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β-Cyclodextrin Inclusion Complexes of Mg^{2+} and Ca^{2+} Salts of Meclofenamic Acid: Preparation and Structural Characterisation

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The magnesium and calcium salts of the non-steroidal anti-inflammatory drug meclofenamic acid (2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid) were prepared and complexed with β-cyclodextrin (β-CD) to yield inclusion complexes with the compositions β-CD-hemi-magnesium meclofenamate·16.8H_2O (1) and β-CD-hemi-calcium meclofenamate·16.5H_2O (2). These complexes were investigated by thermal analysis techniques, elemental analysis, powder X-ray diffraction (PXRD) and single crystal X-ray diffraction at 113 K. The complexes yielded PXRD traces that closely matched that of the known complex β-CD-sodium meclofenamate·16H_2O (3), indicating isostructurality among 1–3, reflected in very close similarities in the modes of inclusion of the anion in β-CD. However, the locations and coordination environments of the Mg^{2+}, Ca^{2+} and Na^+ ions differ significantly in the respective crystals.

Keywords: β-Cyclodextrin; Meclofenamic acid; X-ray structures

INRODUCTION

Meclofenamic acid, 2-[(2,6-dichloro-3-methylphenyl)-amino]benzoic acid, (Scheme 1) is a non-steroidal anti-inflammatory drug (NSAID) and a structural isomer of the widely used analogue diclofenac. NSAIDs have analgesic and antipyretic effects, but most also have negative side effects such as gastrointestinal ulceration and bleeding [1,2]. These side effects may be reduced by administering complexes of the drugs with a cyclodextrin (CD), which in addition may increase the solubility of the drug [3]. Although the CD-complexes of un-ionized drugs are usually more stable, those containing salts typically yield a greater total drug solubility [4]. In the case of the β-CD inclusion complex of sodium diclofenac, an aqueous solubility exceeding 10 mg/ml diclofenac at 20°C and pH 5–7 was observed i.e. significantly higher than that for the pure drug (~1 mg/ml) under the same conditions [5].

While there has been much research on diclofenac inclusion complexes with a variety of cations and CDs, complexes of the meclofenamate anion have received considerably less attention. The crystal structure of the sodium meclofenamate (MNa) β-CD complex (**3**) has been studied and compared with that of the sodium diclofenac β-CD complex [5]. In these complexes the drug anions were found to have essentially the same mode of inclusion, the ring bearing the carboxylate moiety entering the β-CD cavity from the primary side and the sterically more bulky chlorinated ring entering the secondary side of a neighbouring host molecule at a shallow angle. However, the crystal packing in these complexes was different, the diclofenac complex crystallizing in the space group $P6_1$ and the meclofenamate analogue in the space group $P2_12_12_1$.

In an attempt to extend the solid-state chemistry of meclofenamic acid while ensuring pharmaceutical acceptability of new products, we recently prepared its calcium and magnesium salts with the intention of including these in β-CD. Here we report the successful preparation of inclusion complexes with these salts as well as their structural characterization. As the nature of the metal ion can markedly affect the crystal packing for complexes of this type through its coordination to water molecules and/or oxygen atoms of the CD molecule, it was of particular interest

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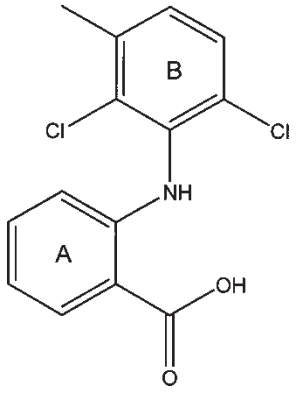

SCHEME 1 Chemical structure of meclofenamic acid.

to establish whether the divalent cations Mg^{2+} and Ca^{2+} might induce different packing arrangements in complex crystals from that observed in the sodium complex of the meclofenamate anion [6].

