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Fluoroquinolones and their complexes with metal ions, studied with density functional theory

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Fluoroquinolone antibiotics might lead to severe side effects, collectively known as fluoroquinolone-associated disability (FQAD). The origin of this phenomenon is unknown, but has been suggested to involve chelation of biologically important ions such as Fe^{3+}. In this study, DFT calculations were used to estimate the Gibbs energies of binding of biologically-relevant ions (Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{3+} and Zn^{2+}) to ciprofloxacin, a prototype of fluoroquinolone antibiotics. The results show preferable binding of Fe^{3+} to ciprofloxacin, with binding affinity that is over 50 kcal mol^{-1}. The binding of the ions to ciptofloxacin is compared to their binding to tetracycline, a metal binding antibiotic that is not a fluoroquinolone. The affinity of Fe^{3+} and most other ions to tetracycline was found to be even higher, which leads to the conclusion that ion binding is not the cause for FQAD. Overall, this study demonstrates the usability of a computational-chemistry based approach to a problem within biomedicine. Methodological and structural aspects of the binding are also discussed.

1. Introduction

Quinolone antibiotics have been used to treat bacterial infections since the 1960s and work by inhibition of bacterial topoisomerases.[1] The incorporation of a flour atom into the pharmacophore has led to more active compounds (advanced generation quinolones) and the quinolones that are in use today are hence fluoroquinolones (FQ).[2] These antibiotics have broad range and many are bioavailable. Hence, they are used to treat many different infections.[3] Structural studies reveal binding to the target enzymes through multitude of interactions, including chelation of an Mg^{2+} ion.

After decades of use, reports of serious and persistent adverse effects following use of FQ have gathered the attention of clinicians. Such severe side effects including weakness, reduced balanced and even psychiatric disorders were verified in an animal model and the term ''FQ-associated disability'', FQAD, was coined to describe them.[4] The use of FQ has since been reduced, but they are still necessary when other antibiotics are insufficient (*e.g.* due to resistance). Thus, there is an urgent need to understand the causes of FQAD and identify useful treatment.

While the molecular mechanism that underlies FQAD is not understood, metal-ion chelation by the drugs has been suggested to play an important, perhaps crucial factor.[5] FQ can chelate many different multivalent ions.[6,7] The chelation of Fe^{3+} appears to be fundamental in this respect. Physiologically relevant concentrations of FQ were enough to reduce the activity of several iron-dependent enzymes.[8] In addition, some of the observed side effects can be related to chelation of other ions, such Mg^{2+} and Zn^{2+}.[5]

Supplementation with essential metal cofactors is one suggested route to treat FQAD, but to support this further research should show that the chelation of ions is indeed important.[5] For this reason, it is important to quantify the affinity of the ions to the drugs. While there are several experimental methods to measure the stability constants between FQ and metals, experimental setups vary which affect the results. A robust theoretical approach is therefore needed which will infer on the binding energies and atomistic interactions involved in ion chelation by FQ. This is the aim of this study. In many previous studies, DFT calculations were used to study ion chelation and for discrimination between ions (*e.g.* ref. 9–11).

Since most FQ have a common skeleton and two titratable groups, one basic and one acidic, it can be expected that differences with respect to ion chelations will be minimal. Here, ciprofloxacin is used as a prototype of FQ since it is a widely used antibiotic with a relatively simple structure. The complexion of ciprofloxacin with the biologically relevant metal ions Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{3+} and Zn^{2+} was studied employing a computational approach. The results shed light on the structural and energetic features associated with ion chelation by FQ. Finally, ion complexes formed with tetracycline are also studied since tetracyclines are known for their ability to chelate metal ions but do not lead to similar disabilities as FQ.

