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1 **Co-binding of pharmaceutical compounds at mineral**
2 **surfaces: mechanistic modeling of binding and co-binding of**
3 **nalidixic acid and niflumic acid at goethite surfaces**

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27

28 **Abstract**

29 Although emerging contaminants rarely exist individually in environmental
30 contaminated systems, only limited information on their adsorption mechanisms in
31 multi-components solutions is currently available. To address this shortcoming, this
32 work examines for the first time the accuracy of a surface complexation model in
33 predicting the cooperative adsorption of nalidixic acid (NA) and niflumic acid (NFA) at
34 goethite (α -FeOOH) surfaces. Our model adequately predicts co-binding of an
35 outer-sphere (OS) complex of NFA onto NA bound to goethite through metal bonded
36 (MB), hydrogen bonded (HB) or OS complexes. More positive charge is introduced in
37 the system via sodium interactions in order to describe the NFA adsorption at high NaCl
38 concentrations in both single and binary systems. Our model confidently predicts
39 multilayers of NA on goethite as well as NFA binding on goethite-bound NA over a
40 large range of pH, salinity as well as NA and NFA loadings. These findings have strong
41 implications in the assessment and prediction of contaminant fate in multi-component
42 contaminated systems by invoking a non-traditional form of ligand-ligand interaction
43 in this field of study.

44 **Introduction**

45 Although emerging contaminants (e.g. pharmaceutical and personal care products)
46 often exist in mixture in environmental systems^{1,2}, they have been often studied
47 individually with respect to the sorption and/or complexation with naturally occurring
48 subsurface solids^{3,4}. At environmental surfaces, the adsorption of multiple
49 contaminants (or pollutant mixtures) can give way to competitive or cooperative
50 binding. While competitive adsorption has been widely investigated⁵⁻⁷, very few
51 studies have resolved the impact of emerging contaminants co-binding at mineral
52 surfaces. Very recently, we have demonstrated using vibrational spectroscopy and
53 quantum chemical calculations⁸, that nalidixic acid (NA, a quinolone antibiotic that is
54 widely used in humans and animals medicine⁹) and niflumic acid (NFA, a non-steroidal
55 anti-inflammatory that is often used for rheumatoid arthritis²) cooperatively adsorb to
56 naturally-occurring mineral particles by intermolecular interactions (van der Waals).
57 This novel finding raised the importance of recognizing drug co-binding as a
58 mechanism contributing to the fate and transport of complex mixtures of antibiotics and
59 anti-inflammatory agents in nature. Because most traditional environmental models are
60 based on a single/individual contaminant basis, little is known on their fate in mixed
61 contaminant systems. Omission of co-binding effects occurring in multi-component
62 solutions might have unknown consequences on the prediction of fate and transport of
63 these contaminants in the environment.

64 Some studies have used predictive models involving empirical adsorption isotherm
65 equations with limited (site specific) applicability to describe the observed data in

66 multi-component solutions^{10,11}. However, these macroscopic models cannot account
67 for co-binding mechanisms for accurately predicting the behavior of antibiotics at
68 mineral/water interfaces under a large range of physico-chemical conditions. In
69 contrast, mechanistic models include details of the surface (in terms of structure), take
70 into account the structure of the electrical interfacial layer¹²⁻¹⁴, and constrain structure
71 and bonding of surface complexes by information from spectroscopic studies and/or
72 theoretical calculations¹⁵⁻¹⁷. Although mechanistic models have extensively been
73 applied to predict pharmaceutical compounds adsorption to metal-(hydr)oxides^{18,19}, no
74 attempt has been made to account for co-binding mechanisms between two or more
75 components. This becomes even more important considering the necessity to
76 adequately account for binding in reactive transport models to be used to predict the
77 fate of antibiotics and anti-inflammatory agents in nature.

78 In this study, we used molecular-level information (Attenuated Total
79 Reflectance-Fourier Transform InfraRed (ATR-FTIR) spectroscopy and quantum
80 chemical calculations) obtained from our previous work⁸, to develop a surface
81 complexation model to account for the pH and salinity dependence of NA and NFA
82 loadings achieved at goethite surfaces. We developed, for the first time, a model that
83 accounts for co-binding of ligands resulting from van der Waals-type interactions. This
84 opens new possibilities to account these generally overlooked forms of interactions in
85 these types of studies in the future.

86

87 2. Materials and Methods

88 2.1. Chemicals

89 All chemicals used were of pro-analytical quality or better and were purchased
90 from Sigma-Aldrich. Ultrapure water was used in all experiments. Goethite was
91 prepared following Mazeina and Navrotsky's work²⁰. Goethite (α -FeOOH) was
92 selected due to its great thermodynamic stability, high surface reactivity with organic
93 and inorganic ligands, and abundance in soils and sediments²¹. It has been characterized
94 in detail in our previous work⁸. The specific surface area was of 81 ± 4 m²/g and the
95 isoelectric point (IEP) is 9.1.

96

97 2.3. Batch experiments

98 The pH (3-10) and NaCl concentrations (3 – 300 mM) dependences of NA and
99 NFA binding to goethite was first investigated in single ($[\text{NA}]_{\text{tot}} = 10$ or 20 μM or
100 $[\text{NFA}]_{\text{tot}} = 20$ μM) and binary ($[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20$ μM) systems. pH adsorption
101 edges in 10 mM NaCl and adsorption isotherms at pH 6 were taken from previous
102 work⁸, while pH-dependence of NA and NFA adsorption in single and binary systems at
103 other NaCl concentrations (3, 100 and 300 mM) were conducted in the present work.
104 Because high background electrolyte concentrations can affect pH measurements, the
105 pH electrode was calibrated using solutions of known $[\text{H}^+]$ (10^{-5} – 10^{-3} M) at different
106 $[\text{NaCl}]$. Therefore, pH refers to the molarity of the proton ($-\log [\text{H}^+]$). Adsorption
107 isotherms were obtained by experiments with (i) equimolar concentrations of NA and
108 NFA (0.1 - 100 μM), (ii) varying concentrations of NFA (0.1 - 100 μM) with 20 μM

109 NA, and (iii) varying concentrations of NA (0.1 - 100 μM) with 20 μM NFA.
110 Additionally, desorption tests conducted at $\text{pH} = 11$ were used to verify the mass
111 balance of NA and NFA in the suspensions. They showed that solutes were removed
112 only by adsorption, and that transformations by, for example, oxidation, did not occur
113 under our experimental conditions (a result that is consistent with previous
114 findings²²).