MATERIALS AND METHODS

Salt Preparation and Preliminary Characterization

The method of salt preparation was based on that reported for the preparation of magnesium diclofenac by Castellari et al. [6]. Two equivalents of meclofenamate sodium (MNa, purchased from Sigma-Aldrich, Germany) were dissolved with stirring in a minimum amount of water at 40°C. One to six equivalents of anhydrous $MgSO_4$ (UNILAB, South Africa) or $CaCl_2$ (BDH, England) were similarly dissolved in water and added to the drug solution. The white precipitate, which formed spontaneously, was filtered and washed with water before being re-dissolved in water and methanol respectively. The solutions were filtered with a 0.45 μm nylon microfilter while hot and allowed to cool to yield colourless crystals of $M_2Mg{\cdot}3H_2O$ $[(C_{14}H_{10}Cl_2NO_2^-)_2\ Mg^{2+}{\cdot}3H_2O]$ (M = meclofenamate anion) and $M_2Ca{\cdot}2CH_3OH{\cdot}0.85H_2O$ $[(C_{14}H_{10}Cl_2NO_2^-)_2\ Ca^{2+}{\cdot}2CH_3OH{\cdot}0.85H_2O]$. Elemental analysis (calculated values in parentheses) yielded C 53.15% (53.16%), H 3.50% (3.51%), N 4.39% (4.43%) for $M_2Mg{\cdot}H_2O$, obtained by partial desolvation of $M_2Mg{\cdot}3H_2O$ on the TGA apparatus described below. $M_2Ca{\cdot}2CH_3OH{\cdot}0.85H_2O$ was not desolvated and yielded C 50.57% (50.76%), H 3.95% (4.22%), N 3.91% (3.95%).

Water content was determined on fresh and partially desolvated crystals by thermogravimetric analysis (TGA) on a Mettler Toledo TGA analyser. Complex crystals were also examined by Differential Scanning Calorimetry (DSC) on a Perkin Elmer PC7-Series System under N_2-purge (flow rate 30 mL/min). Samples were scanned at 10 K/min over the range 30–300°C. Vented pans were used in DSC and the instrument was calibrated with high-purity indium and zinc standards.

Complex Preparation and Preliminary Characterization

M_2Mg and M_2Ca (both unsolvated) were obtained by controlled desolvation (performed directly on the TGA apparatus) of the respective salts $M_2Mg{\cdot}3H_2O$ and $M_2Ca{\cdot}2CH_3OH{\cdot}0.85H_2O$. Each of the unsolvated salts was added to a concentrated solution of β-CD (Cyclolab, Hungary) at 70°C in a 1:1 meclofenamate anion:β-CD molar ratio. The solutions were stirred until clear with small amounts of ethanol being added to the M_2Ca solution to aid dissolution. Slow evaporation of the cooled, filtered (0.45 μm) solution yielded colourless crystals in 3–6 days. Complexation was initially confirmed by PXRD. Elemental analysis of the partially dehydrated complexes yielded the following data (calculated values in parentheses): for $C_{42}H_{20}O_{35}{\cdot}C_{14}H_{10}Cl_2NO_2^-{\cdot}1/2Mg^{2+}{\cdot}6H_2O$, C 43.39% (43.38%), H 5.93% (5.98%), N 0.91% (0.90%) (Mg^{2+} analogue) and for $C_{42}H_{20}O_{35}{\cdot}C_{14}H_{10}Cl_2NO_2^-{\cdot}1/2Ca^{2+}{\cdot}5.5H_2O$, C 43.39% (43.38%), H 5.93% (5.98%), N 0.91% (0.90%) (Mg^{2+} analogue) and C 43.32% (43.42%), H 5.93% (5.92%), N 0.87% (0.90%) (Ca^{2+} analogue). Total mass losses of 17.0(5)% and 17.6(5)% attributed to dehydration were measured for **1** and **2** respectively, leading to the stoichiometries reported in Table I.

Crystal Structure Analysis

Intensity data were collected on a Nonius Kappa CCD diffractometer with 1.2 kW graphite-monochromated MoKα-radiation ($\lambda = 0.71069$ Å) generated by a Nonius FR590 generator at 53 kV and 23 mA. For both the Mg^{2+} complex (**1**) and the Ca^{2+} complex (**2**), a near cubic crystal coated in Paratone N oil (Exxon) was used to collect intensity data at 113 K at a high redundancy level to permit empirical absorption correction with program SADABS [7]. Data-collection (COLLECT software [8]) involved a combination of ϕ- and ω-scans of 0.6° for **1** and 0.3° for **2**.