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2. Theory

2.1. Calculations in implicit solvent

The binding energy ΔG^{b} between an ion and n ligand molecules is calculated as:

$$\Delta G^{b} = G^{\circ}(\text{complex}) - [nG^{\circ}(\text{ligand}) + G^{\circ}(\text{ion})] \quad (1)$$

here, $G^{\circ}()$ refers to the standard Gibbs energy of a molecule or an ion in water, and includes the internal energy of each species and the energy involved in its solvation. In practice, G°(complex) and G°(ligand) are approximated by calculating the value of the energy with DFT in a continuum solvent model. Since such models are inaccurate for many atomistic ions,[12,13] G° (ion) is estimated as:

$$G^{\circ}(\text{ion}) = E(\text{ion}) + \Delta G^{\circ}_{\text{hyd}}(\text{ion}) \quad (2)$$

$\Delta G^{\circ}_{\text{hyd}}$ is the hydration energy of the ion, *i.e.* the energy that is required to transfer an ion from the gas phase (standard state at p = 1 bar) to the solvent (standard state at C = 1 M). Experimental energies, as given in ref. 14 are used here, to which a correction, $\Delta G^{\circ}_{\text{corr}}$ was added:

$$\Delta G^{\circ}_{\text{corr}} = RT\ln\left(V^{0}/V\right) \quad (3)$$

The value of $\Delta G^{\circ}_{\text{corr}}$ is 1.89 kcal mol^{-1} and its addition was needed since the values in ref. 14 refer to the solvent standard state (1 M concentration) rather than the standard state in the gas phase (1 bar pressure).

2.2. Calculations with explicit solvent

Implicit solvent models are highly useful in chemistry, but are not always able to capture all the contributions from the solvent correctly. This calls for the use of explicit solvent, *i.e.* modelling the water molecules explicitly. It is not possible to calculate the binding energy in the same way in explicit solvent, since this would require considering the room temperature dynamics of many water molecules. Realising that the solvent molecules are more important for correctly modelling the hydration of the metal ion (where the charge is concentrated on a single atom) not the ligand (where the charge is delocalised), a mixed model was used here. Consequently, six water molecules were studied in addition to the ion, and implicit solvent is still used. Using even more water molecules makes the problem at hand almost intractable, since there can be multiple minima on the potential energy surface and the additional water molecules do not necessarily making the approximation of the structures and energy more realistic. With this set-up, eqn (1) is replaced by:

$$\Delta G^{b} = G^{\circ}(\text{complex}\cdot(H_2O)_6) - [nG^{\circ}(\text{ligand}) + G^{\circ}(\text{ion}\cdot(H_2O)_6)] \quad (4)$$

Since the hydrated ion complexes are much larger in any case, the exact radius of the ion as used to build the cavity in implicit solvent is of lesser important, and the energies in the right-hand side of eqn (4) can be calculated directly from DFT.

Although two water molecules are enough to complete the hydration shell of the ions in their bound state, six were used in the calculations to allow for fully hydrated ions as reference.

2.3. Ion speciation

Fe and Mn exist in the body in both divalent and trivalent states, however, in both cases one form is dominant and was studied here. For Mn, this was the Mn^{2+} ion. For Fe, Fe^{3+} was used, because it is the form that exist in physiological pH.[15] Fe^{3+} was modelled as is, *i.e.* Fe^{3+} or $[Fe\cdot(H_2O)_6]^{3+}$ rather than $[FeOH]^{2+}$ or $[Fe(OH)(H_2O)_4\text{-}(H_3O)]^{3+}$. This is because the hexa-hydrated species was found to be more stable (using the same level of theory as in the calculations of ΔG^{b}). In an aqueous environment, the excess proton would quickly diffuse thereafter leaving $[Fe(OH)(H_2O)_5]^{2+}$. However, modelling the speciation of the ion in full complexity would require a much larger number of solvent molecules and would not enable the use of accurate quantum mechanical (QM) methods.

3. Computational methods

DFT calculations were performed with ORCA,[16,17] version 6.1.0.[18] Geometry optimisations were performed employing the ωB97-3c composite method[19] in implicit solvent (modelled by SMD[20]). Convergence to minimum energy was verified by calculating the vibration frequencies and ensuring that none of them was negative. Unless otherwise stated, the energy was thereafter calculated with the ωB97M-V functional[21] and the def2-TZVPP basis set.[22] *I.e.* the calculations employed the ωB97M-V(SMD)/def2-TZVPP//ωB97X-3C(SMD) setting. Zero point energy (ZPE) corrections to the energy were calculated at 298 K using the ωB97X-3C(SMD) method.