115 Batch experiments were conducted in 10 mL suspensions of 0.5 g/L goethite in
116 polypropylene tubes under an atmosphere of $\text{N}_2(\text{g})$ in order to avoid the effect of
117 dissolved CO_2 . Suspensions were mixed for a period of 8 h by end-over-end shaking,
118 which is sufficient to reach a steady state⁸. Aliquots of the resulting suspensions were
119 thereafter sampled and filtered (0.2 μm) for analysis. All adsorption experiments were
120 performed at least twice, with a reproducibility of $\sim 5\%$ for NA- and $\sim 10\%$ for
121 NFA-bearing systems.

122 Aqueous concentrations of NA and NFA were determined using high performance
123 liquid chromatography (Waters 600 Controller) equipped with a photodiode array
124 detector (Waters 996) and a reversed-phase C18 column (250 mm \times 4.6 mm i.d., 5 μm).
125 The mobile phase (1 mL/min) was a mixture of acetonitrile/water (60/40 v/v) contained
126 0.1% formic acid. The detector was set to 258 nm for NA, 283 nm for NFA and both
127 molecules could be analyzed with a single injection (NA: 4.5 min; NFA: 10.1 min).

128

129 **2.4. Surface complexation modeling**

130 The geochemical speciation code PHREEQC (version 2)²³ was used for surface

131 complexation calculations using thermodynamic database of Minteq. The pK_a s of NA
132 ($pK_a=6.19$) and NFA ($pK_{a,1}=2.28$ and $pK_{a,2}=5.10$) at infinite dilution were obtained
133 from conditional pK_a values^{24,25} and the Davies equation. NA exists as neutral (NAH,
134 $pH < pK_a$) or anionic form (NA^- , $pH > pK_a$), and NFA as cationic ($NFAH_2^+$, $pH < pK_{a,1}$),
135 anionic (NFA^- , $pH > pK_{a,2}$), neutral ($NFAH^0$) or zwitterionic form ($NFAH^{+/-}$) at $pK_{a,1} <$
136 $pH < pK_{a,2}$. Molecular structures of the different dissolved NA and NFA species and
137 calculated NA and NFA speciation versus pH in 10 mM NaCl solution are shown in
138 Figure S1. Protonation reactions of NA and NFA are given in Table 1.

139 The charge of the goethite/water interface was treated with using the three plane
140 model (TPM)¹³, where charges of the adsorbates can be distributed between the 0-
141 (metal-bonded complexes), 1- (hydrogen-bonded complexes), and 2-planes (Na^+ , Cl^- ,
142 outer-sphere complexes). The TPM requires two capacitances for the 0- (C_1) and the
143 1-plane (C_2) which were taken from a previous study in our group²⁶. Predictions of NA
144 and NFA adsorption to goethite were made using the multi-site complexation (MUSIC)
145 model¹². For goethite, different types of surface sites can exist depending of the
146 proportion of crystal planes, which should have different binding affinities. The
147 goethite surface is considered to exhibit (101), (001) and (210) planes (group Pnma),
148 which represent 63%, 27% and 10% of the total surface area, respectively. Singly
149 ($\equiv FeOH^{-0.5}$), doubly ($\equiv Fe_2OH$) and triply ($\equiv Fe_3O^{-0.5}$ and $\equiv Fe_3OH^{+0.5}$) coordinated
150 oxygens can be found at the goethite surface, depending on the crystal face. To simplify
151 the model, we adopted the 1-pK approximation of the MUSIC model¹², neglecting the
152 contributions of doubly- and part of the triply-coordinated oxygens. Crystallographic

153 site densities in this model are: $[\equiv\text{FeOH}^{-0.5}] = 3.03$ sites/nm² at the (101), 3.34 sites/nm²
154 at the (001) and 7.4 sites/nm² at the (210) planes, and $[\equiv\text{Fe}_3\text{O}^{-0.5}] = 3.03$ sites/nm² at the
155 (101) and 3.34 site/nm² at the (001) planes. The protonation constants of the groups are
156 set to that of the IEP (1-pK approach¹⁴). Formation constants of all surface species are
157 reported in Table 1.

158 NA and NFA are considered to bind only to $\equiv\text{FeOH}^{-0.5}$ groups. From a molecular
159 viewpoint, ligands might also form H-bonds with doubly ($\equiv\text{Fe}_2\text{OH}$) and triply
160 ($\equiv\text{Fe}_3\text{O}^{-0.5}$ and $\equiv\text{Fe}_3\text{OH}^{+0.5}$) coordinated sites. Recently, Boily²⁷ showed that
161 protonation of doubly-coordinated hydroxo groups and one type of triply-coordinated
162 oxo group, which are considered to be proton-silent within the 1-pK approach, may be
163 favored in the presence of strongly binding negatively charged ligand. However, a full
164 version of the MUSIC model for goethite would be required to account for all these
165 sites. This would lead to a drastic increase in the number of parameters and then
166 complexity in the model, and thus not considered in this modeling approach, as
167 generally carried out in literature^{17-19,26,28-30}.

168 The modeling strategy proceeded as follows. First, NA and NFA adsorption was
169 modeled in single systems. The corresponding surface complexation constants were
170 kept constant to model the NA-NFA binary system. All surface complexes reactions
171 involved in binding and co-binding mechanisms were proposed based on our own
172 molecular-level information and theoretical calculations and literature data, as detailed
173 below in section 3.

174 PhreePlot³¹ was used to determine surface complexation constants and related

175 uncertainties for NA and NFA adsorption to goethite (single and binary systems).
176 Charge variations at the 0-, 1- and 2-planes (Δz_0 , Δz_1 , Δz_2 , respectively) are constrained
177 by spatial considerations and are not adjustable parameters. PhreePlot contains an
178 embedded version of the geochemical speciation program PHREEQC and it includes a
179 parameter optimization procedure, which automatically fits a model to experimental
180 data by minimizing the weighted sum of squares of the residuals. A modified
181 Marquardt–Levenberg procedure was applied³². With this method, PhreePlot provides
182 also a statistical uncertainty of the estimated parameters, which is given for each of
183 optimized parameters in Table 1. Note that PHREEQC version 2 uses surface coverage
184 fractions as standard state for surface species^{33,34}.

