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Inclusion of the Niflumic Acid Anion in β-cyclodextrin: A Solution NMR and X-ray Structural Investigation

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We report parallel solution and solid state studies of the inclusion of the anionic form of the non-steroidal anti-inflammatory drug niflumic acid (2-[[3-(trifluoromethyl)-phenyl]-amino]-3-pyridinecarboxylic acid) in the host β-cyclodextrin (β-CD). ^{1}H NMR data for the interaction between host and guest in aqueous solution recorded at 300 MHz indicated a strong preference for insertion of the trifluoromethylphenyl residue, rather than the pyridinecarboxylate moiety, in the host cavity. A 1:1 complex stoichiometry was determined by the continuous variation method utilising chemical shifts of both host and guest protons. Analysis of the data using a new flexible program developed for this purpose yielded an overall association constant K of 336 M^{-1} at 298 K. The NMR data indicate a dynamic equilibrium between complexed and uncomplexed species but do not distinguish guest entry from the primary and secondary sides of the host. Reaction between the Cs^+ salt of niflumic acid and β-CD yielded the crystalline complex $(\beta\text{-CD})_2\cdot(Cs^+niflumate^-)_4\cdot 22H_2O$ whose single crystal X-ray structure was determined. A novel inclusion mode for this host, namely entry of guest trifluoromethylphenyl residues from both the primary and secondary sides, was revealed by the X-ray analysis.

Keywords: β-cyclodextrin; Niflumic acid; Association constant; ^{1}H NMR; X-ray structure

INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDS) are amongst the most commonly used classes of drugs. However, at high dosage levels, most NSAIDS cause ulcerative side effects such as gastric irritation and bleeding [1]. Several approaches have been adopted for preventing or reducing these side effects, including prodrug formulation, microencapsulation and addition of neutralising excipients [2]. One of the more recent methods tested is complexation of NSAIDS with cyclodextrins (CDs) [3]. A survey of the application of simultaneous CD complexation and guest salt formation for improving the pharmaceutical performance of acidic drugs has recently been published in Ref. [4]. For a better understanding of the therapeutic properties of these complexes, complete characterisation in terms of stoichiometry, stability and molecular conformation should be performed. The present report describes a parallel study of inclusion of the anionic form of the NSAID niflumic acid (2-[[3-(trifluoromethyl)phenyl]-amino]-3-pyridinecarboxylic acid, Fig. 1) in the host β-cyclodextrin (β-CD), both in solution and in the solid state using NMR and X-ray techniques, respectively. This approach provides more insight into the nature of the inclusion process than either method by itself.

RESULTS AND DISCUSSION

Solution NMR

Inclusion of the niflumic acid anion (NIF) in the host molecule is shown by changes in the chemical shifts of some of the guest and host protons in comparison with the chemical shifts of the same protons in the free compounds. Partial 300 MHz ^{1}H NMR spectra of the pure compounds and of the equilibrium mixtures

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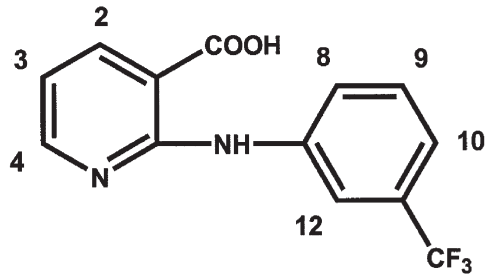

FIGURE 1 Chemical structure of niflumic acid. Numerals correspond to proton positions referred to in the NMR study.

containing the niflumate–β-CD complex and the remaining reagents are displayed in Figs. 2 and 3. Distinct peaks are not observed for a bound and a free form. This fact indicates that complexation is a dynamic process, the included niflumate undergoing rapid exchange (on the NMR time scale) between the free and bound states and only the shifts of the spectral lines are observed.