Examination of the reciprocal lattices revealed Laue symmetry *mmm* indicating that the crystals are orthorhombic. The reflection data were examined with the program LAYER [9], which revealed the presence of three screw axes from the systematic absences $h = 2n + 1$ on $h00$, $k = 2n + 1$ on $0k0$ and $l = 2n + 1$ on $00l$. The space group was thus found to be $P2_12_12_1$, identical to that of **3**, the β-CD complex of sodium meclofenamate [6].

Program XPREP [10] was used to prepare the initial data for structure determination. The structure of **1** was solved by direct methods using SHELXD [11], most of the non-hydrogen atoms of the host and guest molecules being located. It was refined by least-squares against F^2 using SHELXL-97 [12]. Because **1** and **2** were indicated as being isostructural by PXRD (see below), the structure of **2** was solved

TABLE I Crystal data and refinement details for the inclusion complexes **1** and **2**

Complex formula	$C_{42}H_{20}O_{35}{\cdot}C_{14}H_{10}Cl_2NO_2^-$ $1/2Mg^{2+}{\cdot}16.8H_2O$ (**1**)	$C_{42}H_{20}O_{35}{\cdot}C_{14}H_{10}Cl_2NO_2^-$ $1/2Ca^{2+}{\cdot}16.5H_2O$ (**2**)
Formula weight	1744.93	1747.41
Temperature (K)	113	113
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	$a = 15.1691(1)$ Å $b = 17.8431(2)$ Å $c = 29.5625(3)$ Å	$a = 15.2002(3)$ Å $b = 17.8211(3)$ Å $c = 29.4263(6)$ Å
Volume	8001.5(1) Å^3	7971.1(3) Å^3
Z	4	4
Density (calculated)	1.448 g cm^{-3}	1.456 g cm^{-3}
Radiation, wavelength	Mo-Kα, 0.71073 Å	Mo-Kα, 0.71073 Å
Absorption coefficient	0.196 mm^{-1}	0.225 mm^{-1}
F(000)	3708	3712
Crystal size	0.09 × 0.20 × 0.30 mm	0.12 × 0.16 × 0.20 mm
Theta range	3.49 to 25.41°	2.91 to 25.00°
Index ranges	$-18 \le h \le 13$, $-20 \le k \le 21$, $-35 \le l \le 35$	$-18 \le h \le 18$, $-21 \le k \le 21$, $-26 \le l \le 34$
Absorption correction	SADABS	SADABS
Reflections collected	89161	69207
Observed reflections [$I > 2\sigma(I)$]	11089	7371
Data/restraints/parameters	14586/4/1015	13929/5/1013
Goodness-of-fit on F^2	1.051	1.028
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0890$, $wR^2 = 0.2329$	$R_1 = 0.1157$, $wR^2 = 0.2797$
R indices (all data)	$R_1 = 0.1178$, $wR^2 = 0.2521$ $w = 1/[\sigma^2(F_o^2) + (0.1373P)^2 + 18.3610P]$ where $P = (F_o^2 + 2F_c^2)/3$	$R_1 = 0.1344$, $wR^2 = 0.3254$ $w = 1/[\sigma^2(F_o^2) + (0.1433P)^2] + 35.0623P]$ where $P = (F_o^2 + 2F_c^2)/3$
Largest diff. peak and hole	-0.478, 1.219 eÅ^{-3}	-0.446, 1.012 eÅ^{-3}
Extinction correction	0.0022(6)	0.012(1)

by the isomorphous replacement method, the rigid part of the cyclodextrin molecule of **1** being used as a trial model for refinement with SHELXL-97.

In **1**, of the maximum of 16.8 water molecules per host molecule estimated from thermogravimetric analysis, 13.2 were placed; the corresponding data for **2** were 16.5 and 13.5 respectively. The remaining water molecules are disordered and contribute to the overall final difference electron densities ($\Delta\rho_{max}$) in the structures.