185

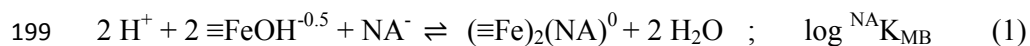
186 **3. Results and discussion**

187 **3.1. Nalidixic acid (NA) adsorption on goethite (single system).** As typically
188 observed for many organic ligands, NA adsorption versus pH showed a bell-shape, and
189 the maximum adsorption amount was observed at a pH near the pK_a (Fig. 1a).
190 Increasing NaCl concentration decreased NA adsorption on the whole investigated pH
191 range ($[NA]_{tot} = 20 \mu M$; Fig. 1), an effect that is generally attributed to non-specifically
192 bound ligands at mineral surfaces^{29,35}.

193 According to the spectroscopic investigations of NA binding to goethite⁸ and in
194 agreement with previous studies on quinolone binding to minerals^{29,36}, MB surface
195 complexes at the goethite (101)/(001) and (210) planes (Pnma group) were expected to

196 form *via* a NA keto group and one oxygen of the carboxylate group. This can be
197 expressed through the surface complexation reaction:

198

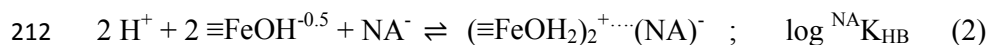


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201 Only singly coordinated ($\equiv\text{FeOH}^{-0.5}$) surface sites were considered to be involved in the
202 latter reaction given the propensity for ligand exchange of these sites. Eq. 1 does not
203 denote the number of Fe(III) octahedra in a complex, but only the number of $\equiv\text{FeOH}^{-0.5}$
204 sites that may or may not be of the same Fe(III) octahedron³⁰. Ideally, the steric
205 constraints at the dominant (101)/(001) planes (Pnma group) should promote bridging
206 between two Fe atoms separated by 3 Å from one another³⁷, while at the (210) plane,
207 two $\equiv\text{FeOH}^{-0.5}$ should be located on the same Fe(III) octahedron, hence our preference
208 for modeling NA binding as a 1:2 NA: $\equiv\text{FeOH}^{-0.5}$ species (Table 1).

209 Hydrogen-bonded (HB) complexation (surface hydration-shared ion pair) was
210 also modeled through singly $\equiv\text{FeOH}^{-0.5}$ sites with:³⁰

211



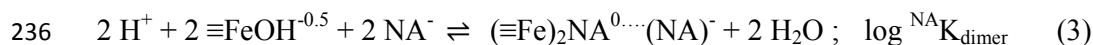
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214 Formation of an outer-sphere (OS) complex (solvent-surface hydration-separated ion
215 pair), where NA keeps its first hydration sphere and its charge is located in the 2-plane,
216 was also considered to form with protonated singly-coordinated sites ($\equiv\text{FeOH}_2^{+0.5}$)
217 (Table 1).

218 As shown in Figure S2, our model satisfactorily predicts the pH dependence of NA
219 adsorption to goethite at low NA loading ($[\text{NA}]_{\text{tot}} \leq 20 \mu\text{M}$; Fig. S2a,b,c), but
220 underestimated the NA adsorption isotherm at pH 6 at high NA loadings (Fig. S2d).
221 Furthermore, the effect of NaCl concentration on NA adsorption is not very well
222 captured in this model, since this effect is small for $[\text{NA}]_{\text{tot}} = 10 \mu\text{M}$ (Fig. S2a) but large
223 for $[\text{NA}]_{\text{tot}} = 20 \mu\text{M}$ (Fig. S2a,b). The corresponding highest adsorbed amount lies at
224 $0.85 \text{ NA}/\text{nm}^2$ (i.e. $1.4 \mu\text{mol}/\text{m}^2$), and did not exceed the estimated NA loadings of ~ 1.5
225 NA/nm^2 that can be expected if all the $\sim 3 \text{ -OH}/\text{nm}^2$ were to be consumed. Attempts to
226 reproduce our data with the model of Boily²⁷ (i.e. using a full version of the MUSIC
227 model for goethite including more surface sites for HB and OS complexes) led to
228 similar conclusions (not shown). We thus conclude that calculated NA adsorption
229 amount at high loading is not limited by the number of available surface sites, but by
230 less favorable electrostatic effects due to surface charge neutralization by NA.

231 In fact, higher loadings favor additional binding mechanisms (e.g. multilayer,
232 dimerization, hydrophobic interactions and surface precipitation) involving direct
233 NA-NA interactions. Drawing from our previous work on intermolecular interactions
234 between naphthoic acids¹⁶, we can write:

235



237

238 In this equation, a NA-NA dimer is formed by co-bonding to individual NA molecules,
239 resulting in an interfacial distribution of charges between the 0- and 1-planes.

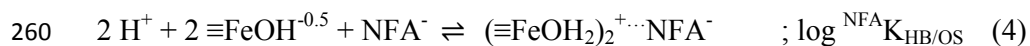
240 Combining the equations with monomer and dimer of NA, the model better predicts
241 NA adsorption at high loadings (Fig. 1d).

242 In summary, surface complexation modeling results (Table 1, Fig. 1 and Fig. S3),
243 predict NA binding as a function of pH (Fig. 1a and Fig. S3 for $[NA]_{tot} = 20$ and $10 \mu\text{M}$,
244 respectively), NaCl concentration (Fig. 1 a,c) and NA loadings (Fig. 1d). In accordance
245 with previous reports on ligand binding (e.g. for benzenecarboxylates³⁰), NA
246 predominantly formed HB and OS complexes at high pH while MB complexes only
247 formed at $\text{pH} < 7$ (Fig. 1a). The model also predicts NA dimer formation with NA
248 between pH 3 and 7 (Fig. 1 a,d).

249

250 **3.2. Niflumic acid (NFA) adsorption on goethite (single system).** NFA binding
251 followed the same pH dependence as NA (Fig. 1b) but is favored at NaCl concentration
252 greater than 50 mM (Fig. 1c). This alongside the weaker dependence of binding on
253 NFA loadings (Fig. 1d) suggests distinct binding mechanisms to those of NA. In fact,
254 based on the disposition of its functional groups, HB and OS complexation should
255 predominate over MB species under all conditions considered in this work, as for
256 example for other monocarboxylate ligands such as acetate, benzoate,
257 cyclohexanecarboxylate or naphthoate^{17,35}. Both HB and OS complexes were
258 expressed by the following reaction:

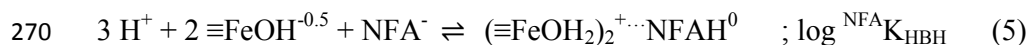
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261

262 here omitting the intervening roles of water. The -1 charge of the HB complex of NFA
 263 is located at the 1-plane ($\Delta z_1 = -1$; $\Delta z_2 = 0$) whereas that of the OS complex is in the
 264 2-plane ($\Delta z_1 = 0$; $\Delta z_2 = -1$). This model adequately accounts for all goethite-NFA data,
 265 except the effect of NaCl concentration. Alternatively, replacing the HB complex with
 266 its zwitterion form provides both an adequate prediction of binding with pH and NaCl
 267 concentration below pH 6, and is consistent with previous accounts^{18,19,38} supporting
 268 this type of species.

