DALTON COMMUNICATION

X-Ray crystal structures of Mg^{2+} and Ca^{2+} dimers of the antibacterial drug norfloxacin

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The hydrothermal reactions of norfloxacin (H-Norf) with $MgCl_2·6H_2O$ and $CaCl_2·6H_2O$ yield two unprecedented dimers containing a direct coordinate bond between H-Norf and a metal $[Mg_2(H_2O)_6(H\text{-}Norf)_2]Cl_4·4H_2O$ 1 and $[Ca_2(Cl)(H\text{-}Norf)_6]Cl_3·10H_2O$ 2.

Many organic compounds used in medicine do not have a purely organic mode of action; some are activated or biotransformed by metal ions, others have a direct or indirect effect on metal ion metabolism.[1,2] Norfloxacin (H-Norf, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid), a quinolone type compound, is a widely used antibacterial drug that targets the bacterial type II DNA topoisomerase (gyrase). Treatment with this drug leads to double-stranded DNA breaks and cell death.[3] The cytotoxicity of the drug is achieved *via* binding strongly to the gyrase–DNA complex in the presence of Mg^{2+}.[4] It is proposed that Mg^{2+} acts as a bridge between the phosphate groups of DNA and the carbonyl and caboxylate moieties of H-Norf,[5] and binding of Mg^{2+} to H-Norf, which is zwitterionic at neutral pH, converts a repulsive negative charge to a positive attractive charge and promotes binding of the drug to DNA.[6] It is also reported that quinolones interact with di- and tri-valent metal ions, and some of the metal complexes formed possess improved water solubility and antibacterial activity.[7] Despite the important role that the divalent metal ions may play in this system, to date, to the best of our knowledge, no structural data for metal-coordinated H-Norf (Chart 1) appear to be available (however,

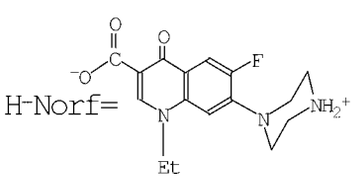

Chart 1

the metal (Cu^{2+} and Ag^{+}) complex crystal structures with related quinolones with a direct coordinate bond between quinolones and a metal ion were reported),[8] although several binding modes of quinolones to Mg^{2+} have been proposed.[9,10] To our surprise, the hydrothermal reactions of H-Norf with $MgCl_2·6H_2O$ and $CaCl_2·6H_2O$ yield two unprecedented dimers $[Mg_2(H_2O)_6(H\text{-}Norf)_2]Cl_4·4H_2O$ **1** and $[Ca_2(Cl)(H\text{-}Norf)_6]Cl_3·10H_2O$ **2**, respectively. Here we report their synthesis and solid state structures which provide a new insight into understanding the mode of action of quinolone type antibiotics and are very important not only for coordination chemists but also for biochemists.

The colorless block crystalline **1** and pale-yellow block crystalline **2** were obtained by the hydrothermal reactions of H-Norf with $MgCl_2·6H_2O$ and $CaCl_2·6H_2O$, respectively.† The IR

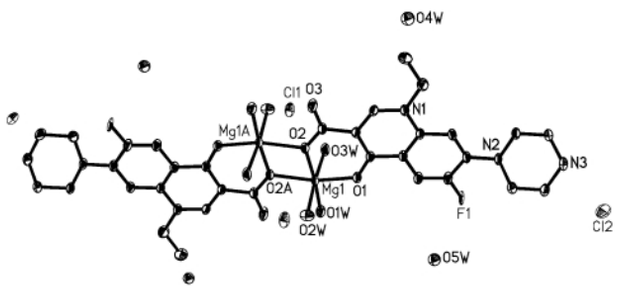

Fig. 1 An ORTEP[13] diagram of $[Mg_2(H_2O)_6(H\text{-}Norf)_2]Cl_4·4H_2O$ **1**. Selected bond lengths (Å) and angles (°): Mg(1)–O(1) 1.997(2), Mg(1)–O(2) 2.084(2), Mg(1)–O(2A) 2.116(2), Mg(1)–O(1W) 2.069(2), Mg(1)–O(2W) 2.059(2), Mg(1)–O(3W) 2.075(2); O(1)–Mg(1)–O(2) 87.18(9), O(1)–Mg(1)–O(2A) 166.91(10).

spectra of both **1** and **2** show two very strong peaks at 1620 and 1489 cm^{-1} for **1** and 1620 and 1490 for **2**, respectively, indicating that the carboxylic acid of H-Norf is deprotonated because of the absence of a medium peak at *ca.* 1700 cm^{-1}, compared to the free H-Norf. The N atom of the piperazine ring is protonated in both **1** and **2** and loses the coordination ability as confirmed by the crystal structure determination (see later).

