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A Theoretical Study on the Mechanism of the Baeyer–Villiger Type Oxidation of 7-Phosphanorbornene 7-Oxides

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ABSTRACT: *DFT computations have been performed on selected stationary points of the reaction path (reactants, intermediates, and products) of the Baeyer–Villiger type oxidation of 7-phosphanorbornene 7-oxide derivatives. Our computations justified the relevance of a Criegee-type intermediate forming in the first step, analogously to the Baeyer–Villiger oxidation of ketones. The energy profile indicated a high-energy barrier from the side of the products, supporting the kinetic character of the mechanism. The computations revealed that the mechanism does not include a previously assumed Berry-pseudorotation step in the Criegee-type intermediate. On the basis of the present results, we suggest that the regioselectivity of the Baeyer–Villiger type oxidation of the 7-phosphanorbornene 7-oxide derivatives may be determined by steric interactions between the leaving meta-chlorobenzoate group and substituents on the 7-phosphanorbornene skeleton in the Criegee-type intermediate.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:759–766, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20366

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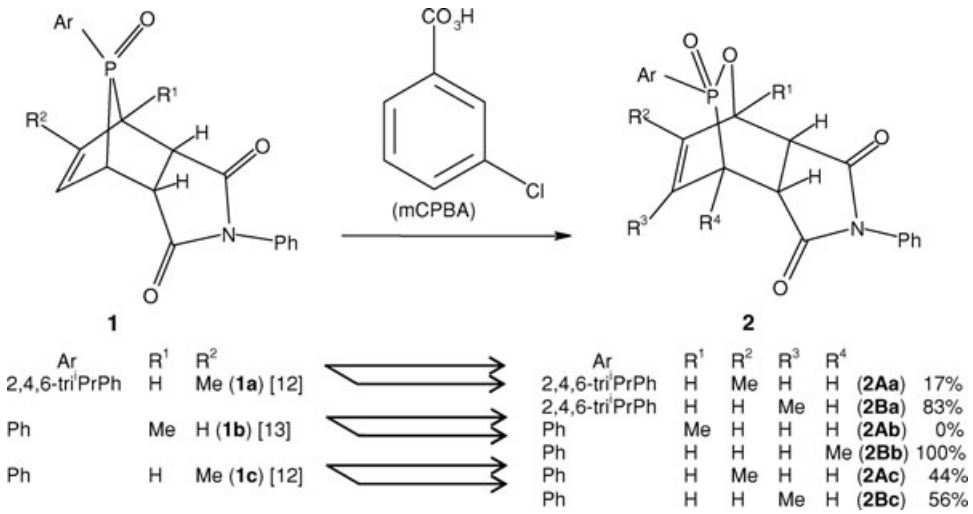
INTRODUCTION

The Baeyer–Villiger reaction is of great importance in organic syntheses, as allows a convenient transformation of acyclic or cyclic ketones into esters or lactones [1]. In the Baeyer–Villiger oxidation, the ketone is treated with a peracid (that is most often commercial *m*-chloro-perbenzoic acid) in the presence of a suitable acid catalyst, although the reaction takes place also (only slower) under noncatalyzed conditions [2,3]. Numerous experimental [2–4] and theoretical studies revealed the mechanism of the O insertion reaction in a satisfactory manner. Recent high-level quantum chemical computations justified the structure of the Criegee intermediate and elucidated the most likely transition states of the two-step reaction [5–7].

The Baeyer–Villiger type oxidation of 7-phosphanorbornene 7-oxide derivatives (Scheme 1) is also of synthetic importance, as the resulting 2,3-oxaphosphabicyclooctane 3-oxide derivatives (Scheme 2) are precursors of low-coordinate fragments, such as metaphosphonic or metaphosphoric species that can be used in phosphonylation or phosphorylation of nucleophiles [8–11]. In the related precedents, Keglevich et al. studied the



SCHEME 1

stereostructure and reactivity of 6- and 5-methyl oxaphosphabicyclooctene oxides with sterically demanding P-aryl substituents (Ar = 2,4,6-triisopropylphenyl, R^2 = Me, R^3 = H, **2Aa** and Ar is the same, R^2 and R^3 is reversed, **2Ba**) obtained by the mCPBA treatment of **1a** [12], and the properties of 1- and 4-methyl (Ar = Ph, R^1 = Me, R^4 = H, **2Ab** and Ar is the same, R^1 and R^4 are reversed, **2Bb**) prepared by the oxidation of **1b** [13] (Scheme 1).