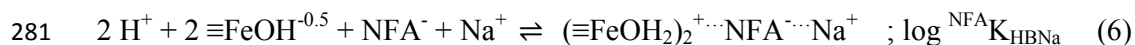
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271

272 Preliminary calculations showed that HB complexes with anionic or zwitterionic form
 273 of NFA occurred in a comparable pH-range (not shown). To simplify the model, the
 274 HB complex with the anionic form was removed from the speciation scheme. The OS
 275 species is however needed to account for the high pH data at NaCl concentrations
 276 below 10 mM. This model accurately predicts NFA adsorption at 10 mM NaCl but
 277 provides a poor description of NaCl effect (Fig. S4). Because of the increasing
 278 adsorption of NFA at high NaCl concentration, a sodium-OS ion pair is however
 279 needed to account for the data above 10 mM NaCl through:

280



282

283 where Na^+ charge is located in the 2-plane. Sodium co-binding has been previously
284 proposed to describe the adsorption of phosphate to goethite³⁹. This model allows a
285 relatively good prediction of NFA adsorption to goethite at various pH (Fig. 1b),
286 [NaCl] (Fig. 1b,c) and [NFA] (Fig. 1d).

287

288 3.3. Binary NA-NFA system

289 NA-NFA co-binding occurred over a large range of pH (Fig. 2a,b), NaCl
290 concentrations (Fig. 2a,b,e) and NA and NFA loadings (Fig. 2c,d). Co-binding effect is
291 more pronounced for NFA, because of its weaker adsorption in single system.
292 However, NA adsorption to goethite is rather strong in single system, and so co-binding
293 with NFA only further stabilizes NA at the surface. As a result, to accurately predict
294 binding in mixed NA-NFA system, the model requires reactions accounting of
295 cooperative effects between NA and NFA besides the competitive binding mechanisms
296 of eqs. 1-6. This is further illustrated in Figure S5, where NA and NFA adsorption in
297 binary system is strongly underestimated when using only eqs. 1-6.

298 For NA, all MB, HB and OS complexes of NA are considered to be formed
299 because of the similar shape of the adsorption edges in mixtures with those of the single
300 system (Figs. 1a and 2a), while only OS complexes are considered for NFA because the
301 maximal loadings of NFA (Fig. 2b) coincided with that achieved in the single system
302 (Fig. 1b). To keep the model at a reasonable level of complexity we however only
303 considered the binary NA-NFA surface complex at the (101)/(001) planes and model
304 co-binding with:

305



308



311



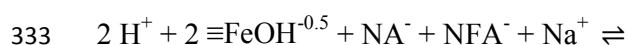
314

315 In eq. 7-9, NFA binds to one NA at the goethite surface predominantly via van der
 316 Waals interactions⁸, and its -1 charge is located at the 2-plane. In contrast, NA is
 317 assumed to form MB, HB and OS complexes with goethite, respectively, and its -1
 318 charge should therefore be located at the 0-plane ($\Delta z_0=+1$; $\Delta z_1=0$; $\Delta z_2=-1$, eq. 7), the
 319 1-plane ($\Delta z_0=+2$; $\Delta z_1=-1$; $\Delta z_2=-1$, eq. 8) or the 2-plane ($\Delta z_0=+2$; $\Delta z_1=0$; $\Delta z_2=-2$, eq. 9).
 320 Note that the reverse case (NA binding to adsorbed NFA) involves the same
 321 stoichiometry and charge distribution over the 0-, 1- and 2-planes. Therefore, they are
 322 equivalent in PHREEQC. However, previous quantum chemical calculations⁸
 323 suggested that the reverse case was less plausible, that is, NA was expected to be
 324 located closer than NFA to the surface.

325 Our first modeling attempts using eqns. 1-9 predicted a decrease of NA/NFA
 326 adsorption with increasing [NaCl], which is inconsistent with experimental

327 observations (see Figure S6). Most notably, experimental NA binding became almost
 328 independent of NaCl concentration (Fig. 2a,e) while NFA binding followed three
 329 stages: (i) slight decrease in loadings below 10 mM, (ii) increased loadings at 10-50
 330 mM, and (iii) constant loadings above 50 mM NaCl (Fig. 2b,e). Including of an ion pair
 331 with sodium

332



335

336 considerably improved model predictions of the effect of NaCl (Fig. 2a,b,e). The best
 337 fit was obtained by allocating charges of both NA and NFA in the 1-plane and Na^+ in
 338 the 2-plane ($\Delta z_0=+2$; $\Delta z_1=-2$; $\Delta z_2=+1$) (Table 1).

339 The full model (i.e. eqs.1-10) provides an accurate description of co-binding data
 340 vs pH and NaCl concentration (Fig. 2a, b) and at a wide range of aqueous concentration
 341 (0.1- 100 μM) (Fig. 2c). This also permits to fit very well the variation of $[\text{NFA}]_{\text{ads}}$ as a
 342 function of $[\text{NA}]_{\text{ads}}$ regardless of the adopted approach : (i) varying $[\text{NA}]_{\text{tot}}$ at constant
 343 $[\text{NFA}]_{\text{tot}}$, (ii) varying $[\text{NFA}]_{\text{tot}}$ at constant $[\text{NA}]_{\text{tot}}$ or (iii) varying equimolar
 344 concentration of both (Fig. 2d).

345 Model predictions of NA and NFA surface speciation for 10 mM NaCl (Figs. 2 a,b)
 346 suggest that NA-NFA dimers remarkably prevail at $\text{pH} > 4$. Although NA adsorption
 347 slightly increased from the single to the binary system, its surface speciation drastically
 348 changes, probably due to competition between the three forms of NA (NA monomer,

349 NA dimer and NA-NFA dimer). Indeed, proportions of monomeric and dimeric forms
350 of NA strongly diminished in favor of NA-NFA surface complexes (Fig. 2a, c). NFA
351 adsorption was, however, mainly dominated by the formation of NA-NFA surface
352 complexes (Fig. 2b, c).