Atom O6D, a primary oxygen atom of β-CD, was found to be disordered over two sites in both complexes and modelled accordingly. As the unit cells of **1** and **2** contain four 1:1 β-CD–meclofenamate units, and therefore two metal ions, it was necessary to assign site occupancy factors of 0.5 to each metal ion. Given the space group, this is an unusual assignment and it is discussed below. All fully occupied non-hydrogen atoms were refined anisotropically except for those water oxygen atoms of **2** with high isotropic displacement parameters ($U_{iso} > 0.10$ Å^2). Hydrogen atoms were identified as far as possible from difference Fourier maps and were added in idealized positions using a riding model with $U_{iso} = 1.2$ times those of the parent atoms. The hydrogen atoms on the secondary amines (N10–H10) of both structures were added in idealized positions using trigonal planar geometry. No attempt was made to locate the hydrogen atoms of the water molecules.

In the final refinement of **1** and **2**, 52 and 59 low-angle reflections respectively were omitted as their measured intensities were severely reduced by beam-stop truncation. The CIF files for the structures have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers CCDC 296747 and 296746).

RESULTS AND DISCUSSION

Powder X-ray Diffraction (PXRD)

The PXRD patterns (Fig. 1) of the materials obtained by kneading β-CD and each of the salts did not match any previously identified isostructural series [13], but they were found to match that of the previously determined β-CD MNa inclusion complex (**3**) [6]. This established compounds **1**–**3** as members of a new isostructural series for inclusion in the library of patterns [14]. Furthermore, this isostructurality was contrary to initial expectations that the divalent metal ions might induce a substantially different crystal packing arrangement from that found in the complex of the Na^+ ion.

Single Crystal X-ray Analysis

Overall Description of the Structures

Crystallographic data for the complexes **1** and **2** are listed in Table I. The unit cell data are comparable to

those of **3** ($a = 15.087(2)$ Å, $b = 17.967(2)$ Å, $c = 29.634(4)$ Å, $V = 8033(2)$ Å^3 at $T = 294$ K). The asymmetric unit in **1** and **2** (Figs. 2 and 3) consists of one β-CD molecule, one meclofenamate anion, half a magnesium or calcium cation and 16.8 or 16.5 water molecules respectively. The magnesium ion (Fig. 4) is coordinated to five water molecules with Mg···O distances in the range 1.93(3)–2.47(2) Å and is not covalently bound to the host or guest anions. In contrast, the calcium ion is coordinated to two host primary oxygen atoms, O2 and O3, of glucose ring A of the β-CD molecule with Ca···O 2.47(1) Å and 2.55(1) Å respectively, and to five water molecules with Ca···O distances spanning the range 2.21(2)–2.49(2) Å.

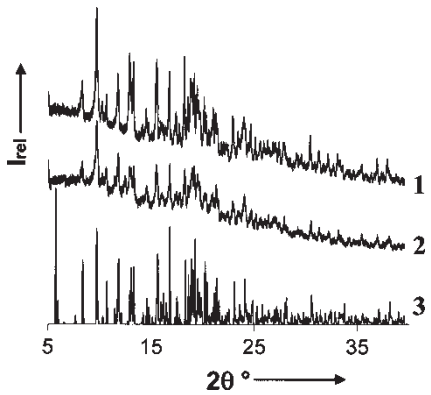

FIGURE 1 Experimental PXRD trace of **1** and **2** and the computed PXRD trace of the sodium analogue **3**.

Guest Conformation and Inclusion

The torsion angles τ1, C12–C11–N10–C1, τ2, C11–N10–C1–C6, and τ3, C1–C6–C7–O9 (Table II) describe the relative orientation of the two rings and the orientation of the carboxylate group of the guest anion. Data for **3** are included for comparison. The close correspondence of equivalent torsion angles shows that in all three inclusion complexes, the meclofenamate anions adopt very similar conformations, partly due to the consistent formation of an intramolecular N–H···O(carboxylate) hydrogen bond. In contrast to the situation in the magnesium and calcium meclofenamate salts [14], the carboxyl group is not coplanar with the phenyl ring. It is hydrogen bonded to the primary hydroxyl group of the β-CD, O6DA–H6DA, in addition to the amine group.

