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Crystal structure resolution of two different chlorhexidine salts

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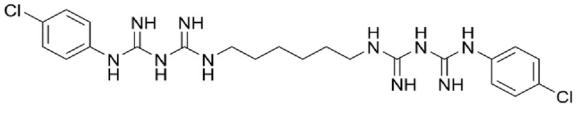
ABSTRACT

Two salts of the chlorhexidine di-cation (H_2CHx^{2+}) – $(H_2CHx)(SO_4)\cdot 3H_2O$ and $(H_2CHx)(CO_3)\cdot 4H_2O$ – have been synthesised and characterised crystallographically.

1. Introduction

Chlorhexidine (**I**, CHx) is a chemical disinfectant and antiseptic with a broad spectrum of action; it is active against Gram positive and Gram negative bacteria, as well as fungi [1]. It is a symmetrical bisbiguanidine, which is a class of chemically related compounds studied for their bactericidal properties. [1], [2] In the last 60 years chlorhexidine has been used as an antiseptic for mucous membranes, skin and wounds, or as a preservative in pharmaceutical formulations of ophthalmic products [2]. Due to its low solubility and ability to form micelles in solution [3], chlorhexidine does not crystallize easily, however, three salts of the chlorhexidine di-cation with anionic calixarenes were characterised crystallographically and reported in 2008 [4].

Herein we report the crystallographic characterisation of two salts of the chlorhexidine di-cation, namely $(H_2CHx)(SO_4)\cdot 3H_2O$ and $(H_2CHx)(CO_3)\cdot 4H_2O$.



I, CHx

2. Results and discussion

2.1. Crystal structures of as-synthesised $(H_2CHx)(SO_4)\cdot 3H_2O$ and $(H_2CHx)(CO_3)\cdot 4H_2O$

Crystals were prepared by reaction of neutral chlorhexidine and sodium sulfate or potassium carbonate in aqueous ethanol, as part of a series of attempts to generate chlorhexidine-containing coordination complexes. Full crystallographic details of both salts are presented in Table 1. Structurally, the two salts are very similar to one another (Fig. 1), with small variations in the conformation of the hexyl chains and intermolecular hydrogen-bonding due to the different arrangement of oxygen atoms between the tetrahedral SO_4^{2-} and the trigonal planar CO_3^{2-} anions, and different protonation sites along the chlorhexidine moiety. The differences in protonation site may be seen by a comparison of Fig. 2a and 2b: in $(H_2CHx)(SO_4)\cdot 3H_2O$, one biguanidine moiety is doubly protonated, whilst the other remains unprotonated; in $(H_2CHx)(CO_3)\cdot 4H_2O$, both biguanidine moieties are singly protonated in an asymmetrical manner. In both instances, the C–N bond lengths within the biguanidine units (1.307 Å to 1.379 Å) indicate that some delocalisation of the double and single bonds is occurring. The protonation of the biguanidine moieties of the chlorhexidine was unexpected, given the alkaline nature of the reaction solution. Chlorhexidine di-cations in both salts adopt a spiral conformation and are arranged into U-shaped 'coils' that extend parallel to the *a*-axis. In the labelling scheme in Fig. 2, the biguanidine moiety N1 to N5 lies at the open end of the U-shaped coils. Within the coils, adjacent

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Table 1
Crystallographic details for $(H_2CHx)(SO_4)\cdot 3H_2O$ and $(H_2CHx)(CO_3)\cdot 4H_2O$.

	$(H_2CHx)(SO_4)\cdot 3H_2O$	$(H_2CHx)(CO_3)\cdot 4H_2O$
Empirical formula	$C_{22}H_{38}Cl_2N_{10}O_7S$	$C_{23}H_{40}Cl_2N_{10}O_7$
Molecular weight	657.58	639.55
Temperature (K)	173(2)	173(2)
Wavelength (Å)	1.54187	1.54187
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/a$	$P2_1/a$
a (Å)	9.349(4)	8.497(2)
b (Å)	19.270(8)	21.0858(10)
c (Å)	17.365(7)	17.738(5)
β (°)	98.105(7)	91.930(5)
V (Å^3)	3097(2)	3176.2(12)
Z	4	4
ρ (g cm^{-1})	1.410	1.337
μ (mm^{-1})	3.011	2.321
F(000)	1384	1352
GooF	1.182	1.124
Reflections/data/parameters	30743/5566/433	31375/5718/440
R_{int}	0.0984	0.0875
Final R indices ($I > 2\sigma(I)$)	$R1 = 0.1061$	$R1 = 0.0642$
	w$R2 = 0.2772$	w$R2 = 0.1411$
Final R indices (all data)	$R1 = 0.1288$	$R1 = 0.1026$
	w$R2 = 0.3047$	w$R2 = 0.1705$

H_2CHx^{2+} cations alternate between left- and right-handed conformations, so that each coil is not helical overall (Fig. 3). The coils are held together by hydrogen bonds to the sulfate or carbonate anions and water molecules that occupy the spaces between coils.