353 Finally, our proposed model not only explains batch adsorption data generated for
354 this work but also concentration profiles of dominant species extracted by a
355 chemometric analysis⁴⁰ of our previously published⁸ Fourier Transform Infrared
356 spectra on these systems (Fig. 2f). Our work had shown that vibration spectra of mixed
357 NA+NFA+goethite could not be explained as a linear combination of isolated
358 NA+goethite and NFA+goethite systems. The concentration profiles in Fig. 2f show
359 that increasing fractions of NA-NFA complexed with increasing $[NA]_{tot}$ (constant
360 $[NFA]_{tot}$) or with increasing $[NFA]_{tot}$ ($[NA]_{tot}$) are well-predicted by the model. This
361 adds further confidence to the ability of our proposed model to account for NA and
362 NFA binding in single and mixed systems.

363

364 **Implications for reactive transport modeling.** Because of the increase of multiple
365 contaminations in aquatic ecosystems worldwide, environmental subsurface and
366 groundwaters often contain multiple contaminants including nonprescription drugs,
367 antibiotics, hormones and prescription drugs⁴¹. Protection of groundwater resources
368 requires an accurate assessment of processes controlling the contaminant fate and
369 transport in complex environmental mixtures.

370 The development of new surface complexation models to account for co-binding at

371 mineral surfaces is central to the prediction of the fate of contaminants in
372 multi-component systems. We demonstrate, for the first time, that co-binding of
373 emerging organic contaminants (e.g. NA and NFA) can be predicted over a large range
374 of environmentally relevant conditions using a mechanistic model based on insights
375 from vibration spectroscopy and quantum chemical calculations⁸. The modeling
376 approach accounting for new forms of drugs co-binding at mineral surfaces is
377 becoming a powerful tool for implementation of co-binding phenomena in reactive
378 transport models, and for the accurate prediction of the transport of antibiotics and
379 anti-inflammatory agents in soils and sediments.

380

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386

387 **Supporting information available**

388 NA and NFA aqueous speciation versus pH and additional modeling tests. This
389 information is available free of charge via the Internet at <http://pubs.acs.org/>.

390

391 **References**

392

393 (1) Gothwal, R.; Shashidhar, T. Antibiotic Pollution in the Environment: A Review.
394 *CLEAN--Soil, Air, Water* **2015**, *43* (4), 479–489.

395 (2) Fatta-Kassinos, D.; Meric, S.; Nikolaou, A. Pharmaceutical residues in
396 environmental waters and wastewater: Current state of knowledge and future
397 research. *Anal. Bioanal. Chem.* **2011**, *399* (1), 251–275.

398 (3) Xu, X.-R.; Li, X.-Y. Sorption and desorption of antibiotic tetracycline on marine
399 sediments. *Chemosphere* **2010**, *78* (4), 430–436.

400 (4) Kulshrestha, P.; Giese, R. F.; Aga, D. S. Investigating the molecular interactions
401 of oxytetracycline in clay and organic matter: insights on factors affecting its
402 mobility in soil. *Environ. Sci. Technol.* **2004**, *38* (15), 4097–4105.

403 (5) Hiemstra, T.; Van Riemsdijk WH. Surface Structural Ion Adsorption Modeling
404 of Competitive Binding of Oxyanions by Metal (Hydr)oxides. *J. Colloid*
405 *Interface Sci.* **1999**, *210* (1), 182–193.

406 (6) Conkle, J. L.; Latta, C.; White, J. R.; Cook, R. L. Competitive sorption and
407 desorption behavior for three fluoroquinolone antibiotics in a wastewater
408 treatment wetland soil. *Chemosphere* **2010**, *80* (11), 1353–1359.

409 (7) Xing, B.; Pignatello, J. J. Competitive sorption between 1, 3-dichlorobenzene or
410 2, 4-dichlorophenol and natural aromatic acids in soil organic matter. *Environ.*
411 *Sci. Technol.* **1998**, *32* (5), 614–619.

412 (8) Xu, J.; Marsac, R.; Costa, D.; Cheng, W.; Wu, F.; Boily, J. F.; Hanna, K.

- 413 Co-Binding of Pharmaceutical Compounds at Mineral Surfaces: Molecular
414 Investigations of Dimer Formation at Goethite/Water Interfaces. *Environ. Sci.*
415 *Technol.* **2017**, *51* (15), 8343–8349.
- 416 (9) Zhang, T.; Li, B. Occurrence, Transformation, and Fate of Antibiotics in
417 Municipal Wastewater Treatment Plants. *Crit. Rev. Environ. Sci. Technol.* **2011**,
418 *41* (11), 951–998.
- 419 (10) Limousin, G.; Gaudet, J. P.; Charlet, L.; Szenknect, S.; Barthès, V.; Krimissa, M.
420 Sorption isotherms: A review on physical bases, modeling and measurement.
421 *Appl. Geochemistry* **2007**, *22* (2), 249–275.
- 422 (11) Liu, S. Cooperative adsorption on solid surfaces. *J. Colloid Interface Sci.* **2015**,
423 *450*, 224–238.
- 424 (12) Hiemstra, T.; Van Riemsdijk, W. H. A surface structural approach to ion
425 adsorption: the charge distribution (CD) model. *J. Colloid Interface Sci.* **1996**,
426 *179* (2), 488–508.
- 427 (13) Filius, J. D.; Hiemstra, T.; Van Riemsdijk, W. H. Adsorption of Small Weak
428 Organic Acids on Goethite: Modeling of Mechanisms. *J. Colloid Interface Sci.*
429 **1997**, *195* (2), 368–380.
- 430 (14) Gaboriaud, F.; Ehrhardt, J. J. Effects of different crystal faces on the surface
431 charge of colloidal goethite (α -FeOOH) particles: An experimental and
432 modeling study. *Geochim. Cosmochim. Acta* **2003**, *67* (5), 967–983.
- 433 (15) Hiemstra, T.; Barnett, M. O.; van Riemsdijk, W. H. Interaction of silicic acid
434 with goethite. *J. Colloid Interface Sci.* **2007**, *310* (1), 8–17.