Fig. 1 shows the crystal structure of a biologically-relevant complex formed between H-Norf and Mg^{2+}, $[Mg_2(H_2O)_6(H\text{-}Norf)_2]Cl_4·4H_2O$ **1**.‡ Complex **1** can be described as a 2:2 dimer in which the two Mg^{2+} ions are bridged by two oxygen atoms from carboxylate groups of the two drug molecules to give rise to a four-membered ring [Mg(1)O(2)Mg(1A)O(2A)]. Each Mg^{2+} is coordinated in an octahedral coordination environment, with the oxygen atom of the quinolone carbonyl and one of the two oxygen atoms in the carboxylate chelating to Mg^{2+} ions, resulting in the formation of a stable six-membered ring. The coordination mode of carboxylate in **1** can be considered as a monodentate bridging type.[11] This structural feature is unexpected and quite different from those proposed previously for Mg^{2+}–quinolone complexes.[5b,10] It has been suggested that quinolone drugs form 2:2 dimer or even higher equimolar drug:Mg^{2+} complexes in solution,[5b,10] however, this appears to be the first structural evidence for such complexes.

Unlike **1**, although **2**, shown in Fig. 2, is also a dimer, the bridging group is a chloride ion rather than a carboxylate oxygen atom. In addition, a higher molar ratio (3) of drug:Ca^{2+} is observed in the reaction system of H-Norf with Ca^{2+} ion. The coordination geometry around each Ca^{2+} ion can best be described as approximately pentagonal bipyramidal in which three H-Norfs act in a bidentate coordination mode through the oxygen atom of the quinolone carbonyl and one of the two oxygen atoms in the carboxylate moiety to chelate Ca^{2+} ions, resulting in the formation of a stable six-membered ring, and chloride ion completes the seven-coordination around the Ca^{2+} ion. The coordination mode of three bulky H-Norfs with Ca^{2+}

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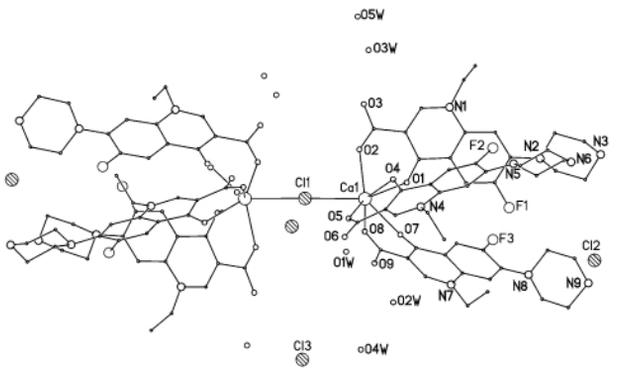

Fig. 2 A perspective view of $[Ca_2(Cl)(H\text{-Norf})_6]Cl_3\cdot 10H_2O$ **2**. Selected bond lengths (Å) and angles (°): Ca(1)–Cl(1) 2.8629(6), Ca(1)–O(1) 2.413(2), Ca(1)–O(2) 2.387(3), Ca(1)–O(4) 2.384(2), Ca(1)–O(5) 2.395(3), Ca(1)–O(7) 2.410(2), Ca(1)–O(8) 2.383(3); O(1)–Ca(1)–O(2) 71.62(9), O(4)–Ca(1)–O(5) 72.06(9), O(7)–Ca(1)–O(8) 72.01(8), O(8)–Ca(1)–Cl(1) 82.86(6), O(2)–Ca(1)–Cl(1) 81.43(7), O(5)–Ca(1)–Cl(1) 80.05(6).

