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Regular Article

Structures and mechanisms in clay nanopore trapping of structurally-different fluoroquinolone antimicrobials

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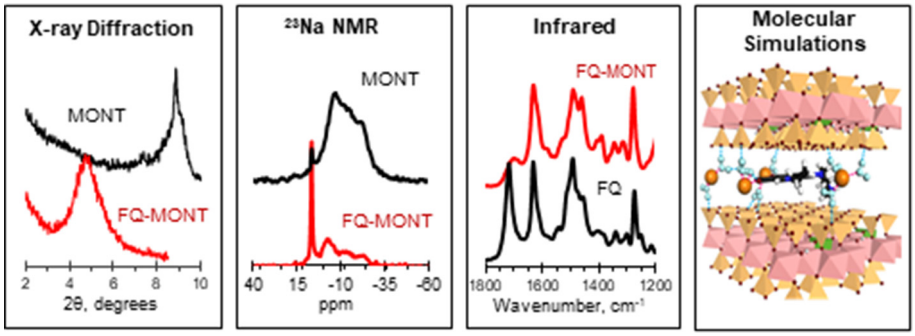
GRAPHICAL ABSTRACT



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ABSTRACT

Smectite clay nanoparticles are implicated in the retention of antimicrobials within soils and sediments; these clays are also inspected as drug carriers in physiological systems. Cation exchange is considered the primary adsorption mechanism of antimicrobials within smectite nanopores. However, a dual role of acid-base chemistry and adsorptive structures is speculated by recent studies. Using the prototypical smectite clay montmorillonite, we employed a combination of X-ray diffraction (XRD), nuclear magnetic resonance, attenuated total reflectance-Fourier transform infrared spectroscopy, and molecular dynamics simulations to investigate the interlayer nanopore trapping of two structurally-different fluoroquinolone (FQ) antimicrobials with similar acid-base chemistry: ciprofloxacin (a first-generation FQ) and moxifloxacin (a third-generation FQ). Greater sorption at pH 5.0 than at pH 7.0 for both FQs was consistent with cation-exchange of positively-charged species. However, the clay exhibited a near twofold higher sorption capacity for moxifloxacin than for ciprofloxacin. This difference was shown by the XRD data to be accompanied by enhanced trapping of moxifloxacin within the clay interlayers. Using the XRD-determined nanopore sizes, we performed molecular dynamics simulations of thermodynamically-favorable model adsorbates, which revealed that ciprofloxacin was adsorbed parallel to the clay surface but moxifloxacin adopted a tilted conformation across the nanopore. These conformations resulted in more slowly-exchanged than quickly-exchanged Na complexes with ciprofloxacin compared with moxifloxacin. These different Na populations were also captured by ^{23}Na nuclear magnetic resonance. Furthermore, the simulated adsorbates uncovered different complexation interactions that were corroborated by infrared spectroscopy. Therefore, beyond acid-base chemistry, our findings imply that distinct

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adsorbate structures control antimicrobial trapping within clay nanopores, which can promote persistence in environmental matrices and stable delivery in biological systems.

1. Introduction

Due to their broad-spectrum antimicrobial activity, fluoroquinolone (FQ) antimicrobials are widely used in both human and veterinary medicine [1–3]. These compounds have been detected in wastewater effluents [4–7], sewage sludge [7,8], sediments [9,10], surface waters [3,4,7,10–12], soils [2,3,8,13], and groundwater [3,4]. They can be found in surface waters at concentrations of ng L^{-1} to μg L^{-1} [4,7,12]. Applications of manure and wastewater sewage sludge on agricultural lands have resulted in FQ-contaminated soils at a range of 2–450 μg FQ per kg soil [3]. There are three generations of FQs that are classified based on their antimicrobial potency and characterized by similar structural features [14]. First-generation FQs, which include ciprofloxacin (CFX, Fig. 1A) and ofloxacin, were developed in the 1980s from the non-fluorinated fully synthetic antibiotic nalidixic acid [14] by the addition of a fluorine atom and a piperazine group [Supplementary Information (SI), Fig. S1]. This modification led to antimicrobial activity against aerobic gram-positive bacteria but lacked activity against anaerobic bacteria [15]. Second-generation FQs such as sarafloxacin and fleroxacin, which possess up to two additional fluorine atoms, exhibit potency against gram-negative bacteria [15,16]. The latest third-generation FQs, which are distinguished by modifications of the piperazine group and a greater potency against anaerobes and pneumococci, include moxifloxacin (MFX, Fig. 1B), gemifloxacin, and trovafloxacin [15]. Mineral content and pH conditions have been reported as important factors controlling the fate of FQs in soils and sediments [3,8]. Accordingly, of special interest are the adsorption mechanisms underlying the retention of different types of FQ compounds within clay minerals [2,12,17–24].