Ciprofloxacin was modelled in its zwitterionic state which is dominant in physiological pH. Tetracycline was modelled in its negatively charged, base state (with two negative and one positive charge, yielding formal charge of −1). The molecule's basic group pK_a = 9.6 and most acidic group (pK_a = 3.3) are charged over a wide range of pH values. Its second acidic group has pK_a of 7.8, meaning that some of the molecules will be charged at physiological pH. Because the neutral state is favoured, the binding affinity for tetracycline was shifted by 1.06 kcal mol^{-1} which corresponds to the distribution of neutral and charged species:

$$\Delta G^{\text{pH}_{\text{corr}}} = RT\ln\left(10^{\text{p}K_a\ -\ \text{pH}}\right).$$

Transition metal ions (Mn^{2+} and Fe^{3+}) where modelled in their high spin state that was found to be more stable in complexes with the water and drugs using the same level of theory as reported above, except for Mn^{2+} with tetracycline where the energy of the complex was slightly lower when Mn^{2+} adopted a lower spin (quartet) state.

4. Results

4.1. Models with implicit solvent

Ciprofloxacin and its coordination with the various metal ions were first studied with a fully implicit solvent model. While

such models are simpler and might be less accurate, they alleviate the need to consider the explicit placement of water molecules that can quantitatively modify the results. The coordination of the ion is considered first, followed by binding energies.

4.1.1. Ion coordination in ciprofloxacin : metal 1 : 1 complexes. Three atoms in FQ can coordinate with the metal ions, namely two carboxylate and one keto oxygen. Given the zwitterionic form of these molecules in physiological conditions, there will be a negative charge distributed between those oxygens and the ions are expect to bind two of them, as shown in Fig. 1A and B. All complexes are more stable when the oxidised ring oxygen participates in the coordination, as in Fig. 1A (Table S1).

Binding energies, ion–oxygen distances and oxygen–ion–oxygen angles for the complexes are given in Table 1. These calculations show favourable binding of Mg^{2+}, Mn^{2+} and Fe^{3+} but only by few kcal mol^{-1}. The interaction between Ca^{2+} and Zn^{2+} and the drug is repulsive. Mg^{2+}, Ca^{2+} and Zn^{2+} are hard ions with filled electronic shells; the small size of Mg^{2+} however makes it fit well between the oxygens. Zn^{2+} can also be close to the oxygen atoms but the filled d-shell makes repulsive interactions with the oxygens, making the O–ion–O angle larger and opposes binding. The transitions metals Mn^{2+} and Fe^{3+} bind the drug but not strongly as mentioned. Binding energy calculations in implicit solvent are Gibbs (free) energies, since the solvent contributions are approximated as solvation free energies. However, ZPE corrections are normally considered to be useful and were included here. It is worth mentioning that if ZPE are not considered, binding energies are almost the same except that the binding energies for Mn^{2+} and Fe^{3+} become slightly positive (Table S2).

4.1.2 The multicharged ions bind much better in ciprofloxacin : metal 2 : 1 complexes. Models of ciprofloxacin complexation with metals suggest that the metal binds with multiple drug molecules (*e.g.* ref. 23). Indeed, using two molecules of the drug instead of one resulted in favourable binding for all ions (Table 2). The binding (Fig. 2) was most favourable for Fe^{3+}, with $\Delta G^b = -73.4$ kcal mol^{-1} and least for Ca^{2+}. The formation of a larger complex decreases the degrees of freedom within each ciprofloxacin molecule, which led to a significant contribution of ZPE opposing binding (Table S3, average ZPE contribution 16.6 kcal mol^{-1}). The structures of the complexes had C_2 symmetry. The ions bound in a distorted tetrahedral coordination, leaving room for two extra waters. Structural details are given in Table 2. Ion–oxygen distances are ~2.0 Å, except in complex with Ca^{2+} where they are much larger and with Fe^{3+} where they are <1.9 Å. O–ion–O angles are similar except with Ca^{2+}. Most notably, the O_C–ion–O_C angle is close to 180° with Ca^{2+} compared to ~120° with the other ions. This is because Ca^{2+} binds more weakly to the drugs, and as a consequence the charged carboxylate oxygens that bind it avoid one another. The O_C–O_C and O_K–O_K distances are similar to each other in every complex, except for the complex with Ca^{2+} where the O_C–O_C distance is larger.