Details of the inclusion mode are shown in Fig. 6. These meclofenamate complexes adopt the same mode of inclusion as observed in the Na^+ complex **3**, which in turn is similar to that of the diclofenac inclusion complexes in the solid state [6]. The phenyl ring bearing the carboxylate group (Scheme 1, ring A) of the meclofenamate anion penetrates deeply into the β-CD cavity from the primary hydroxyl side while the bulkier dichlorophenylmethyl ring (ring B) enters the secondary face of a symmetry related β-CD cavity at a shallow angle. In each complex the carboxylate oxygen atom O9 of the guest forms a hydrogen bond with the primary hydroxyl oxygen atom (O3B) of a symmetry-related host molecule [6].

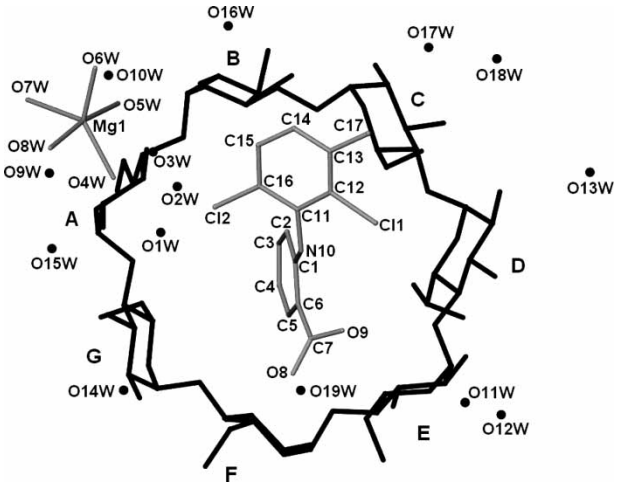

FIGURE 2 Asymmetric unit of **1** with atom assignments. The guest is shown in grey while β-CD and water molecules are shown in black. Hydrogen atoms have been omitted for clarity.

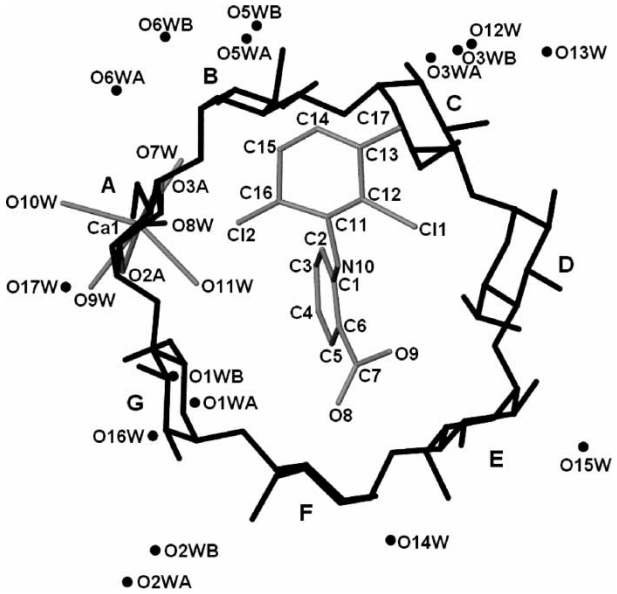

FIGURE 3 Asymmetric unit of **2** with atom assignments. The guest is shown in grey while β-CD and water molecules are shown in black. Hydrogen atoms have been omitted for clarity.

Host Conformations

Table III lists the parameters defining the conformations of the β-CD molecules. The α-D-glucose moieties of both host molecules are in the $^4C_1$ chair conformation with the primary hydroxyl groups directed away from the cavity in the (−)-*gauche*

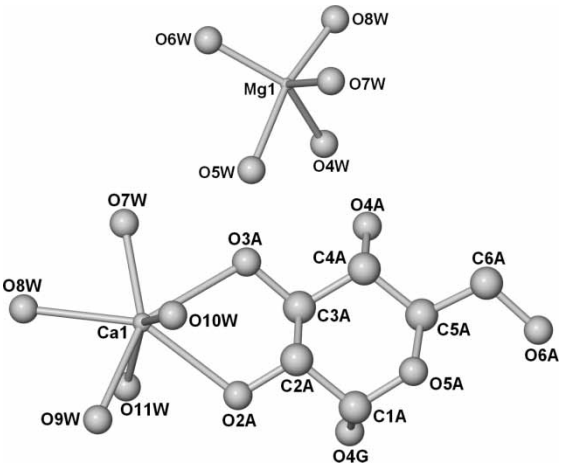

FIGURE 4 Co-ordination of the magnesium ion in complex **1** and the calcium ion in complex **2**.