Each oxyanion participates in hydrogen-bonding interactions with chlorhexidine cations from three different coils. Carbonate anions are involved in hydrogen bonds with two chlorhexidine cations from one coil, in addition to one cation from each of two adjacent coils as shown in Fig. 4. Sulfate anions form hydrogen bonds with three cations from one coil, plus one cation from each of two adjacent coils. Due to the difference in shape of the SO_4^{2-} and CO_3^{2-} anions, the hydrogen-bonding interactions within the coils are slightly different. The SO_4^{2-} anion forms hydrogen bonds to three adjacent chlorhexidine cations of both left- and right-handed conformation. When viewed along the *a*-axis, the sulfate anions are located towards the centre of the open end of the U-shaped coil and can interact with both halves of the U-shape. This generates a three-dimensional hydrogen-bonded framework of SO_4^{2-} anions and H_2CHx^{2+} cations. The CO_3^{2-} anion, however, can participate in intra-chain hydrogen bonds with two non-adjacent chlorhexidine cations that both have the same conformation (either left- or right-handed). When viewed along the *a*-axis, the carbonate anions sit almost aligned with the two sides of the U-shape, and so are only able to interact with the chlorhexidine cations along one side of the U-shape. This generates a two-dimensional hydrogen-bonded framework of CO_3^{2-} anions and H_2CHx^{2+} cations that extends parallel to the *ac*-plane (Fig. 5). Water molecules of crystallisation occupy the remaining space between the coils and form hydrogen bonds with both the oxyanions and the chlorhexidine cations so that both compounds contain a complex three-dimensional hydrogen-bonded network. A list of the hydrogen bonds found in both compounds presented in Supporting Information.

3. Conclusions

The carbonate and sulfate salts of the chlorhexidine di-cation have been synthesised and characterised crystallographically. Investigations showed that the two salts are structurally similar to each other, although differences in the conformations of the hexyl

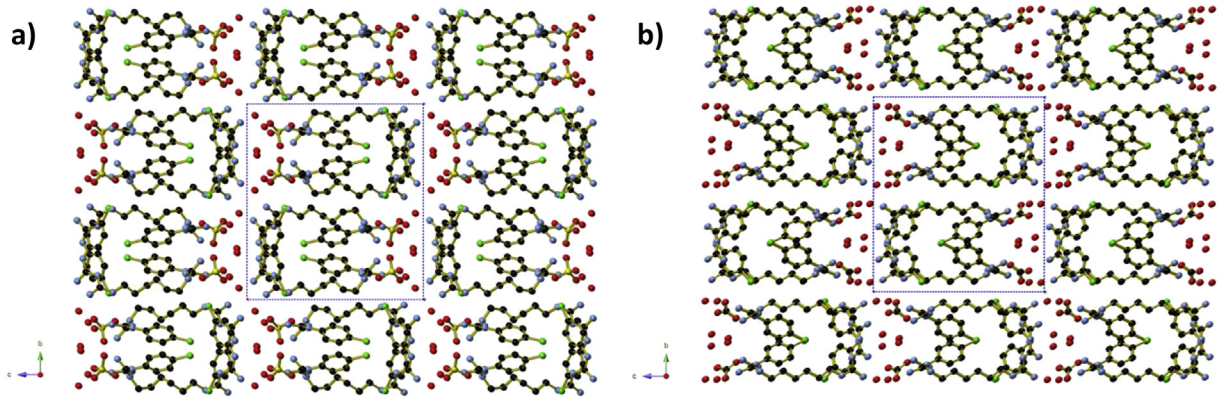

Fig. 1. A view along the *a*-axis of **a)** $(H_2CHx)(SO_4)\cdot 3H_2O$ and **b)** $(H_2CHx)(CO_3)\cdot 4H_2O$, showing the structural similarities between the two compounds.

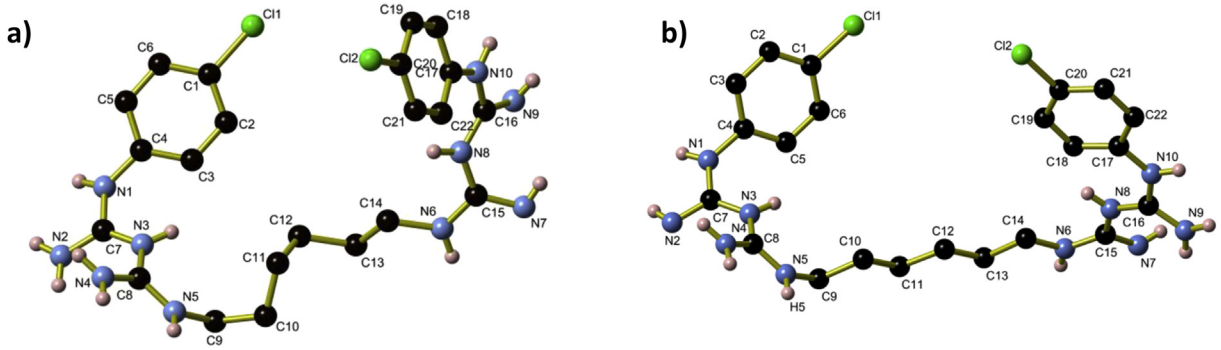

Fig. 2. A view along the chlorhexidine cation found in **a)** $(H_2CHx)(SO_4)\cdot 3H_2O$ and **b)** $(H_2CHx)(CO_3)\cdot 4H_2O$. Aromatic and aliphatic hydrogen atoms have been omitted for clarity.