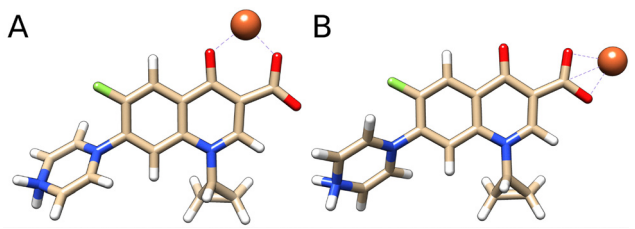

Fig. 1 Possible placements of a metal ion that interacts with a single ciprofloxacin molecule. Optimised structures are shown with Fe^{3+}.

Table 1 Binding energies, ion–oxygen distances and oxygen–ion–oxygen angles in 1 : 1 ciprofloxacin : metal complexes. d(ion–O_C) is the distance to the coordinating carboxylate oxygen and d(ion–O_K) is the distance to the keto oxygen. In this and the following tables energies are in kcal mol^{-1}, distances are in Å and angles are in degrees

Ion	ΔG^b	d(ion–O_C)	d(ion–O_K)	∠O–ion–O
Mg^{2+}	−5.6	1.95	1.93	93.6
Ca^{2+}	6.5	2.22	2.19	78.7
Mn^{2+}	−1.5	1.97	1.95	93.4
Fe^{3+}	−0.7	1.91	1.88	95.9
Zn^{2+}	17.1	1.86	1.84	108.0

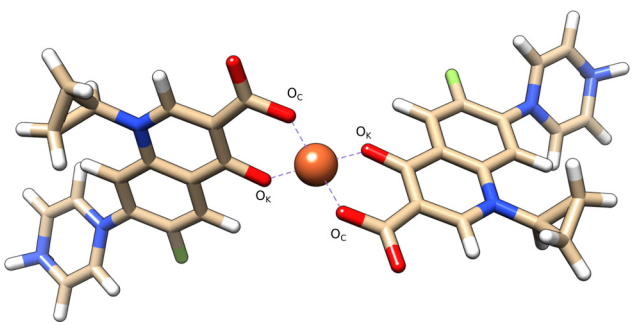

Fig. 2 The optimised ciprofloxacin$_2$$Fe^{3+}$ complex. The marks O_C and O_K refer to the carboxylate and keto oxygens.

Table 2 Binding energies, ion–oxygen distances and oxygen–ion–oxygen angles in 2 : 1 ciprofloxacin : metal complexes. O_K = keto oxygen, O_C = carboxylate oxygen. The notations 'same' and 'other' refer to the oxygens being on the same molecule or not

		Angles							
Ion	ΔG^b	d(ion–O_K)	d(ion–O_C)	O_K–ion–O_C, same	O_K–ion–O_C, other	O_K–ion–O_K	O_C–ion–O_C	d(O_K–O_K)	d(O_C–O_C)
Mg^{2+}	−42.4	1.98	1.96	90.9	118.1	122.1	119.7	3.46	3.38
Ca^{2+}	−24.9	2.28	2.26	76.7	106.8	115.3	173.8	3.85	4.53
Mn^{2+}	−45.2	2.05	2.02	88.6	118.7	122.0	124.0	3.58	3.57
Fe^{3+}	−73.4	1.88	1.87	95.1	115.5	119.5	117.8	3.25	3.19
Zn^{2+}	−45.0	1.95	1.93	95.6	115.7	115.5	120.2	3.30	3.35