TABLE II Torsion angles (°) describing the meclofenamate anion conformation

	1	2	3
τ1	−125.7(7)	−130(1)	−126(1)
τ2	−176.7(6)	−173(1)	−176.1(8)
τ3	−41.4(9)	−39(2)	−42(1)

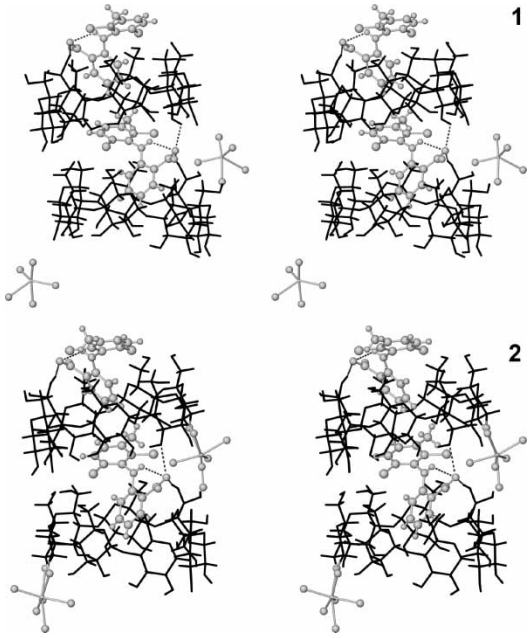

FIGURE 5 Stereoviews of the inclusion modes in complexes **1** and **2**.

conformation (torsion angle, τ), except for residues A and D. In the latter case, there is twofold disorder with the minor component in the (+)-*gauche* conformation (site-occupancies 0.41 and 0.44 in **1** and **2** respectively) so that it points into the cavity to hydrogen bond to O9 of the carboxylate group of the guest molecule. This is identical to the type of disorder observed in **3**.

Water Structure

There are two distinct types of water molecules in these structures. Some are coordinated to the metal ions while others are hydrogen bonded to the host molecule, the latter being less tightly bound in the crystal than the former. The X-ray structural results are thus consistent with multi-step mass losses that were observed in the TG traces (not shown). This differential behaviour of water molecules, manifested as multiple endotherms in DSC traces and multi-step mass losses in TG, was described

TABLE III Geometrical parameters for the host β-CD in **1** and **2**

		D[†] (Å)	Φ[‡] (°)	D[¶] (Å)	α[§] (°)	D_3[‖] (Å)	τ[#] (°)
1	A	4.405	124.49	−0.184	87.67	2.795	−177.4
	B	4.379	131.87	−0.033	88.82	2.747	48.9
	C	4.341	127.20	0.232	74.63	2.780	47.7
	D	4.348	128.60	−0.081	75.85	2.834	A: 165.8
							B: 159.2
	E	4.320	126.20	−0.222	87.05	2.849	58.5
	F	4.407	130.95	0.229	81.26	2.898	55.0
	G	4.277	128.94	0.060	70.91	2.835	65.4
	Average e.s.d.			±0.003	±0.148	±0.007	±0.7
2	A	4.390	124.12	−0.204	89.0	2.788	−178.2
	B	4.385	131.20	−0.061	88.6	2.804	50.8
	C	4.378	128.11	0.252	75.1	2.797	52.7
	D	4.329	128.48	−0.055	75.6	2.809	A: 159.4
							B: 57.3
	E	4.320	125.19	−0.257	87.8	2.846	55.9
	F	4.437	131.42	0.217	82.7	2.892	59.4
	G	4.260	129.50	0.108	70.7	2.894	56.6
	Average e.s.d.			±0.006	±0.3	±0.011	±1.2

[†] Glycosidic O4n···O4(n + 1) distance; [‡] O4(n − 1)···O4n···O4(n + 1) angle; [¶] Deviations of O4n atoms from their least-squares mean planes; [§] Dihedral angle between the mean O4n plane and the mean C2n, C3n, C5n, O5n plane of each residue; [‖] Inter-ring hydrogen bond O2n···O3(n − 1) distances; [#] Torsion angle C4n–C5n–C6n–O6n.

