Dechlorination helps defluorination: Insights into the defluorination mechanism of florfenicol and DFT calculations on the reaction pathways

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ABSTRACT: Defluorination of organic chemicals is challenging under ambient conditions. Florfenicol ($C_{12}H_{14}Cl_2FNO_4S$, FF) is a broad-spectrum antibiotic and a ubiquitous environmental contaminant that can be effectively dechlorinated by sulfidated nanoscale zerovalent iron (S-nZVI), yet a comprehensive investigation of the defluorination mechanism is lacking. Herein, we used experimental data and density functional theory (DFT) calculations to reveal how defluorination of alkyl F in FF is facilitated by dechlorination through four pathways. We found sequential and complete dechlorination of FF by S-nZVI to form deschloro (dFF) and dideschloro FF (ddFF) within 24 hours and up to 37.0% of defluorination in 15 days. The dominant pathway to defluorination is the indirect hydrolysis of ddFF, which is initiated by an intramolecular substitution attack from the carbonyl O to alkyl F, resulting in hydrolyzed ddFF. This pathway does not rely on the presence of S-nZVI and is limited for dFF and FF because of the electron-withdrawing Cl. The removal of Cl also makes the reductive defluorination of ddFF by S-nZVI amenable, as indicated by the unique byproduct. The other two minor but more rapid defluorination pathways occur in synergy with the dechlorination of FF and dFF and involve the nucleophilic substitution of alkyl F mediated by the reactive carbanion intermediates, resulting in the corresponding hydrolyzed byproducts. The reliability of the proposed pathways was demonstrated by the consistency of theoretical calculations with experimental data. These dechlorination-facilitated defluorination mechanisms are first identified, providing valuable insights into the degradation of Cl and F-containing chemicals.

INTRODUCTION

F-containing pharmaceuticals, or fluoro-pharmaceuticals, have rapidly developed since their first use in 1954 and now account for approximately 20% of the drug market.[1] F imparts these drugs with improved properties, such as metabolic stability, selectivity, bioavailability, and membrane permeability.[1-3] However, F also increases their persistence, biotoxicity, and antibiotic resistance after they are released into the environment following poor metabolism in consumers and limited removal by conventional wastewater treatments.[1,3-5] Florfenicol (FF, **Figure 1**) is a widely used fluoro-derivative of thiamphenicol and a broad-spectrum antibiotic in veterinary medicine and aquaculture.[6] FF residues are commonly detected in biotic samples, wastewater effluents, and other aquatic systems,[7-11] and have been found to cause damage to organisms, ranging from growth inhibition of microalgae to hemopoiesis and immune dysfunction of piglets.[12-15] The frequent detection of the antibiotic resistance gene of FF in human pathogens indicates its spread from animals and potential threat to human health.[6,16] FF is persistent under ambient conditions, though hydrolysis at the amide and alkyl F (RCH_2F to RCH_2OH, **Figure 1**) moieties can be promoted at elevated temperatures and under acidic or basic conditions.[17] Therefore, investigating the degradation mechanism of FF is crucial to eliminate the contamination either before waste discharge or during the remediation of the impacted area.

FF contains two C–Cl and one C–F bonds, making it recalcitrant to degradation by conventional water treatments. Incomplete dehalogenation, particularly defluorination, can result in halogenated byproducts that are still biotoxic to the ecosystem and induce novel antibiotic resistant genes and bacteria.[18,19]As a result, dehalogenation pretreatment is considered necessary to eliminate the