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Starting Computational Study of the Chlorination Mechanism Reaction of 2-Naphthol with PIDA and $AlCl_3$ via $PhICl_2$ Formation as a Chlorinating Reagent †

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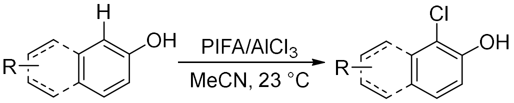
Abstract: Recently we described the first chlorination of mono- and bis-annular phenols by using the non-described PIFA/$AlCl_3$ system. Looking for a mechanistic pathway to elucidate this novel procedure, we decided to explore all the plausible path. In order to determine the best energy profile which, provide us the lower-in-energy mechanism, herein we present an initial computational study for the chlorination reaction of 2-naphthol exploring PIDA [diacetoxyiodo(benzene)] and $AlCl_3$. The developed first mechanism that considers the $PhICl_2$ formation as the plausible chlorinating intermediate was analized by DFT calculations at the (SMD:acetonitrile)ω-B97XD/(6-311G(d,p),LANL08d)//ω-B97XD/6-31G(d) level indicated that the reaction proceed through a cationic pathway.

Keywords: DFT; computational chemistry; hypervalent iodine(III); reaction mechanism

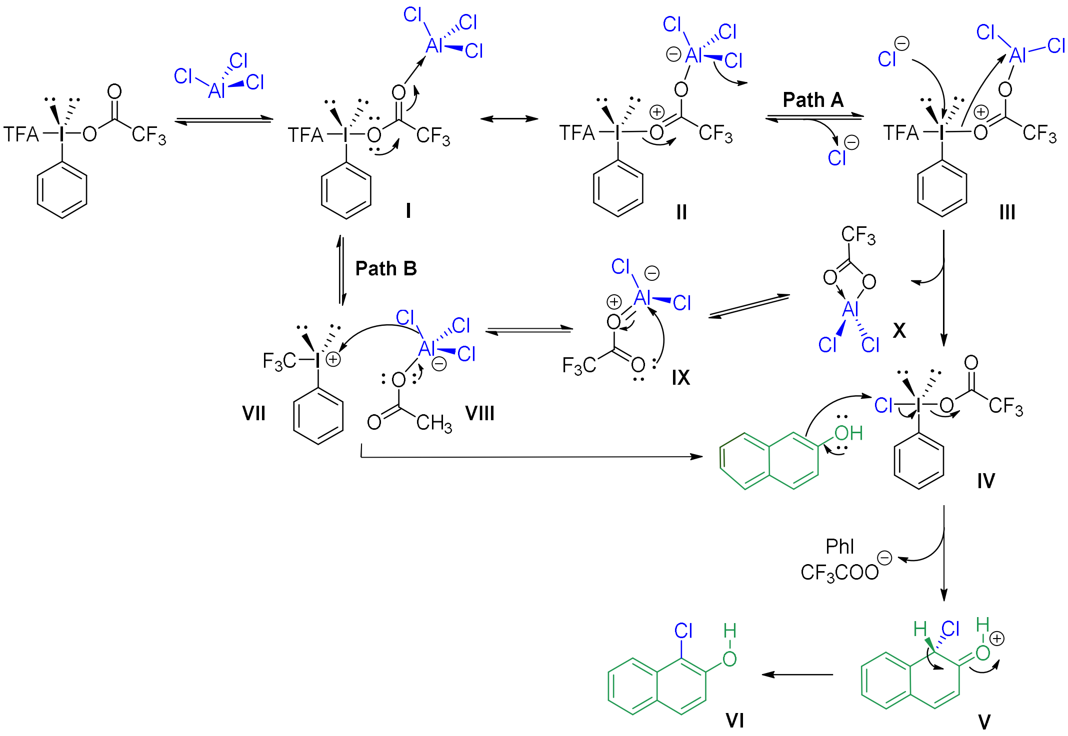
1. Introduction

The chlorination of arenes using hypervalent iodine(III) reagents has been experimentally described due to the mild, non-toxic and soft chlorination reaction conditions [1]. In 2018, our group described a new protocol (Scheme 1) for the chlorination of arenes mono- and bis-annular using the system PIFA [Bis(trifluoroacetoxy)iodobenzene] and $AlCl_3$, which it was not described yet and achieving to synthetize up to 29 chlorinated products [2].