- 435 (16) Boily, J. F.; Sjöberg, S.; Persson, P. Structures and stabilities of Cd(II) and
436 Cd(II)-phthalate complexes at the goethite/water interface. *Geochim.*
437 *Cosmochim. Acta* **2005**, *69* (13), 3219–3235.
- 438 (17) Hanna, K.; Boily, J.-F. Sorption of two naphthoic acids to goethite surface under
439 flow through conditions. *Environ. Sci. Technol.* **2010**, *44* (23), 8863–8869.
- 440 (18) Paul, T.; Machesky, M. L.; Strathmann, T. J. Surface complexation of the
441 zwitterionic fluoroquinolone antibiotic ofloxacin to nano-anatase TiO₂
442 photocatalyst surfaces. *Environ. Sci. Technol.* **2012**, *46* (21), 11896–11904.
- 443 (19) Paul, T.; Liu, J.; Machesky, M. L.; Strathmann, T. J. Adsorption of zwitterionic
444 fluoroquinolone antibacterials to goethite: A charge distribution-multisite
445 complexation model. *J. Colloid Interface Sci.* **2014**, *428*, 63–72.
- 446 (20) Mazeina, L.; Navrotsky, A. Surface Enthalpy of Goethite. *Clays Clay Miner.*
447 **2005**, *53* (2), 113–122.
- 448 (21) Schwertmann, U.; Taylor, R. M. Iron oxides. Pp. 379-438 in: Minerals in Soil
449 Environments (JB Dixon and SB Weed, editors). *Soil Sci. Soc. Am. Madison,*
450 *Wisconsin, USA* **1989**.
- 451 (22) Clervil, E.; Usman, M.; Emmanuel, E.; Chatain, V.; Hanna, K. Sorption of
452 nalidixic acid onto sediments under batch and dynamic flow conditions. *Chem.*
453 *Geol.* **2013**, *335*, 63–74.
- 454 (23) Parkhurst, D. L.; Appelo, C. A. J.; others. User's guide to PHREEQC (Version
455 2): A computer program for speciation, batch-reaction, one-dimensional
456 transport, and inverse geochemical calculations. **1999**.

- 457 (24) Ross, D. L.; Riley, C. M. Aqueous solubilities of some variously substituted
458 quinolone antimicrobials. *Int. J. Pharm.* **1990**, *63* (3), 237–250.
- 459 (25) Takács-Novák, K.; Tam, K. Y. Multiwavelength spectrophotometric
460 determination of acid dissociation constants: Part V: microconstants and
461 tautomeric ratios of diprotic amphoteric drugs. *J. Pharm. Biomed. Anal.* **2000**,
462 *21* (6), 1171–1182.
- 463 (26) Hanna, K.; Martin, S.; Quilès, F.; Boily, J.-F. Sorption of Phthalic Acid at
464 Goethite Surfaces under Flow-Through Conditions. *Langmuir* **2014**, *30* (23),
465 6800–6807.
- 466 (27) Boily, J.-F. Water structure and hydrogen bonding at goethite/water interfaces:
467 Implications for proton affinities. *J. Phys. Chem. C* **2012**, *116* (7), 4714–4724.
- 468 (28) Venema, P.; Hiemstra, T.; van Riemsdijk, W. H. Multisite adsorption of
469 cadmium on goethite. *J. Colloid Interface Sci.* **1996**, *183* (2), 515–527.
- 470 (29) Marsac, R.; Martin, S.; Boily, J.-F.; Hanna, K. Oxolinic acid binding at goethite
471 and akaganéite surfaces: implications for aquaculture-induced pollution.
472 *Environ. Sci. Technol.* **2016**, *50* (2), 660–668.
- 473 (30) Boily, J.-F.; Persson, P.; Sjöberg, S. Benzenecarboxylate surface complexation
474 at the goethite (α -FeOOH)/water interface: II. Linking IR spectroscopic
475 observations to mechanistic surface complexation models for phthalate,
476 trimellitate, and pyromellitate. *Geochim. Cosmochim. Acta* **2000**, *64* (20),
477 3453–3470.
- 478 (31) Kinniburgh, D.; Cooper, D. PhreePlot: Creating graphical output with

- 479 PHREEQC. <http://www.phreeplot.org>. **2011**.
- 480 (32) Powell, M. J. D. A Method for Minimizing a Sum of Squares of Non-Linear
481 Functions Without Calculating Derivatives. *Comput. J.* **1965**, *7* (1), 303–307.
- 482 (33) Lützenkirchen, J.; Marsac, R.; Kulik, D. A.; Payne, T. E.; Xue, Z.; Orsetti, S.;
483 Haderlein, S. B. Treatment of multi-dentate surface complexes and diffuse layer
484 implementation in various speciation codes. *Appl. Geochemistry* **2015**, *55*,
485 128–137.
- 486 (34) Wang, Z. M.; Giammar, D. E. Mass Action Expressions for Bidentate
487 Adsorption in Surface Complexation Modeling: Theory and Practice. *Environ.*
488 *Sci. Technol.* **2013**, *47* (9), 3982–3996.
- 489 (35) Norén, K.; Persson, P. Adsorption of monocarboxylates at the water/goethite
490 interface: The importance of hydrogen bonding. *Geochim. Cosmochim. Acta*
491 **2007**, *71* (23), 5717–5730.
- 492 (36) Gu, C.; Karthikeyan, K. G. Sorption of the antimicrobial ciprofloxacin to
493 aluminum and iron hydrous oxides. *Environ. Sci. Technol.* **2005**, *39* (23),
494 9166–9173.
- 495 (37) Boily, J. F.; Kozin, P. A. Particle morphological and roughness controls on
496 mineral surface charge development. *Geochim. Cosmochim. Acta* **2014**, *141*,
497 567–578.
- 498 (38) Gu, X.; Tan, Y.; Tong, F.; Gu, C. Surface complexation modeling of
499 coadsorption of antibiotic ciprofloxacin and Cu (II) and onto goethite surfaces.
500 *Chem. Eng. J.* **2015**, *269*, 113–120.