The oxidation of 7-phosphanorbornene oxides with mCPBA was observed to proceed with retention of P-configuration [14]. The postulated mechanism [15] is analogous with that of the Baeyer–Villiger oxidation of ketones [4]. Hence, in the first step, the oxidizing agent attacks the P-atom forming pentacoordinated intermediates of the Criegee-type **3A** or **3B** with a trigonal bipyramid around the phosphorus (Scheme 2). In **3A**, C_1 is equatorial and C_4 is axial, whereas in **3B** it is the other way round. A pseudorotation around the aryl substituent was supposed to place the peroxy group into an equatorial position to result in species **4A** and **4B** that are suitable to undergo the migration of the C—P bond to C—O. Note that until now neither experimental nor theoretical evidence is available for the existence of a Criegee-type molecule in P(V) chemistry.

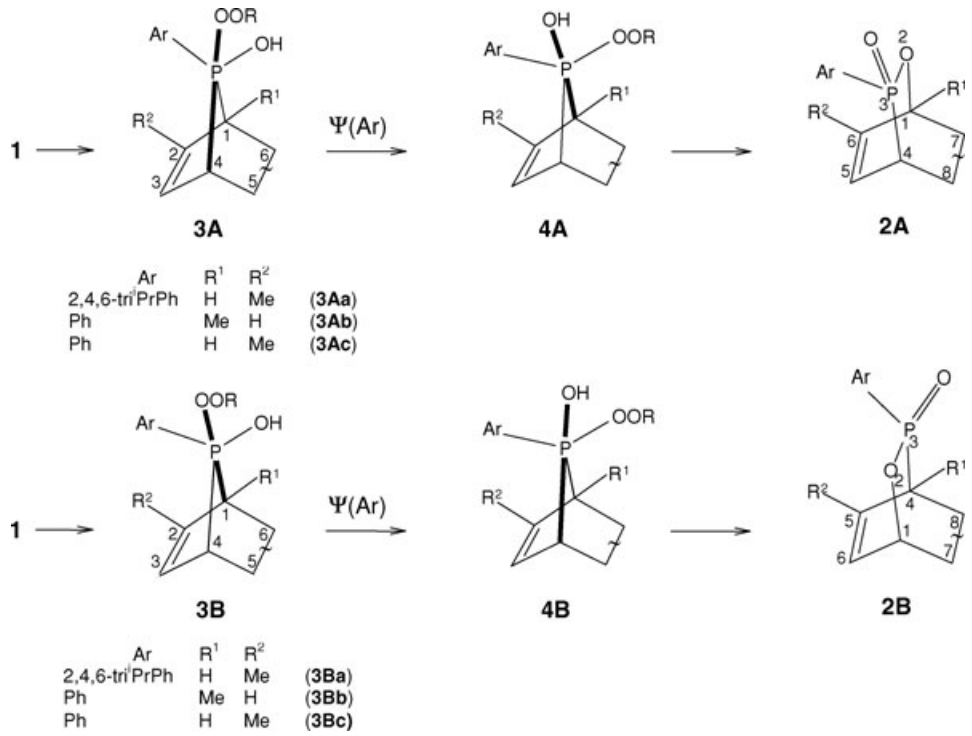
It was a challenge for us to try to evaluate at least a part of the above mechanism by quantum chemical calculations. One of our aims was to justify the relevance of the Criegee-type intermediate in the title reaction, that it corresponds really to a minimum on the potential energy surface, and to elucidate its structural properties in the view of an eventual Berry pseudorotation. In order to avoid any error from simplification, we performed computations exactly on **2b**, that is, without any replacement of large groups with smaller ones. On the other hand, we skipped the study of **2a**, where the ^{i}Pr substituents in Ar (larger size and large number of possible rotational isomers) would require enormous computational costs. To elucidate the effect of the 1(2)-methyl position, we performed computations on phenyl derivatives **2b** and **2c**. The latter compound has already been studied in the literature [12].

