DFT Study of Cyclophosphamide/Ifosfamide Chlorination: Effects of Speciation, Conformation and Explicit Solvation

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Quantum-chemical methods are essential for mechanistic elucidation of chlorination reactions of environmentally relevant pharmaceuticals. Our previous studies have shown that a correct mechanistic description of chlorination of formally inert nitrogen-containing functionalities requires three elements: (i) a suitably benchmarked theoretical protocol, (ii) identification of the chemically relevant reactive species, including the appropriate ionization state and/or tautomeric form, and (iii) an explicit and chemically meaningful description of the aqueous medium. In the case of amides (e.g. acetaminophen), accurate reproduction of experimental chlorination kinetics required consideration of the less stable but much more reactive iminol tautomer, together with water-assisted transition structures and benchmarking against higher-level methods [1].

The same principle was confirmed recently for sulfonamides, where the chlorination mechanism could only be described correctly after explicit consideration of speciation and tautomerism (e.g. sulfamethoxazole). In neutral aqueous solution, the anionic form was identified as the relevant reactant, whereas under acidic conditions the neutral form and its tautomeric imide structures may also contribute. In addition, explicit water molecules were found to be essential for obtaining realistic transition structures and barriers [2].

In the present work we extend this mechanistic framework to phosphorodiamidates, specifically cyclophosphamide (CPA) and ifosfamide (IFO). In contrast to amides and sulfonamides, chlorination of phosphorodiamidates is additionally conformation-dependent, meaning that not only ionization and isomeric states but also the conformational properties of the reactant must be taken into account. Accordingly, a realistic mechanistic treatment of CPA and IFO chlorination requires benchmarking of the computational method, differentiation between the neutral and anionic chlorination pathways, and evaluation of the relevant isomeric/conformational space of the parent reactants.

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