Adsorption of FQs has been reported to be higher in smectite-type clay minerals than in non-swelling clays [19–21,25,26]. Smectite clays, which are 2:1 aluminosilicate clays, consist of layers composed of one aluminum-oxide octahedral sheet sandwiched between two silica tetrahedral sheets [27,28]. These clays are important for the trapping of contaminants due to their high surface area, cation exchange capacity, and particularly their swelling properties that can facilitate the interlayer adsorption of contaminants [23,25,29–31]. Smectite clays carry negative structural charges due to isomorphic substitutions, Al^{3+} for Si^{4+} in the tetrahedral sheet or Mg^{2+} for Al^{3+} in the octahedral sheet [27]. These negative charges are balanced by metal cations in the interlayer space [27,28]. These charge-compensating metal cations can in turn be exchanged with positively-charged antimicrobials such as FQs [12], tetracyclines [29,32], and sulfonamides [33]. Intercalation within MONT interlayers has also been implicated in enhancing the photostability of drugs [31]. Furthermore, hybrids of drugs and smectite or related synthetic clay minerals have been studied for use as drug delivery systems [34–37]. Therefore, a comprehensive understanding of clay interlayer trapping of pharmaceutical compounds including FQs is relevant both to environmental and physiological behaviors.

At acidic pH, FQs are primarily cationic due to the protonated piperazine group, which can thus replace exchangeable cations in the mineral interlayers [12,20]. In accordance with a cation-exchange as the primary adsorption mechanism, a study on the adsorption of CFX on three smectite-type clay minerals (MONT, illite and rectorite) reported a positive correlation between the amount of desorbed exchangeable cations and the amount of CFX adsorbed [20]. In basic pH conditions, decreased adsorption is explained by the repulsion between the negatively charged clay minerals and anionic FQ species [12,18,25,26]. Using X-ray diffraction (XRD), Wang et al. (2010) measured an increase in the layer-to-layer spacing (d_{001}) of Ca-MONT as the amount of adsorbed CFX increased [12]. This positive correlation between interlayer spacing and adsorption capacity was also reported for the adsorption of nalidixic acid [21] and two other FQs [25] (enrofloxacin and

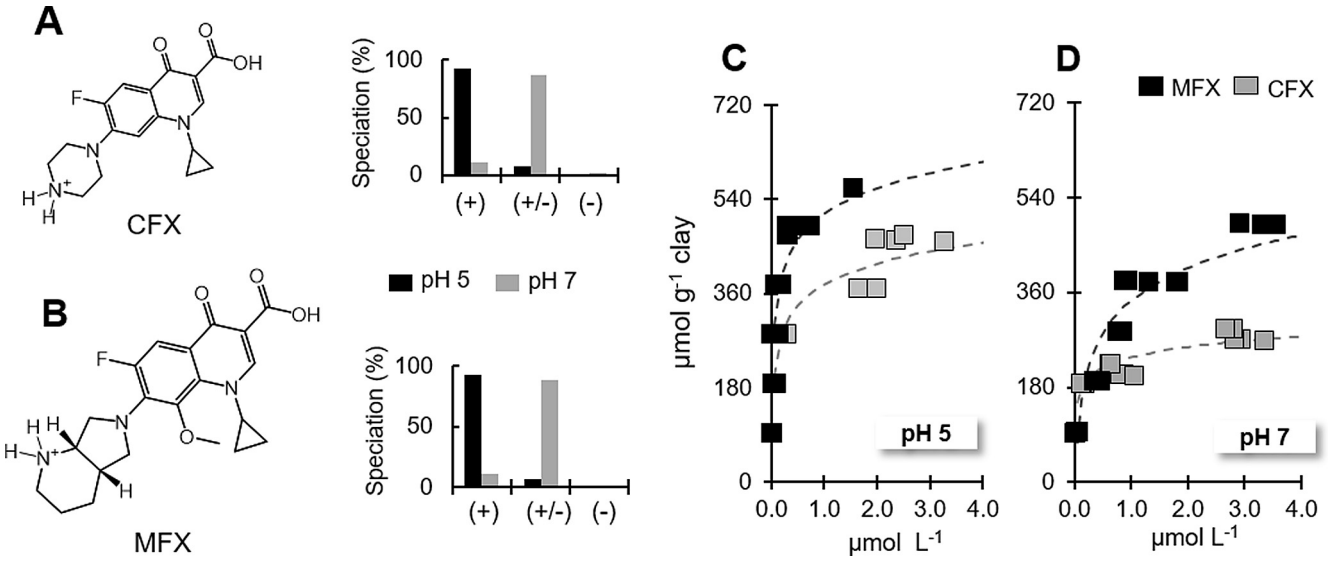

Fig. 1. Chemical structure and speciation of (A) ciprofloxacin (CFX) and (B) moxifloxacin (MFX). Amount of adsorbed FQ versus equilibrium FQ concentration at (C) pH 5.0 and (D) pH 7.0 for CFX (gray-filled squares) and MFX (black-filled squares). In A and B, the different FQ species in the speciation plots at pH 5.0 (black bars) and pH 7.0 (gray bars) are cationic (+), zwitterionic (+/−), and negatively-charged (−) species. In C and D, the lines are meant to be guides to the eyes for the general trend in the data points.