4.2. Models with implicit and explicit solvent

4.2.1. Ion coordination in ciprofloxacin : metal : water 1 : 1 : 6 complexes. The ions that were studied here all adopt six-coordinated octahedral structures in water. When optimised with water molecules in the vicinity of the ion, complexes were formed were the ion was ligated by two oxygens of ciprofloxacin and 4–5 water molecules, with the additional waters forming a second shell, Fig. 3. The complexes with Mg^{2+} and Zn^{2+} had coordination number (CN) of 6 and an octahedral arrangement. Ca^{2+} and Fe^{3+} complexes, with CN = 7 adopted pentagonal bi-pyramidal geometries, that were closer to an ideal arrangement with Ca^{2+}. Finally, the complex with Mn^{2+} was in a capped octahedral arrangement.

Examination of the binding energies (Table 3) reveals favourable binding for all ions, with a strong preference for Fe^{3+}, ΔG^{b} = −20.9. Mn^{2+} bound with the least favourable Gibbs energy. The distances to the nearest oxygens of ciprofloxacin were ∼2 Å for Mg^{2+}, Fe^{3+} and Zn^{2+} and larger for Mn^{2+} and Ca^{2+}. Distances were larger in comparison to the implicit-ion structures (Table 1).

4.2.2 Ion coordination in ciprofloxacin : metal : water 2 : 1 : 6 complexes. With two ciprofloxacin molecules, all ions bound in an octahedral conformation (Fig. 4). As in all previous calculations, binding was most favourable with Fe^{3+}. Surprisingly, Zn^{2+} showed repulsive interactions with the two drug molecules and the water, indicating that the ion will only bind one residue. The deviation in distances between pairs of similar oxygen atoms and Zn^{2+} was the largest among all ions and the octahedral coordination with Zn^{2+} was much distorted. The increased binding affinity upon incorporation of the second ciprofloxacin molecule was even larger than with the first one for Mn^{2+} and Fe^{3+} but not for Mg^{2+} and Ca^{2+}.

Table 3 Binding energies, ion–oxygen distances, oxygen–ion–oxygen angles, coordination numbers and geometries in 1 : 1 : 6 ciprofloxacin : metal : water complexes. d(ion–O_C) is the distance to the coordinating carboxylate oxygen and d(ion–O_K) is the distance to the keto oxygen. In this and the following tables energies are in kcal mol^{-1}, distances are in Å and angles are in degrees. Oh = octagedral, B-Py = bipyramidal, C-Oh = capped octahedral

Ion	ΔG^{b}	d(ion–O_K)	d(ion–O_C)	∠O–ion–O	CN	Geometry
Mg^{2+}	−9.7	2.06	2.01	86.8	6	Oh
Ca^{2+}	−9.3	2.40	2.34	72.2	7	B-Py
Mn^{2+}	−6.4	2.21	2.10	81.7	7	C-Oh
Fe^{3+}	−20.9	2.02	1.91	87.8	7	B-Py
Zn^{2+}	−13.6	2.04	2.00	89.8	6	Oh

4.2.3. Complexes with three ciprofloxacin molecules. Some studies, *e.g.* ref. 6, 23 and 24 suggest that ions can coordinate even three ciprofloxacin molecules. Indeed, It was possible to obtain optimised structures of 3 : 1 : 6 ciprofloxacin : ion : water complexes (Fig. S1). However, calculations of the binding energies for these complexes showed highly unfavourable interactions.