Scheme 1. Reaction general of chlorination of phenols by using the system PIFA/AlCl3.

The mechanism proposed (Scheme 2) for the reaction was divided in two possible routes and start from the same intermediate. The first step is the coordination of $AlCl_3$ to PIFA, generating the intermediate I, which is in resonance with II. Pathway A continues with the formation of III with the release of a chloride ion. The chloride ion attacks the electrophilic iodine center to produce a by-product of aluminium X and the intermediate VI, proposed as the chlorinating reagent formed in situ. Subsequently, the naphthol attacks regioselectively in the *ortho* position to the chlorine in IV to produce V. Finally, the aromatization of V occurs with the loss of the proton in *ortho* position giving the chlorinated naphthol. On the other hand, pathway B continues from II, dissociating the aluminium coordinated to trifluoroacetoxy ion in an equilibrium giving VII and VIII. In this equilibrium aluminium can liberate a chloride ion and generate IX an that chloride attacks to VII to produce the plausible plausible chlorinating species IV. The rest of the mechanism proceeds in the same way it was described in route A.

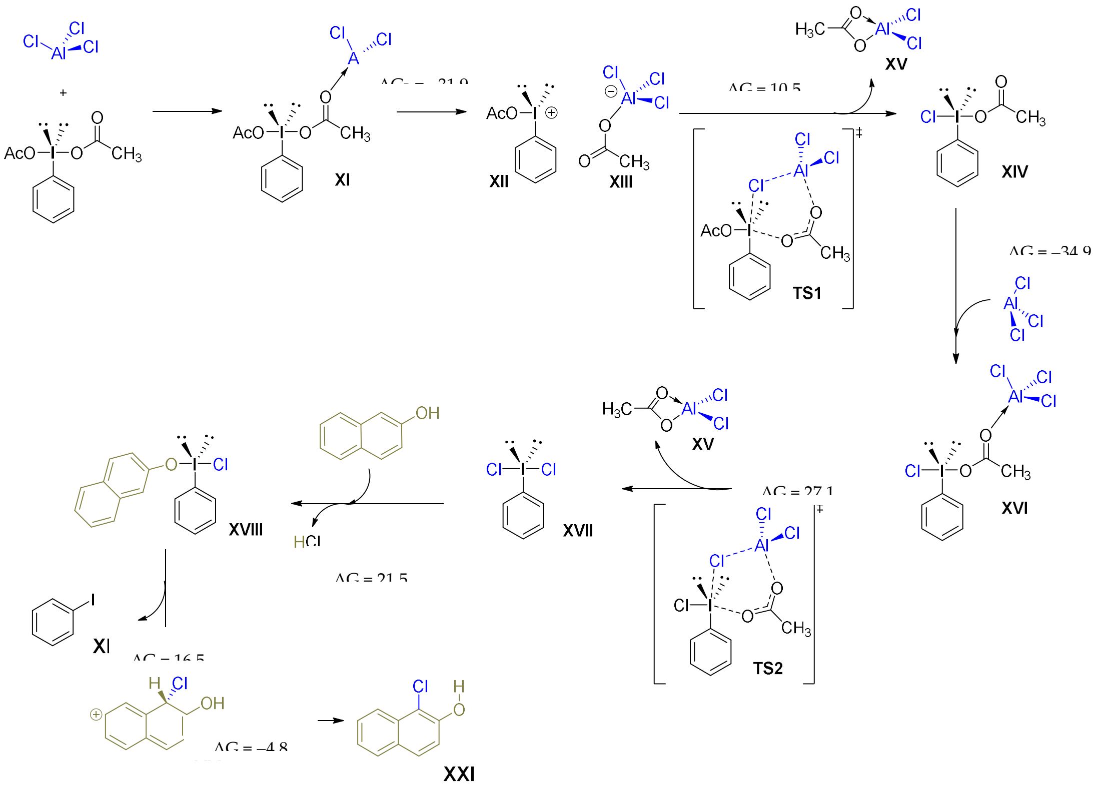


Scheme 2. Pathway A and Pathway B proposed for the chlorination reaction with the system PIFA/AlCl3.