RESULTS AND DISCUSSION

Structural Characteristics of **2** *and* **3**

The first important message of our study is that we found the Criegee-type intermediate, proposed previously for the Baeyer–Villiger oxidation of phosphorus heterocycles [15], to be indeed a minimum on the potential energy surface. In this way, we could provide a partial theoretical support for the analogy of the mechanism with that of the Baeyer–Villiger oxidation of ketones. However, to get more insight into the mechanism, a detailed analysis of the structural and energetic properties of the formed molecules (**2,3**) is necessary.

The molecules **2**, and particularly **3**, can form several structural isomers. Beyond the **A/B** regioisometry, they have several possible conformers due to the rotation of the Ph (**2**) and the Ph, mCPB, and OH groups (**3**). In order to find the most stable conformers, we investigated first the energetic consequences of the different relative orientations of the above substituents in **2b** and **3b**. Selected conformers of **2b** and **3b** are shown on Figs. 1 and 2, respectively.



SCHEME 2

The rotation of the Ph groups plays a negligible role in **2b**. We found that the P—Ph group can have only one orientation, as different initial structures converged always to the orientation shown in Fig. 1.

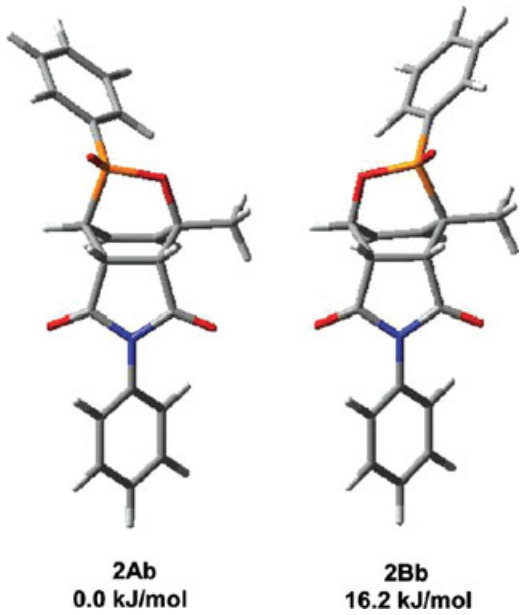


FIGURE 1 Computed structures and relative stabilities (ΔG°, including solvent effects from single-point computations) of the regioisomers of **2b**.

On the other hand, the N—Ph group can have two different orientations, both having a ca. 45° torsion angle with the plane of the succinic-imide moiety. Because of the local symmetry of the succinic-imide ring and its distance from the P atom, the rotation of the N—Ph group has a marginal (0.05 kJ/mol) effect on the relative stability of **2b**.

The conformational analysis of **3b** revealed an analogous role of the rotation of the two Ph groups like found in **2b**. Thus, because of its sterically crowded environment, the P—Ph group is not able to establish another stable rotamer beyond the one presented in Fig. 2, whereas the rotation of the N—Ph group causes again only marginal changes (around 0.05 kJ/mol) in the relative stability.

Owing to their intramolecular interactions, the rotation of the OH and mCPB groups can influence considerably the relative stabilities. The most favored orientation of the OH hydrogen is obviously the one presented in Fig. 2, turned toward the C=O and peroxy moieties. In this way, it can form a bifurcated hydrogen bond with two appropriate oxygens with length between 1.7 and 2.3 Å (cf. Fig. 2). Note that this hydrogen-bonding interaction is probably established already during the approach of mCPBA to **1** reducing the activation energy. If the OH hydrogen points away from the oxygens, no hydrogen-bonding stabilization is