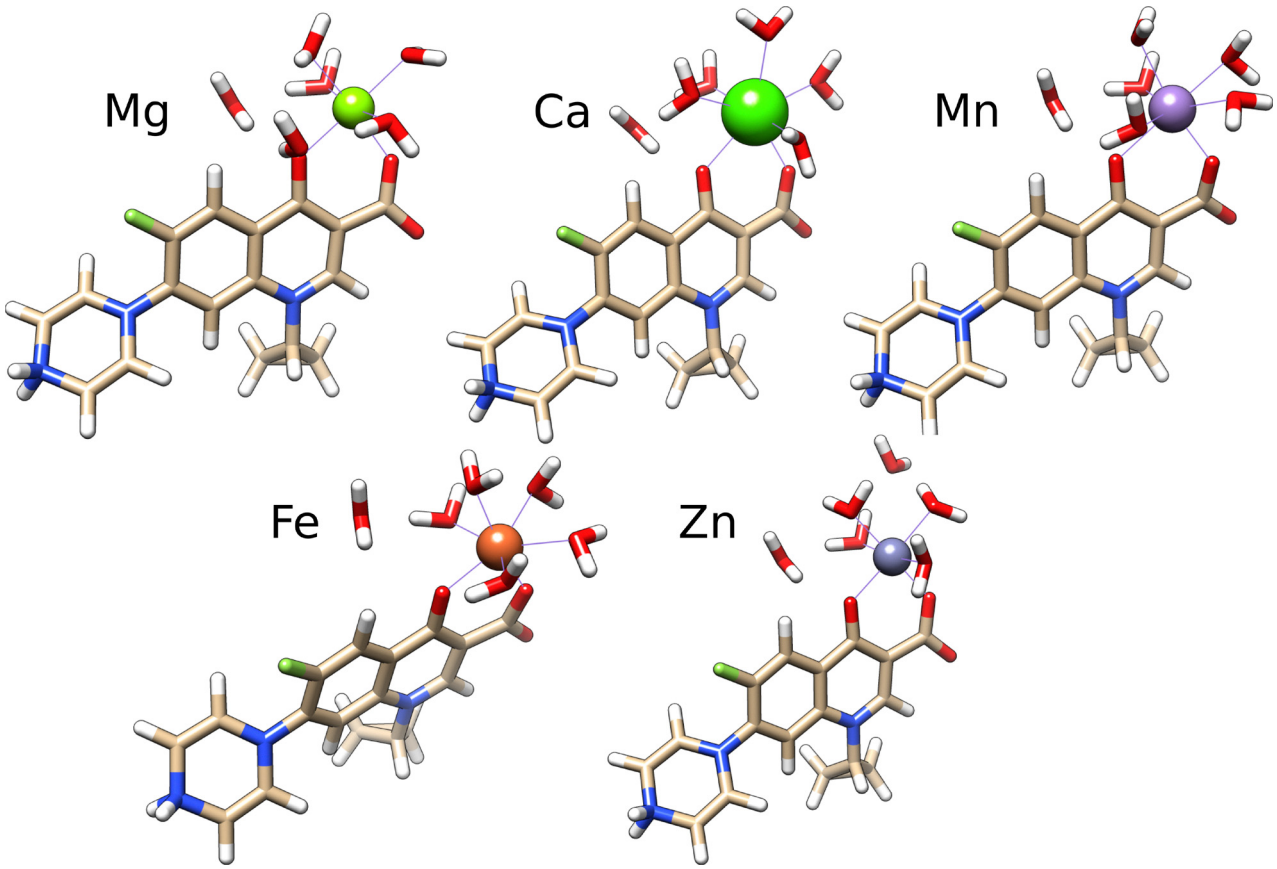

Fig. 3 Optimised structures of complexes between ciprofloxacin and the various ions, optimised with six water molecules at the ion binding site.

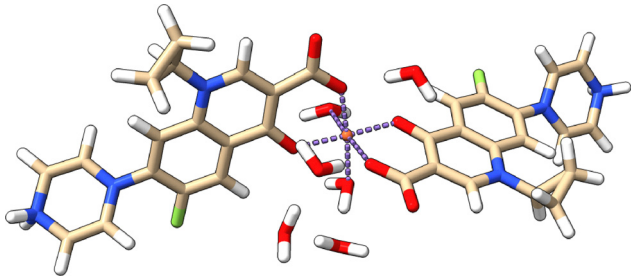

Fig. 4 The optimised structures of the complexe between two ciprofloxacin molecules and Fe^{3+}, optimised with six water molecules at the ion binding site. The structures of such complexes were similar for all ions.

