs*) in compounds **1-3** (Figures 2, 3). In conclude the stereoelectronic effects corresponding to Generalized Anomeric Effects (*GAEs*) are benefit to determine the variation of the axial conformation stability in compounds **1-3** compared to their according equatorial conformations.

Table 2. Calculated stabilization energies *E*2 / (kcal.mol^{-1}), *GAE* / kcal.mol^{-1}, orbital occupancies / e, orbital energies / a.u., dipole moments μ / Debye, Wiberg Bond Index (*WBI*) and Comparison of HOMO, LUMO energy gaps / a.u. calculated for axial and equatorial conformations of compounds **1-3**.

Compound	**1**		**2**		**3**	
Conformational State	Eq	Ax	Eq	Ax	Eq	Ax
Resonance energy (E_2)						
$(LP_{eq(1)Y} \rightarrow \sigma^*_{P\text{-}X})^*2$	5.02		2.86		2.8	1.24
$(LP_{ax(2)Y} \rightarrow \sigma^*_{P\text{-}X})^*2$	1.88	11.64	1	10	3.3	24.38
$(LP_{2X} \rightarrow \sigma^*_{P\text{-}Y})^*2$	2.88	5.9	2.18	4.12	3.34	6.96
$(LP_{3X} \rightarrow \sigma^*_{P\text{-}Y})^*2$	5.68	3.46	4.42	2.42	8.1	3.06
$(\sigma_{C3\text{-}Y4} \rightarrow \sigma^*_{P5\text{-}O7})^*2$	1.18	3.9		4.06		2.4
$(\sigma_{C3\text{-}Y4} \rightarrow \sigma^*_{P5\text{-}X8})^*2$	-		-		2.3	
$(\sigma_{P5\text{-}X8} \rightarrow \sigma^*_{C3\text{-}Y4})^*2$	1.14		2.26		2.86	
$(\sigma_{P5\text{-}O7} \rightarrow \sigma^*_{C3\text{-}Y4})^*2$		1.64		1.56		1.38
Σ	17.78	26.54	12.72	22.16	22.7	39.42
GAE	**-8.76**		**-9.44**		**-16.72**	
μ / Debye	5.966	6.914	5.552	6.840	5.437	6.790
$\Delta(\mu_{ax} - \mu_{eq})$	0.95		1.29		1.35	
$\Delta(E_{acceptor} - E_{donor})$						
$\Delta(E\ \sigma^*_{P\text{-}X} - E\ LP_{ax(2)Y})$	0.79		0.77		0.62	
$\Delta(E\ \sigma^*_{P\text{-}Y} - E\ LP_{2X})$	0.92		0.90		0.79	
Occupancy						
$\sigma^*_{P5\text{-}X}$	0.101		0.134		0.096	
$LP_{ax(2)Y}$	1.913		1.902		1.910	
$\sigma^*_{P\text{-}Y}$	0.098		0.098		0.115	

LP_{2X}	1.955	1.957	1.954
WBI			
P-Y	0.739	0.750	0.728
P-X8	0.671	0.622	0.901
ΔWBI(P-Y_{eq} - P-Y_{ax})	0.01	0.01	0.01
ΔWBI(P-$X8_{ax}$ - P-$X8_{eq}$)	0.05	0.09	0.09
HOMO-LUMO energy gaps			
E_{HOMO}	-0.309	-0.325	-0.305
E_{LUMO}	-0.016	-0.017	-0.022
($E_{LUMO} - E_{HOMO}$)	0.29	0.31	0.28

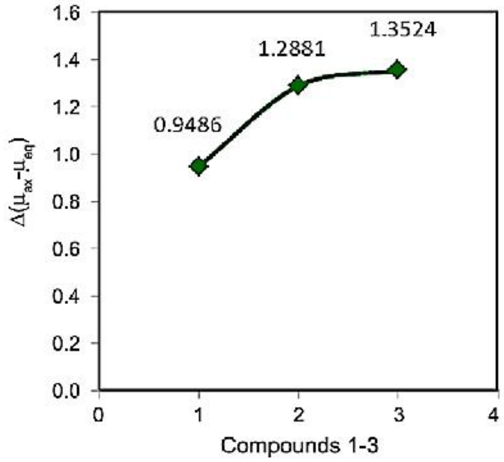


Figure 2. The calculated dipole moments differences $\Delta(\mu_{ax}-\mu_{eq})$ values between the axial and equatorial conformations of compounds **1-3**.