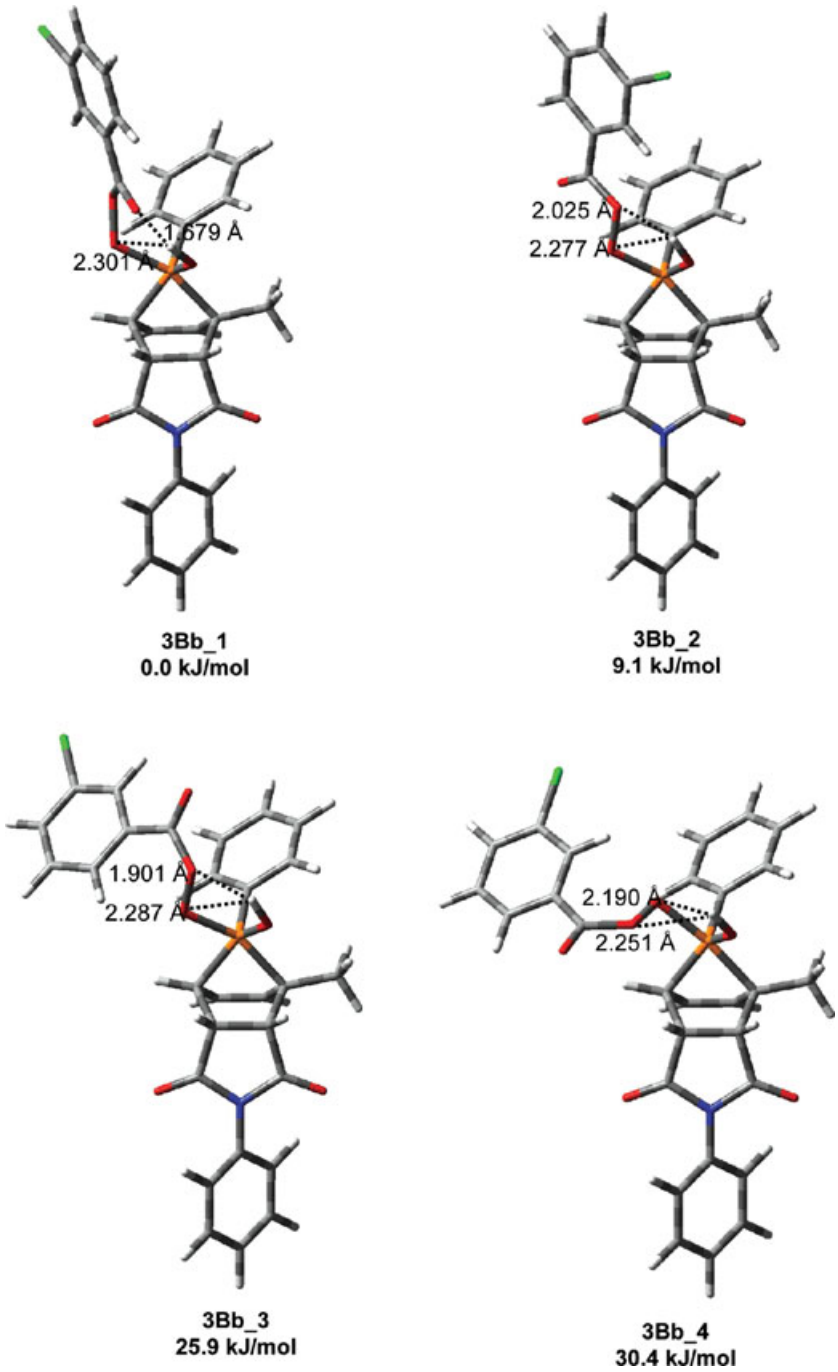


FIGURE 2 Computed structures, relative stabilities (ΔG°, including solvent effects from single-point computations) and O—H $\cdots$ O_{peroxy} hydrogen bond lengths of selected conformers of **3Bb**.

possible whereas disadvantageous steric interactions appear with the P—Ph and Me or with the 7-H/8-H hydrogens leading to considerably less stable structures.

The rotation of the mCPB group can result in numerous conformers as it has four torsional angle variables represented by the P—O, O—O, O—C, and C—$C_{1'}$ axes. It is beyond the goal of the present study to analyze all the possible rotamers of the mCPB group. Therefore, we focused only on the most reasonable ones with the aim to determine the lowest energy conformer. The optimized structures of selected **3Bb** conformers are given in Fig. 2. Note that an analogous energy ordering (with deviations of a few kJ/mol) was found for the conformers of **3Ab, 3Ac**, and **3Bc** as well.