4.2.4. Comparing ciprofloxacin with tetracycline. So far, the calculations reveal that ciprofloxacin strongly binds to ions that are common and important in human physiology, with clear preference for binding Fe^{3+}. While not causing similar disabilities, tetracycline antibiotics are also known for their ability to bind metal ions.[25–27] Thus, it was interesting to compare the binding of tetracycline to the ions. Since tetracyclines were not the focus of this study, only 2 : 1 : 6 drug : ion : water complexes were studied. These complexes were octahedral though slightly deformed (Fig. 5) with all ions, and involved four oxygens from the two drug molecules and two water molecules. Binding energies (Table 5) were favourable for all ions except Mn^{2+}. For all other ions, ΔG^b indicated a higher affinity for tetracycline.

5. Discussion

5.1. Explicit *versus* implicit solvent in calculations of the metal binding affinities

Calculations of absolute (rather than relative) binding energies are known to be challenging and consideration of the modelled reaction is of high importance. Here, these calculations were carried out in implicit solvent, while considering the ion's solvation shell in explicit or implicit terms. As will be outlined below, the calculations suggest that the use of combined explicit/implicit solvation leads to better results.

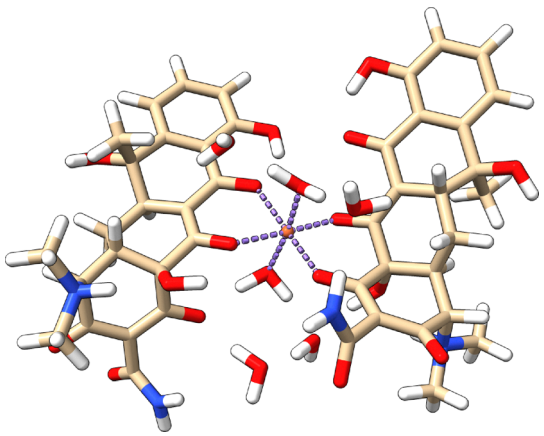

Fig. 5 The optimised structures of the complexe between two tetracycline molecules and Fe^{3+}, optimised with six water molecules at the ion binding site. The structures of such complexes were similar for all ions.

Table 4 Binding energies, and ion–oxygen distances in 2 : 1 : 6 ciprofloxacin : metal : water complexes. d(ion–O_C) are the distances to the coordinating carboxylate oxygen, d(ion–O_K) to the keto oxygens and d(ion–OW) to the water oxygens

Ion	ΔG^b	d(ion–O_K)	d(ion–O_C)	d(ion–OW)
Mg^{2+}	−14.6	2.00, 2.00	1.93, 1.95	2.09, 2.09
Ca^{2+}	−14.1	2.36, 2.38	2.31, 2.30	2.42, 2.42
Mn^{2+}	−22.3	2.17, 2.19	2.12, 2.13	2.24, 2.25
Fe^{3+}	−54.7	1.98, 1.98	1.94, 1.95	2.09, 2.12
Zn^{2+}	9.3	1.96, 2.10	2.03, 2.08	2.29, 2.27

Table 5 Binding energies, in 1 : 2 : 6 tetracycline : metal : water complexes

Ion	ΔG^b
Mg^{2+}	−24.3
Ca^{2+}	−24.8
Mn^{2+}	32.3
Fe^{3+}	−60.2
Zn^{2+}	−28.4

In terms of the structure, calculations with a single drug always show that the ion and its O ligands from the drug are on the same plane with the aromatic rings (Fig. 1 and 3). However, by considering the solvation shell, differences in the coordination between the ions become obvious (Fig. 1 and Table 3). It is clear that different ions bind the single drug with different geometries.

In terms of energies, single ion calculations in implicit solvent suggest that ciprofloxacin does not bind Zn^{2+} and Ca^{2+} and barely binds Mn^{2+} and Fe^{3+}, which stands against multiple lines of experimental evidence.[23,28] In contrast, considering the water shell leads to the conclusion that all ions favourably bind to ciprofloxacin at a 1 : 1 stoichiometry. At 2 : 1 stoichiometry, implicit water calculations lead to the conclusions that all of the ions bind to ciprofloxacin (Table 2), whereas the explicit/implicit water reveal that Zn^{2+} would not bind in such case.