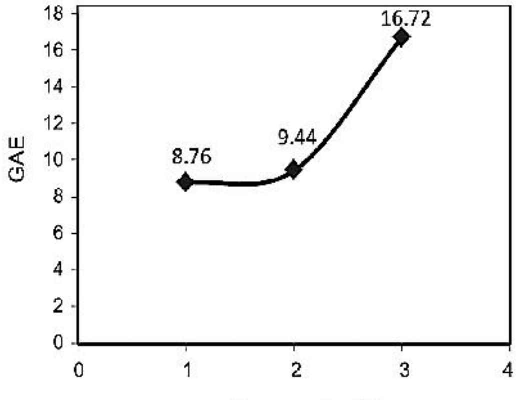
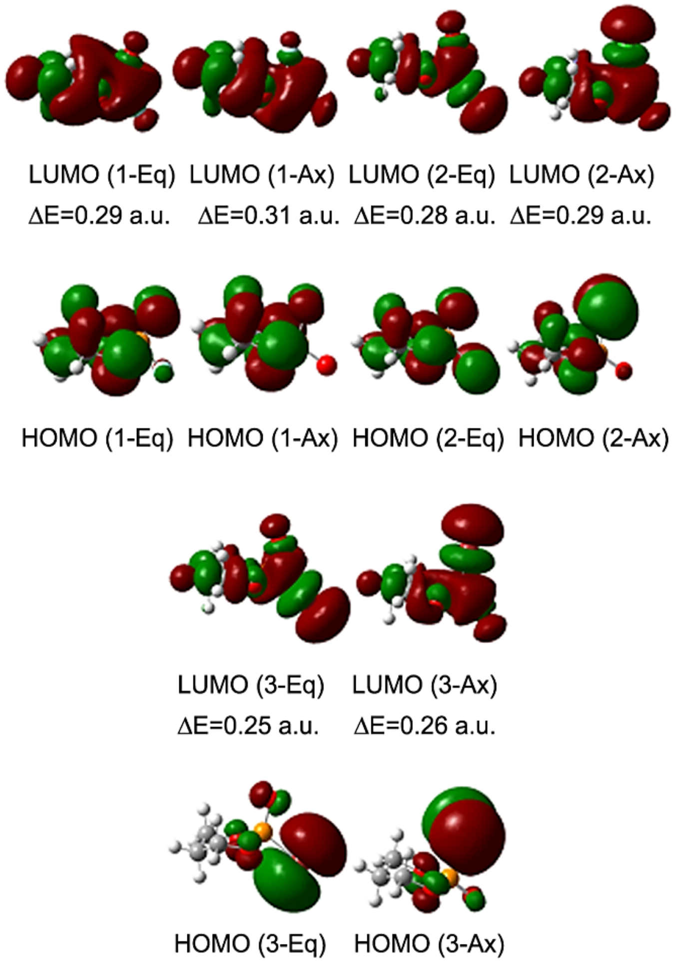


Figure 3. The calculated generalized anomeric effect *(GAE)* values between the axial and equatorial conformations of compounds **1-3**.

The NBO analysis calculated the energy differences between bonding (*E*LPaxY) and antibonding (*Eσ**P-X) orbitals for the conformations of compounds **1–3**. The obtained results show that, the strong bonding–antibonding orbital interactions LPaxY→σ*P-X could be anticipated in the axial conformation of compound 1 to 3 with decreasing the energy differences between donor and acceptor orbitals *Δ(Eσ**P-X − *E*LPaxY)]. Considerably the NBO analysis indicates that, the LPaxY orbital occupancies decrease but the σ*P-X orbital occupancies increase from the axial conformations of compounds **1** to **3** (see Table 2). Based on the results, the calculated bond orders (Wiberg Bond Index) for P2-Y bonds in axial conformations of compound **1–3** are more than in its similar equatorial conformation. In contrary, the calculated bond orders (*WBIs*) values for the P2-X8 bonds of the axial conformations are less than in their corresponding equatorial conformations of compound **1-3.** It is considerable that, the variation of the bond orders of P-Y and P-X bonds in the axial and equatorial conformations of compounds **1–3** attributed to LPaxY→σ*P-X electron delocalizations for the axial conformations of compounds 1–3. The molecular orbital analysis of the LUMO and HOMO of axial and equatorial conformations of compounds 1-3 indicates that, the LUMO of π nature (heterocyclic ring), is situated over the whole bonds. In contrast, the HOMO is placed over endocyclic heteroatoms and over the high part of ring. Accordingly the most charge density transfer from endocyclic heteroatoms to exocyclic bonds. The HOMO−LUMO energy gaps of 2-halo-2-oxo-1,3,2-dioxaphosphorinanes are calculated at the B3LYP/6-311+G** level of theory by NBO analysis (Figure 4).