The most stable conformer from our survey proved to be **3Bb_1** with O=P–O–O, P–O–O–C, O–O–C=O, and O–C–$C_{1'}$–$C_{2'}$ torsion angles of 70°, −92°, 16°, and 9° respectively. In this structure, the P–Ph and the ring of mCPB face each other, the planes of the two aromatic rings having an angle around 65°. The structures in which the ring of mCPB turns away from the P–Ph group are considerably (at least by 25 kJ/mol) less stable. On the other hand, the rotation around the C–$C_{1'}$ axis has a marginal (around 1 kJ/mol) effect on the relative stability.

We assessed the hydrogen-bonding interactions of the **3b** conformers looking for a correlation with the relative stabilities. The bifurcated hydrogen bonds of the O–H hydrogen with the oxygens are of strong to moderate character (between 1.68–2.30 Å). The strongest hydrogen bond appears in the most stable **3b_1** conformers with the C=O group (1.679 Å in **3Bb_1**, cf. Fig. 2) in agreement with an important role of hydrogen bonding for the relative stabilities. However, the correlations are less satisfactory for other conformers, e.g., **3Bb_3** with the 1.901 Å hydrogen bond is less stable by 16.8 kJ/mol than **3Bb_2** with the longer 2.025 Å hydrogen bond (cf. Fig. 2). This indicates that the relative stabilities of the isomers are determined by superimposed weak interactions: hydrogen bonding, steric and (probably) hyperconjugation interactions.

Conclusions on the Mechanism

Our computations facilitated an assessment of the Berry pseudorotation supposed to transform **3** to **4** before the O-insertion (cf. Scheme 2). It was supposed to be a necessary step, as the mCPBA reactant arrived in an axial position in **3**, whereas for O-insertion an equatorial position of the OOR moiety would be more suitable [12]. However, our efforts to find any local minimum on the potential energy surface corresponding to **4** were unsuccessful. A closer inspection of the conformers' geometries of **3** revealed that the arrangement of the ligands around P does not correspond to a regular trigonal bipyramid, but a distorted one. We demonstrate this with the enlarged central moiety of **3Ab_1** in Fig. 3. The P, C_1, $C_{1'}$, and hydroxyl O atoms form a plane with bond angles close to the ideal 120° (max. deviation 6°). Considerable distortion is manifested, however, in the O_2–P–C_4 axial–axial bond angle being 164° instead of the ideal 180°. Another strong indications of the distorted axial orientations are the axial–equatorial bond angles (e.g., C_4–P–C_1, 78.7°; cf. Fig. 3) deviating from the ideal value of 90°. In fact,

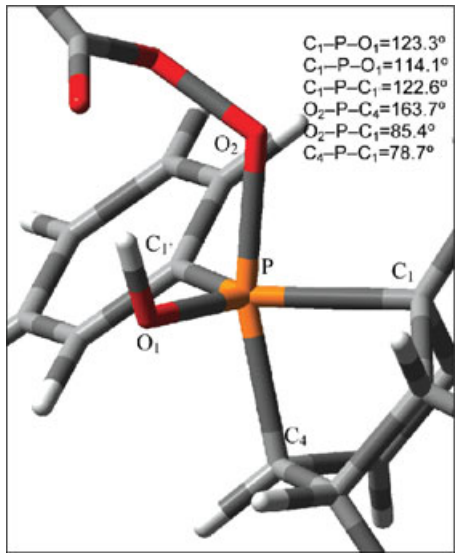


FIGURE 3 Enlarged fragment of the surroundings of P in **3Ab_1**.

this arrangement can also be considered as a distorted square pyramid with the P–Ph group in the apical position, which is the transition state of a regular Berry pseudorotation [16]. It is not surprising, therefore, that we could not find any local minimum on the potential energy surface corresponding to **4**. The initial structure with C_1 and O_1 in the axial position (as assumed for **4Ab**) converged to **3Ab_1**. It seems that the strained (by hydrogen bonding and the phosphanorbornene skeleton) arrangement of the groups connected to P does not facilitate the existence of another isomer corresponding to **4**.