- 501 (39) Rahnemaie, R.; Hiemstra, T.; Van Riemsdijk, W. H. Geometry, charge
502 distribution, and surface speciation of phosphate on goethite. *Langmuir* **2007**, *23*
503 (7), 3680–3689.
- 504 (40) Jaumot, J.; Gargallo, R.; de Juan, A.; Tauler, R. A graphical user-friendly
505 interface for MCR-ALS: a new tool for multivariate curve resolution in
506 MATLAB. *Chemom. Intell. Lab. Syst.* **2005**, *76* (1), 101–110.
- 507 (41) Schwarzenbach, R. P.; Escher, B. I.; Fenner, K.; Hofstetter, T. B.; Johnson, C. A.;
508 von Gunten, U.; Wehrli, B. The challenge of micropollutants in aquatic systems.
509 *Science* **2006**, *313* (5790), 1072–1077.
- 510
- 511

512 **Table 1. Model parameters.**

	Complex	log K	Δz_0	Δz_1	Δz_2
$\text{NA}^- + \text{H}^+ = \text{NAH}$		6.19			
$\text{NFA}^- + \text{H}^+ = \text{NFAH}$		5.10			
$\text{NFAH} + \text{H}^+ = \text{NFAH}_2^+$		2.28			
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{H}^+ \rightleftharpoons \equiv\text{Fe}_3\text{OH}^{+0.5}$		9.1	+1	0	0
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{H}^+ + \text{Cl}^- \rightleftharpoons \equiv\text{Fe}_3\text{OH}_2^{+0.5}\cdots\text{Cl}^-$		8.1	+1	0	-1
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{Na}^+ \rightleftharpoons \equiv\text{Fe}_3\text{OH}^{-0.5}\cdots\text{Na}^+$		-1	0	0	+1
$\equiv\text{FeOH}^{-0.5} + \text{H}^+ \rightleftharpoons \equiv\text{FeOH}_2^{+0.5}$		9.1	+1	0	0
$\equiv\text{FeOH}^{-0.5} + \text{H}^+ + \text{Cl}^- \rightleftharpoons \equiv\text{FeOH}_2^{+0.5}\cdots\text{Cl}^-$		8.1	+1	0	-1
$\equiv\text{FeOH}^{-0.5} + \text{Na}^+ \rightleftharpoons \equiv\text{FeOH}^{-0.5}\cdots\text{Na}^+$		-1	0	0	+1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 + 2 \text{H}_2\text{O}$	MB	19.7±0.1	+1	0	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-$	HB	20.0±0.1	+2	-1	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-$	OS	20.8±0.1	+2	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + 2 \text{NA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 \cdots \text{NA}^-$	dimer	22.2±0.1	+1	-1	0
$3 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFAH}$	HBH	27.0±0.1	+2	0	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFA}^-$	OS	19.9±0.1	+2	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- + \text{Na}^+ \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFA}^-\cdots\text{Na}^+$	HB-Na	20.8±0.1	+2	-1	+1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 \cdots \text{NFA}^-$	MB-OS	23.2±0.2	+1	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\cdots\text{NFA}^-$	HB-OS	23.2±0.2	+2	-1	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\cdots\text{NFA}^-$	OS-OS	25.4±0.2	+2	0	-2
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- + \text{Na}^+ \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\text{NFA}^-\cdots\text{Na}^+$	HB-HB-Na	26.3±0.2	+2	-2	+1

513

514 TPM with $C_1=2.3 \text{ F/m}^2$, $C_2=1.07 \text{ F/m}^2$; 63% of (101), 27% of (001) and 10% of (210). Site
515 densities: $[\equiv\text{FeOH}^{-0.5}]=3.03$, 3.34 and 7.4 site/nm² at the (101), (001) and (210) planes,
516 respectively; $[\equiv\text{Fe}_3\text{O}^{-0.5}]=3.03$ and 3.34 site/nm² at the (101) and (001) planes, respectively. HB,
517 OS and binary NA-NFA complexes are considered to form at all planes ((101)/(001)/(210)). NA
518 and NFA surface complexation constants and uncertainty obtained with Phreeplot. All other
519 parameters were fixed.

520

521 **Figure captions**

522

523 **Figure 1.** Single systems. Adsorption of 20 μM (a) NA and (b) NFA to goethite (0.5
524 g/L) versus pH and $[\text{NaCl}]$ (3-100 mM). (c) Adsorption of 20 μM NA or NFA (20 μM)
525 on goethite (0.5 g/L) versus $[\text{NaCl}]$ at pH 5. (d) NA-goethite and NFA-goethite
526 adsorption isotherms at pH 6 in 10 mM NaCl, where NA surface speciation is shown
527 (“total” refers to overall modeled adsorption results). In all graphs, full lines correspond
528 to overall adsorption predicted by surface complexation modeling. In (a) and (b) NA
529 and NFA surface speciation is shown as discontinuous lines (for 10 mM NaCl). MB,
530 HB and OS denote metal-bonded, hydrogen-bonded and outer-sphere complexes,
531 respectively.

532

533 **Figure 2.** Binary NA-NFA system. Adsorption of (a) NA and (b) NFA to goethite (0.5
534 g/L) versus pH and $[\text{NaCl}]$ (3-300 mM) for $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20 \mu\text{M}$. (c) NA and
535 NFA adsorption isotherms at pH 6 in 10 mM NaCl for $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}}$. (d) $[\text{NFA}]_{\text{ads}}$
536 vs $[\text{NA}]_{\text{ads}}$ for three experimental conditions: (i) ($[\text{NFA}]_{\text{tot}} = 20 \mu\text{M}$, varying $[\text{NA}]_{\text{tot}}$,
537 black), (ii) ($[\text{NA}]_{\text{tot}} = 20 \mu\text{M}$, varying $[\text{NFA}]_{\text{tot}}$, red), and (iii) varying both compounds
538 with $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}}$ (blue). (e) Adsorption of NA and NFA ($[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20$
539 μM) on goethite (0.5 g/L) versus $[\text{NaCl}]$ at pH 5. In all graphs, full lines correspond to
540 overall adsorption predicted by surface complexation modeling (using the same color
541 as the corresponding symbol). In (a), (b) and (c) NA and NFA surface speciation is
542 shown as discontinuous lines (for 10 mM NaCl). “total” refers to overall modeled
543 adsorption results in (c). (f) Concentration profiles extracted by chemometric modeling
544 of FTIR data⁸ for the series corresponding to constant $[\text{NA}]_{\text{tot}}$ and varying $[\text{NFA}]_{\text{tot}}$
545 (black) or constant $[\text{NFA}]_{\text{tot}}$ and varying $[\text{NA}]_{\text{tot}}$ (red).