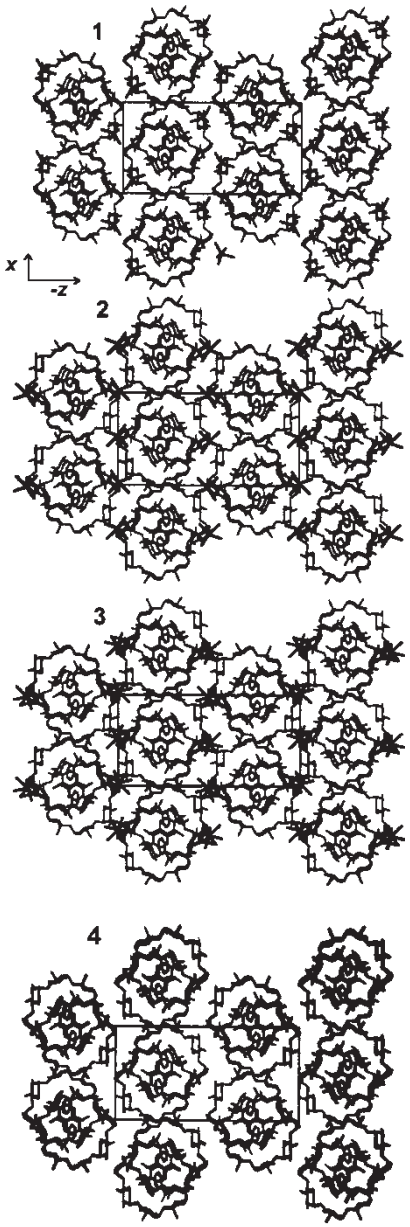

FIGURE 6 Packing diagrams viewed down the b-axis of the β-CD inclusion complexes of **1** M_2Mg, **2** M_2Ca, **3** MNa [6] (M = meclofenamate anion) and **4** superposition of **1**, **2**, and **3** with the metal ions omitted to illustrate the isostructurality.

earlier for a series of CD inclusion complexes of metal salts [15].

In **1**, 13.2 of the 16.8 waters estimated from the TG analysis were placed, eight with s.o.f.'s of 1.0 each, the five coordinated water molecules with s.o.f.'s of 0.5 and the remaining water molecules disordered over six sites. In **2** 13.5 of the predicted 16.5 water molecules were located, six with s.o.f.'s of 1.0, the five coordinated water molecules with s.o.f.'s of 0.5 and the remaining four water molecules are disordered over two sites each. The unplaced water molecules are variously disordered and contribute to the overall final difference electron densities in the structures.

Crystal Packing Arrangements

The levels of isostructurality among the three inclusion complexes can be assessed from the packing diagrams (Fig. 6). While the β-CD molecules and their included anions retain a constant, common framework throughout the series, the metal ions are arranged differently owing to their varied coordination environments described above and shown for **1** and **2** in detail in Figs. 4 and 5.

CONCLUDING REMARKS

A common mode of inclusion of the meclofenamate ion within the β-CD cavity has now been confirmed for three inclusion complexes. Furthermore, this mode of inclusion is analogous to that of diclofenac in β-CD [5,6].

The crystal structure of **3**, the sodium meclofenamate complex of β-CD [6], is evidently a very stable one. This is inferred from the fact that, despite their divalent nature, the magnesium and calcium ions form complexes that crystallize in essentially the same arrangement as **3**, necessitating the unusual assignment of site-occupancy factors of 0.5 to the metal ions occupying the general equipoints of $P2_12_12_1$ to reconcile the complex stoichiometries with the crystallographic data.

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