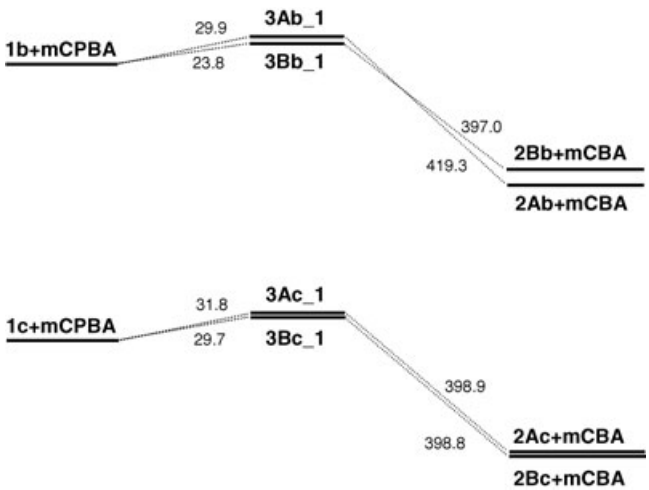


FIGURE 4 Energy profiles (kJ/mol) of the **1b** → **3b** → **2b** and **1c** → **3c** → **2c** reactions evaluated from the computed Gibbs free energies corrected for solvation effects and basis set superposition error.

In order to decide on the thermodynamic/kinetic character of the title reaction, we computed the energy profile including the initial reactants **1** and mCPBA, the intermediate **3** and the products **2** and mCBA. The profiles of the **1b** → **3b** → **2b** and **1c** → **3c** → **2c** reactions depicted in Fig. 4 give useful information on the thermodynamic/kinetic character of the reactions. The ΔG° data include both the effect of the $CHCl_3$ solvent and basis set superposition error (BSSE), the latter estimated by the computed BSSE between fragments after breaking the P—O and O—O bonds in **3Bb_1**.

As can be seen in Fig. 4, the large energy differences between **3** and **2** imply a high-activation barrier from the side of **2**, hence a thermodynamic control (in which the relative stabilities of the regioisomers of **2** determine the yield) is unlikely.

The irrelevance of a thermodynamic control is also supported by our previous experimental work on **2b** [13]. As the computed Gibbs free-energy data