LUMO (1-Eq) LUMO (1-Ax) LUMO (2-Eq) LUMO (2-Ax)
ΔE=0.29 a.u. ΔE=0.31 a.u. ΔE=0.28 a.u. ΔE=0.29 a.u.

HOMO (1-Eq) HOMO (1-Ax) HOMO (2-Eq) HOMO (2-Ax)

LUMO (3-Eq) LUMO (3-Ax)
ΔE=0.25 a.u. ΔE=0.26 a.u.

HOMO (3-Eq) HOMO (3-Ax)

Figure 4. Composition of the HOMO and LUMO frontier molecular orbitals of axial and equatorial conformations of compounds 1-3.

The calculated structural parameters for the equatorial and axial conformations of compounds **1–3** at the B3LYP/6–311+G** level of theory are exhibited in Table 3. In the axial conformations of compounds **1–3**, the P2-Y3 bond lengths are decreased compared to those in their equatorial conformations; to the contrary, the P2-X8 bond lengths are increased with those in their equatorial conformations. It is reasonable that, these findings can be interpreted by the *endo-GAE* associated with $LP_{ax}Y \rightarrow \sigma^*$P2-X8 electron delocalization. In the axial conformations of compounds **1–3** in comparison with the equatorial conformers the P2-Y3-C4 bond angles are increased, but the Y1-P2-Y3-C4 torsional angles are decreased. In conclude, the variation of the structural parameters of the axial and equatorial conformers has been explained by stereoelectronic effects.

Table 3. Calculated structural parameters for the equatorial and axial conformations of compounds **1-3**.

Compound	1		2		3	
State	**Eq**	**Ax**	**Eq**	**Ax**	**Eq**	**Ax**
Bond lengths / Å						
$r_{\mathrm{Y1\text{-}P2}} = r_{\mathrm{P2\text{-}Y3}}$	1.604	1.597	1.613	1.602	1.615	1.604
$r_{\mathrm{P2\text{-}X8}}$	1.572	1.603	2.026	2.075	2.203	2.253
$\Delta(r_{\mathrm{P\text{-}Y(eq\text{-}ax)}})$	0.01		0.01		0.01	
Bond angles / °						
$\theta_{\mathrm{P2\text{-}Y3\text{-}C4}} = \theta_{\mathrm{6\text{-}Y1\text{-}P2}}$	116.9	119.7	116.7	120.5	117.0	120.7
$\theta_{\mathrm{Y1\text{-}P2\text{-}X8}}$	100.6	101.5	101.9	103.3	102.0	103.7
$\Delta(\theta_{\mathrm{P2\text{-}Y3\text{-}C4(ax\text{-}eq)}})$	2.8		3.8		3.7	
Torsion angels / °						
$\phi_{\mathrm{Y1\text{-}P2\text{-}Y3\text{-}C4}} = -\phi_{\mathrm{6\text{-}Y1\text{-}P2\text{-}C2\text{-}Y3}}$	-49.6	-40.4	-50.3	-39.4	-49.6	-39.0
$\phi_{\mathrm{6\text{-}Y1\text{-}P2\text{-}X8}}$	153.4	-65.1	155.8	-68.4	155.2	-69.4
$\Delta(\phi_{\mathrm{Y1\text{-}P2\text{-}C2\text{-}Y3(ax\text{-}eq)}})$	9.2		10.9		10.6	

Conclusion

The hybrid-density functional theory; ab initio molecular orbital calculations and NBO analysis are used to study of stereoelectronic interactions associated with electron delocalization to rationalize the conformational behavior of compounds **1–3**. The stereoelectronic interactions have a determining contribution in conformational preference of compounds **1–3** compared to the electrostatic model. The results of NBO analysis revealed that the *GAE* succeeds in accounting qualitatively for the axial preferences of compounds **1–3**. The variation of the calculated thermal relative energy differences $\Delta(E_{0eq\text{-}ax})$, Gibbs free energy differences (ΔG_{eq-ax}) and dipole moments differences $\Delta(\mu_{ax}\text{-}\mu_{eq})$ values is in accordance with the variation of the calculated GAE from compound 1 to 3. The variation of structural parameters $(r_{P2\text{-}Y3},\ \theta_{P2\text{-}Y3\text{-}4},\ \phi_{Y1\text{-}P2\text{-}Y3\text{-}4})$ could be proposed as a criterion for the evaluation of the GAE values which is the most important factor on the conformational properties of compound 1-3.

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