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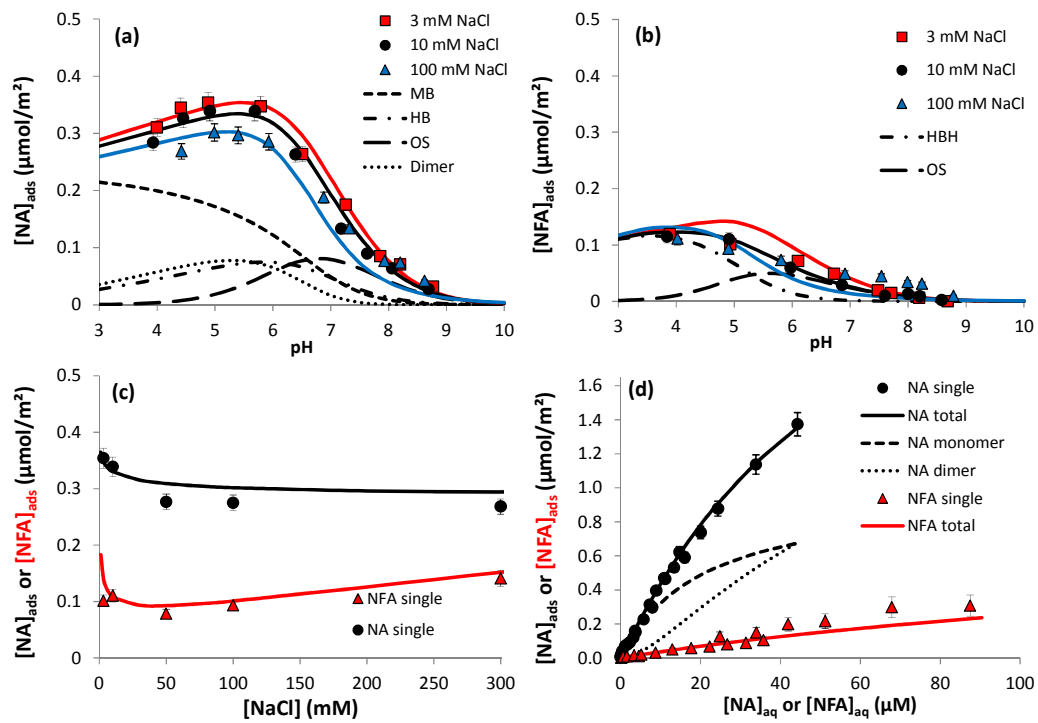
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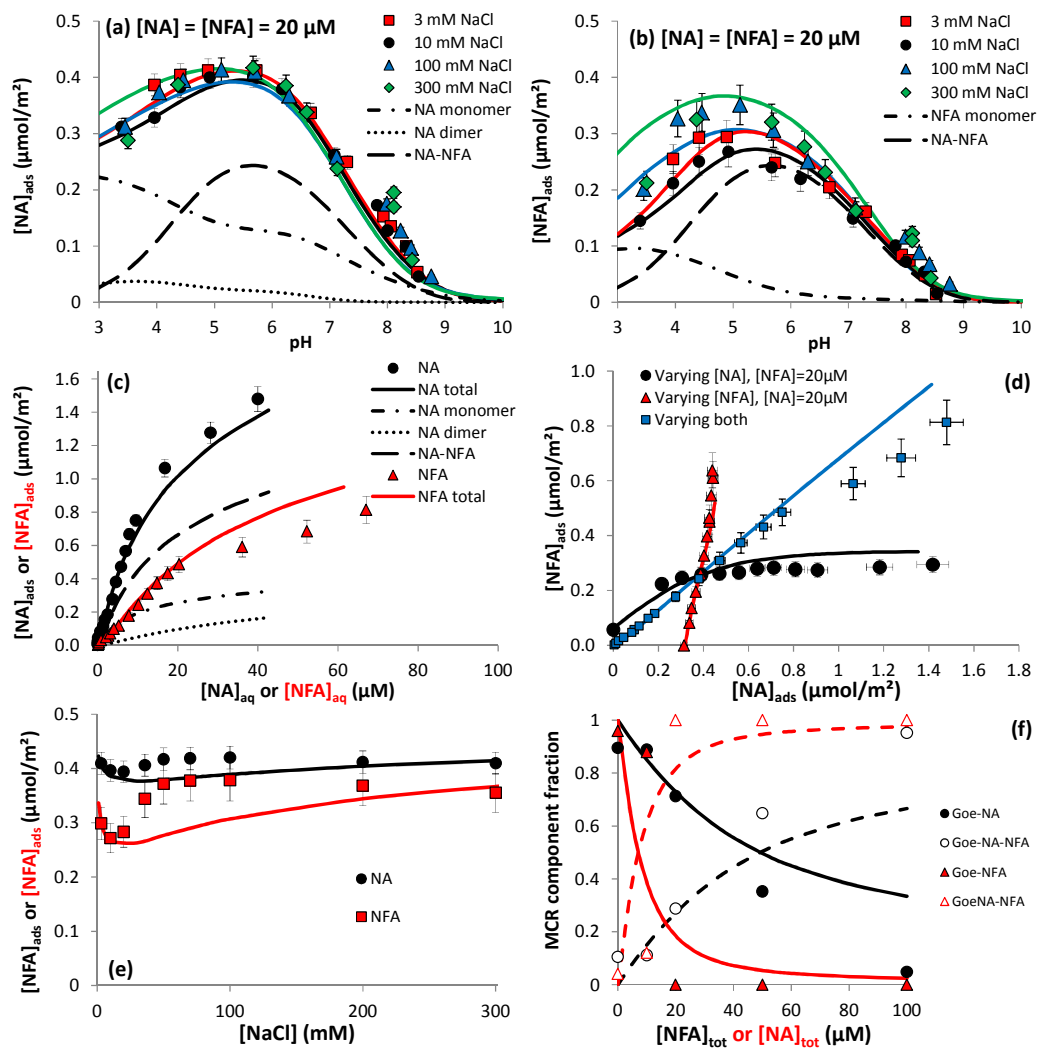
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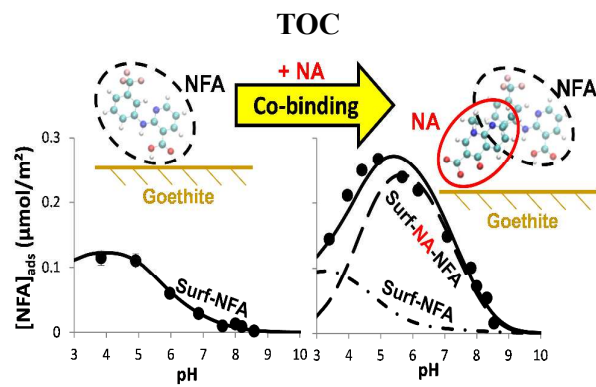
Figure 1



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Figure 2

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