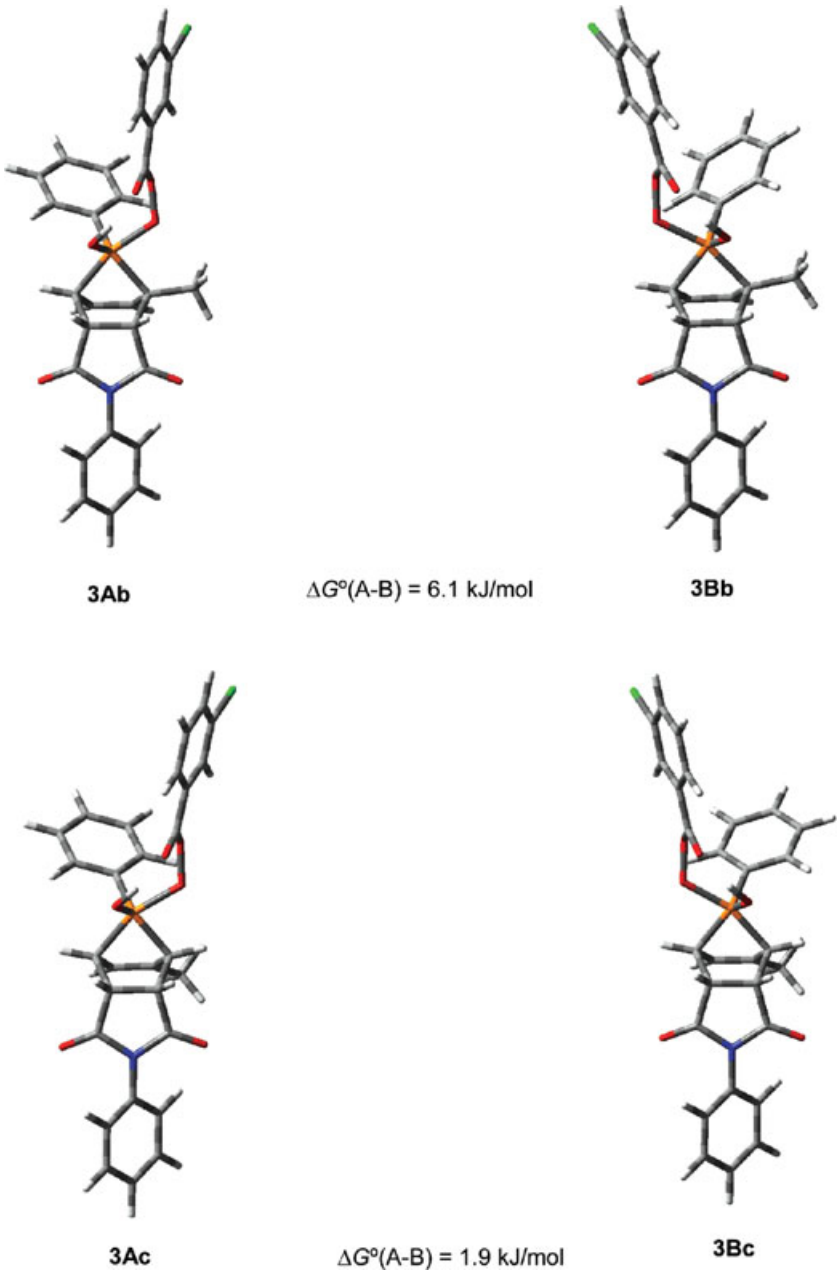


FIGURE 5 Comparison of the most stable conformers of the **A/B** regioisomers of **3b** and **3c**. The relative stabilities (ΔG°) include solvent effects from single-point computations.

depicted in Fig. 1 show, **2Ab** is favored by 16.2 kJ/mol due mainly to the unfavorable steric interactions between the 4-Me and 3-Ph groups in **2Bb**. In the synthesis, however, the **2Bb** regioisomer was obtained with a yield of 100% [13]. Altogether, these evidences support another analogy with the Baeyer–Villiger reaction of ketones, which has also been found to be driven by kinetic control [3,5–7].

There are two possible choices for transition states in which the regioselectivity in the title reaction could be determined. The first one is on the path of the addition of mCPBA to **1**. The relevance of this transition state for the regioselectivity can be disclosed on the basis of the found exclusive formation of the **2Bb** regioisomer [13]. Namely, the relative stabilities of the intermediates **3Ab** and **3Bb** are very close (cf. Fig. 5) which indicates that the steric effects of the 1(4)-Me group are almost negligible in these structures. This should be valid for the transition states as well. Hence, it is very likely that the **3Ab** and **3Bb** intermediates form in a comparable amount in the step **1b** + mCPBA. However, because of the close absolute energies of **1b** + mCPBA and **3b** (cf. Fig. 4) and if the energy barrier of **1b** + mCPBA ↔ **3b** is sufficiently low, **3Ab** and **3Bb** may be present in a dynamic equilibrium. The found slower formation of **2Bb** with respect to the synthesis of **2a** [13] may be attributed to a gradual production of **3Bb** in the proposed equilibrium.

The transition state that determines most likely the regioselectivity can be derived from **3b** by lengthening of the O—H and peroxy O—O bonds, strengthening of the O···H hydrogen-bonding interaction, and by a parallel approach of the migrating O to the P—C bond (Fig. 6). Note that this transition state structure is analogous with that found for the second step in the Baeyer–Villiger oxidation of ketones [6]. We considered an application of the Hammond principle [17], which would work if the transition state geometry requires only small changes from the geometry of **3b**. In this hypothetical case, the relative energies of the **3b** regioisomers would determine which product is formed. However, in the view of the above shown complex way to derive the geometry of the transition state, an applicability of the Hammond principle is unlikely. Moreover, the shown marginal differences in the relative stabilities of **3Bb** and **3Ab** (cf. Fig. 5) do not conform with the exclusive formation of **2Bb** [13].