Differences in the binding energies in binding to ions (Table 1 compared to Table 3, Table 2 compared to Table 4) are substantial and stem from the contribution of the water molecules to the binding of the ions and the solvation of the drug's oxygens. These are apparently not well captured by the implicit solvent representation, although it works well in many other cases.

5.2. Limitations of the model

Neither experimental nor theoretical studies where binding affinities are estimated are devoid of limitations. Here, the aim was to approximate the binding of drugs to ions that take place under physiological condition in solution while relying on static calculations in implicit solvent. The limitations of the approach are clear. The alternative would be to perform explicit water, out-of-equilibrium simulations such as free energy perturbation or umbrella sampling. Such simulations take into

account the multiple degrees of freedom of the system and multiple configurations. Free energy perturbation (FEP) calculations necessitate the use of a molecular mechanics (MM) forcefield to represent the element that is perturbed (here, the ion), because they involve a transformation between the bound and unbound states. Unfortunately, even if forcefield parameters for the ions included in this study could be obtained, considering change-of-coordination is not modelled correctly with such approach.[29,30] While machine-learning interatomic potentials can be used for FEP[31] this would require the development of potentials that are good enough to model the interactions and geometries as presented which in itself is far from trivial and was hitherto not achieved for such systems. Umbrella sampling calculations can in principle be carried out using quantum mechanical potentials, but the computational cost for systems as modelled here is prohibitive unless very approximate potentials (and small solvation boxes) are used, which would present other limitations.

5.3. Binding to tetracyclines

Similar to ciprofloxacin, the calculations show that all but one ion (Mn^{2+}) form complexes with favourable interaction energies with tetracycline, as a structural representative of tetracycline antibiotics. Experimental studies suggest that tetracycline binds Mn^{2+} under specific experimental conditions (*e.g.* at the present of oxygen[32]). It is likely that Mn^{2+} binds preferably to one molecule of tetracycline rather than two, but since this was not the focus of this study further calculations were not carried out.

5.4. Ion chelation does not seem to be a major mechanism for FQAD

Although the results show that FQ bind very strongly to Fe^{3+}, this study does not support the mechanism by which the chelation of Fe^{3+} leads to FQAD. Tetracycline appear to bind Fe^{3+} with higher affinity than ciprofloxacin, yet this does not lead to any known disabilities. It might be hypothesised that FQ, either complexed by metals or not, bind off-target in some patients for reasons that are currently unknown.

5.5. Ion supplementation might not be a good therapy for FQAD

There is little support for using ion supplements (in the form of Mg- or Ca-salts) as therapy for FQAD following the results presented here. Fe^{3+} and Mn^{2+} should not be used for chelation of FQ due to risk for toxicities. Ca^{2+} and Mg^{2+} have more modest binding affinities, of less than 15 kcal mol^{-1}. Consequently, none of the ions is expected to be an effective chelator of residual FQ in physiological conditions.

6. Conclusions

Accurate calculations of the binding energies of biologically-relevant, multivalent metal ions were performed in order to examine the postulation that FQAD is the result of iron chelation. Consideration of the ions' solvation shell led to more convincing results. While the calculations support strong binding between ciprofloxacin and Fe^{3+}, with ΔG^{b} = −54.7 kcal mol^{-1}, an even stronger binding was shown for tetracycline, which does not lead to similar disabilities in patients. Mg^{2+} and Ca^{2+} show more moderate affinity towards ciprofloxacin which limit their usability as drug chelators *in vivo*.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): Supplementary materials (Tables S1–S3 and Fig. S1) are available in the SI file. Optimised molecular structures are freely available at https://www.doi.org/10.6084/m9.figshare.30515897. See DOI: https://doi.org/10.1039/d5cp04229a.

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