In this sense, to determinate the lower-in-energy mechanism for the chlorination reaction we decided to explore the behavior of PIFA and PIDA. We started the computational study to analyze the best pathway of reaction with PIDA considering to $PhICl_2$ as the plausible chlorinating reagent.

2. Results and Discussion

The mechanism explored (Scheme 3) with PIDA (1 equiv) and $AlCl_3$ (2 equiv), via formation of $PhICl_2$ starts in the same way with the coordination of the first equivalent of $AlCl_3$ to PIDA, generating **XI**. The dissociation of **XI** leads to ions **XII** and **XIII**. With a transfer of the chlorine atom from **XIII** to **XII** carries out to the intermediate **XIV** and the by-product from aluminium **XV**. The second equivalent of $AlCl_3$ creates the coordination to the other acetoxy in **XIV** producing **XVI**. Thus, a second transfer of a chlorine ion the intermediate **XVII** is produced and a second equivalent of **XV** is formed. The explored chlorinating species $PhICl_2$ is formed *in situ*. An attack from the hydroxy group from the naphthol to the electrophilic iodine and the liberation of HCl result in the indermediate **XVIII**. The isomerization of **XVIII** occurs to release iodobenzene **XIX** and **XX**, which after an aromatization process leads to the chlorinated product **XXI**.



Scheme 2. Mechanism calculated of the chlorination reaction with PIDA/AlCl3 at (SMD:acetonitrile)ω-B97XD/(6-311G(d,p),LANL08d)//ω-B97XD/6-31G(d) level theory. **Relative energy values are expressed in kcal·mol^{-1}**.

This mechanism is high-in-energy because the determinant step is the second transfer of the chlorine atom from **XIV** to **XV**I has a ΔG = 27.1 kcal·mol^{-1}. The reaction is carried out to room temperature and we expect a lower-in-energy mechanism for the chlorination of the 2-naphthol. We will explore different routes with a diverse plausible chlorinating species in order to determinate the best mechanism.

3. Experimental Section

Gas-phase geometry optimizations were performed using the Gaussian09 program [3]. This reaction mechanism was developed exploring the potential energy surface of the hybrid, range-separated density-functional ω-B97XD, [4] which considers dispersion interaction through a range separation (22% for short range and 100% Hartree-Fock for long range). The electronic configurations of the molecules belonging to this mechanism were described with a Pople's split-valence basis set of double-ζ quality with one polarization function (for heavy atoms), 6-31G(d), for all the atoms. Geometry optimizations were carried out without symmetry constraints, and the stationary points were characterized by analytical frequency calculations, i.e. energy minima (reactants, intermediates and products) must exhibit only positive harmonic frequencies whereas each energy maximum (transition state) exhibits one and only one negative frequency. From these last calculations, zero-point energy (ZPE) and thermal and entropy corrections were obtained, which were added to the electronic energy to express the calculated values as Gibbs free energies.

Calculations were also performed to include the solvent effect through the PCM model using the SMD parameters according to Truhlar's model [5] with benzene as solvent (ε = 2.2706). In order to improve the numerical results, single-point calculations were carried out on the gas-phase optimized geometries using a mixed basis set of triple-ζ quality with one polarization function, 6-311G(d,p), for all the atoms except Br and I, which were treated with the LANL08d relativistic pseudopotential [6]. These energies were added to the gas-phase calculations reported as the final energy values. As a result the composite level of theory can is the following: (SMD:acetonitrile)ω-B97XD/(6-311G(d,p),LANL08d)//ω-B97XD/6-31G(d).

4. Conclusions

In summary, DFT calculations revealed that the mechanism explored via formation of $PhICl_2$ resulted high-in-energy for a reaction to room temperature. We believe this is not the route of the reaction of chlorination of 2-Naphthol. There are other plausible routes starting with the same steps and might result in a lower-in-energy route. We will continue working in order to determinate the most possible mechanism.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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