In the likely transition state for the O-migration (Fig. 6), the C atom in the P—C bond approached by the negatively charged oxygen should have a partial positive charge. This charge can be stabilized by the inductive effect of the nearby 1-Me group in the A regioisomer. On the other hand, the steric effect of this 1-Me group works against the approach of the peroxy oxygen to C_1. The steric repulsion is probably more effective than the inductive stabilization of the positive charge on C_1, making the insertion of O into the P—C_4 bond more favorable.

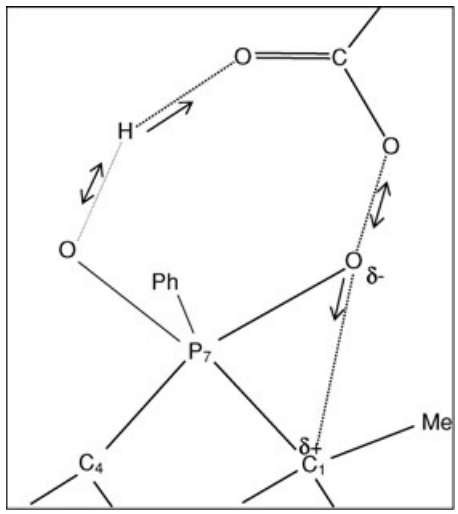


FIGURE 6 Proposed transition state of the O-insertion.

The steric repulsion between the Me substituent and the approaching oxygen is much weaker when the Me group is attached to C_2 (in compounds **3a** and **3c**). In these compounds, the (although weaker) inductive effect of 2-Me may be comparable with the very weak steric repulsion. Indeed, the synthesis of **2a** produced a mixture of the isomers **2Aa** and **2Ba** in a ratio of 3:2 [12]. In a future work, we plan additional experimental studies on **2c** with the aim to get more insight into the role of the steric effects of the P—Ar group, in which **1a** and **1c** differ. The present computations predicted the thermodynamic preference of **2Bc** over **2Ac** by 1.9 kJ/mol.

CONCLUSIONS

Our DFT computations provided insight into the mechanism of Baeyer–Villiger type oxidation of 7-phosphanorbornene 7-oxide derivatives. The energy profile of the reaction path **1** → **3** → **2** supported that the reaction is exotherm with a high-energy barrier from **2** → **3**, justifying the kinetic character of the mechanism. Founding the Criegee-type intermediate (**3**) to be a minimum on the potential energy surface, our computations justified its probable role in the title reaction. The computed structures of **3** revealed that the mechanism does not include a well-defined Berry-pseudorotation step: the strained steric conditions result in distorted square pyramidal arrangement around P, close the transition state

of a regular Berry-pseudorotation. Accordingly, no local minimum corresponding to the product of a Berry-pseudorotation could be found on the potential energy surface. The regioselectivity of the Baeyer–Villiger type oxidation of the rather symmetric **1** is probably determined in step **3** → **2** by steric interactions between the leaving mCPB group and substituents on the 7-phosphanorbornene skeleton. In order to justify the proposed mechanism (by investigating the transition states), we plan extensive theoretical studies on smaller systems.

Computational Details

The molecular geometries were optimized using the B3LYP [18,19] exchange-correlation functional in conjunction with a 6-31G** basis set for all the atoms. The minimum characters of the found stationary points were verified by frequency calculations. The computations have been performed using the Gaussian 03 program [20]. The solvent effects of chloroform were taken into account by reaction field calculations using the IEF–PCM model [21–23]. As our geometry optimizations within the IEF–PCM model failed for the large intermediate molecules **3**, the solvation energies were evaluated by single-point calculations on the geometries obtained for the vacuum. Test calculations on **2b** showed that the effect of geometry optimization within the IEF–PCM model is negligible (0.1 kJ/mol) for the energy differences of the **A/B** regioisomers.

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