can be considered as a three-fold package if the chloride ion is omitted. Thus, the shape of **2** looks like a molecular dumbbell. Compared to Mg^{2+} in **1**, the larger ionic radius of Ca^{2+} may allow the chloride ion to sit between two Ca^{2+} ions. Also, the higher coordination-number of Ca^{2+} is normal in main group metals. The bond distance of Ca(1)–Cl(1) (2.8629(6)) is, as expected, slightly longer than those found in $Ca–Cl_{bridging}$ (2.711–2.750) and $Ca–Cl_{monodentate}$ (2.841–2.847 Å).[12]

In conclusion, this study provided the first direct evidence of the metal-bound antibacterial drug norfloxacin. The structural data show that H-Norf binding to divalent metal ions is mainly ion-radius-dependant. Such metal-driven structural alterations of H-Norf such as those seen in the Mg^{2+} and Ca^{2+} complexes may influence greatly drug properties such as cell membrane permeability. It remains to be seen whether the metal-modified H-Norf binds to DNA or DNA–gyrase complexes differently from the parent drug.

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Notes and references

† Compound **1**: Samples of 1 mmol of $MgCl_2\cdot 6H_2O$ and 1 mmol of H-Norf were thoroughly mixed in a mortar with a pestle, and placed in thick-walled Pyrex tubes (*ca*. 20 cm long). After addition of 0.5 ml of EtOH and 1.5 ml of H_2O (pH *ca*. 6.0), the tube was frozen with liquid N_2, evacuated under vacuum and sealed with a torch. The tube was heated at 110 °C for one day to give colorless block crystals (only one phase, 0.277 g) in 55% yield based on H-Norf (Found: C, 38.12; H, 5.45; N, 8.03; Calc.: C, 38.08; H, 5.59; N, 8.33%). IR (KBr, cm^{-1}): 3251(vs, br), 1620(s), 1571(m), 1489(s), 1372(m), 1342(m), 1327(m), 1262(s), 1174(w), 1131(w), 1025(w), 927(w), 892(w), 819(m), 748(w) and 620(w).

Compound **2**: The procedures are identical to those of **1** and $CaCl_2\cdot 6H_2O$ (molar ratio of $CaCl_2\cdot 6H_2O$: H-Norf is 1 : 3) (the mixture solution pH is also about 6.0). The pale-yellow block crystals (one phase, 0.753 g) were harvested, with a yield of 65% based on H-Norf (Found: C, 49.58; H, 5.49; N, 11.13; Calc.: C, 49.74; H, 5.57; N, 10.88%). IR (KBr, cm^{-1}): 3400(s), 2998(w), 1620(s), 1580(m), 1490(s), 1380(s), 1330(s), 1270(s), 1190(m), 1140(w), 1120(w), 1020(m), 930(m), 900(w), 820(m), 750(m), 700(w) and 630(w).

‡ Crystal data for **1**: $C_{16}H_{28}Cl_2FMgN_3O_8$, $M_r = 504.62$, triclinic, $P\bar{1}$ (No. 2), $a = 8.8109(5)$, $b = 10.8325(7)$, $c = 11.6965(7)$ Å, $\alpha = 85.8250(10)$, $\beta = 87.1270(10)$, $\gamma = 85.4620(10)°$, $V = 1108.80(12)$ Å^3, $Z = 2$, $\rho_{calc} = 1.511$ g cm^{-3}, $\mu = 0.377$ mm^{-1}, $R1 = 0.0632$, $wR2 = 0.1653$ for 2751 observed reflections from 5207 independent reflections, GOF = 0.908.

Crystal data for **2**: $C_{96}H_{128}Ca_2Cl_4F_6N_{18}O_{28}$, $M_r = 2318.12$, monoclinic, $C2/c$, $a = 26.49430(10)$, $b = 15.35450(10)$, $c = 27.8604(2)$ Å, $\beta = 109.2440(10)°$, $V = 10700.50(11)$ Å^3, $Z = 4$, $\rho_{calc} = 1.439$ g cm^{-3}, $\mu = 0.301$ mm^{-1}, $R1 = 0.0771$, $wR2 = 0.1733$ for 6500 observed reflections from 12224 independent reflections, GOF = 0.947. CCDC reference number 186/2216. See http://www.rsc.org/suppdata/dt/b0/b006806n/ for crystallographic files in .cif format.

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