To establish the stoichiometry of the complex, the continuous variation method was used to follow the changes in chemical shifts of protons H-5, H-3, and H-6 of β-CD (Fig. 4) and protons 9, 10 and 12 of the niflumate anion (Fig. 5), which show the most marked variations. Although the shapes of the curves in Figs. 4 and 5 are not highly symmetrical, the maximum does not deviate significantly from $r = 0.5$, indicating the existence of a complex with 1:1 stoichiometry within the range of concentrations investigated. On the other hand, the changes in chemical shifts of protons H-3 ($\Delta\delta_{obs}^{max} = 0.133$ ppm) and H-5 ($\Delta\delta_{obs}^{max} = 0.131$ ppm) of β-CD do not conclusively indicate which side of the β-CD cavity is involved in complex formation, because no significant differences were detected. The signals of the included niflumate are shifted by complexation to a variable extent. The pyridine ring protons experience very little perturbation. Conversely, the phenyl ring protons are strongly affected by the formation of the inclusion complex. The chemical shift difference for the protons belonging to the phenyl ring are higher than that for the pyridine ring by a factor of 10. These results clearly support the assumption that the trifluoromethylphenyl residue of the niflumate anion enters the β-CD cavity.

The association constant for the 1:1 complex was calculated by a non-linear least squares regression analysis of the observed chemical shift changes of the drug and β-CD NMR lines, as a function of β-CD concentration. Specifically, K was evaluated from the observed differences in chemical shifts for niflumate (9, 10 and 12) and β-CD (H-3, H-5 and H-6) protons, based on Eq. (1) (see "Materials and methods" section). This equation involves no approximations and correlates the total concentrations of the guest and host molecules with the observed difference in

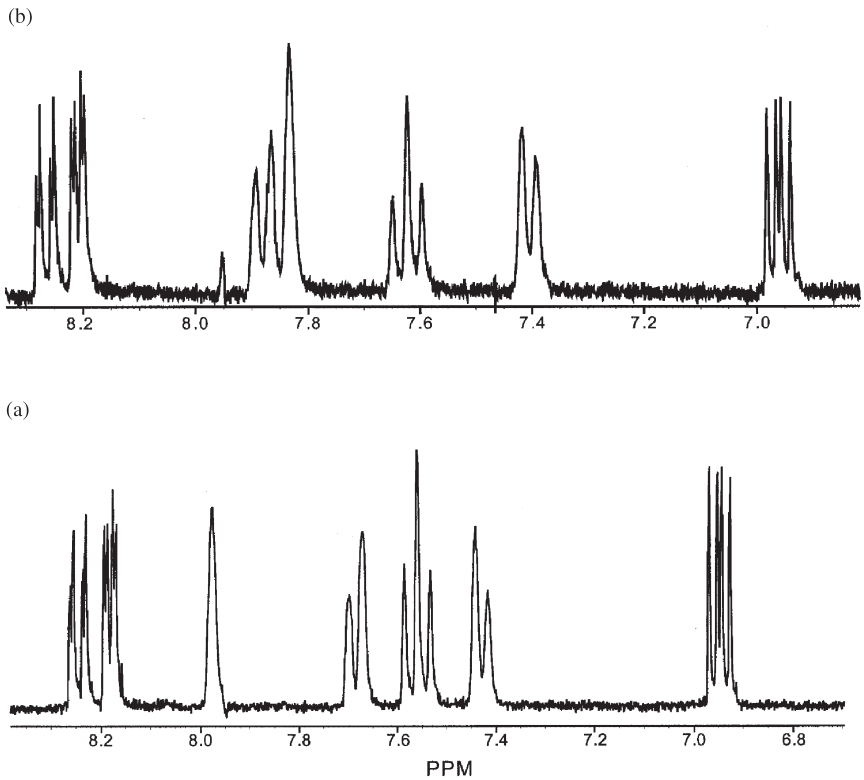

FIGURE 2 Partial 300 MHz spectra of (a) 10 mM Na niflumate and (b) 5 mM Na niflumate and 5 mM β-CD.

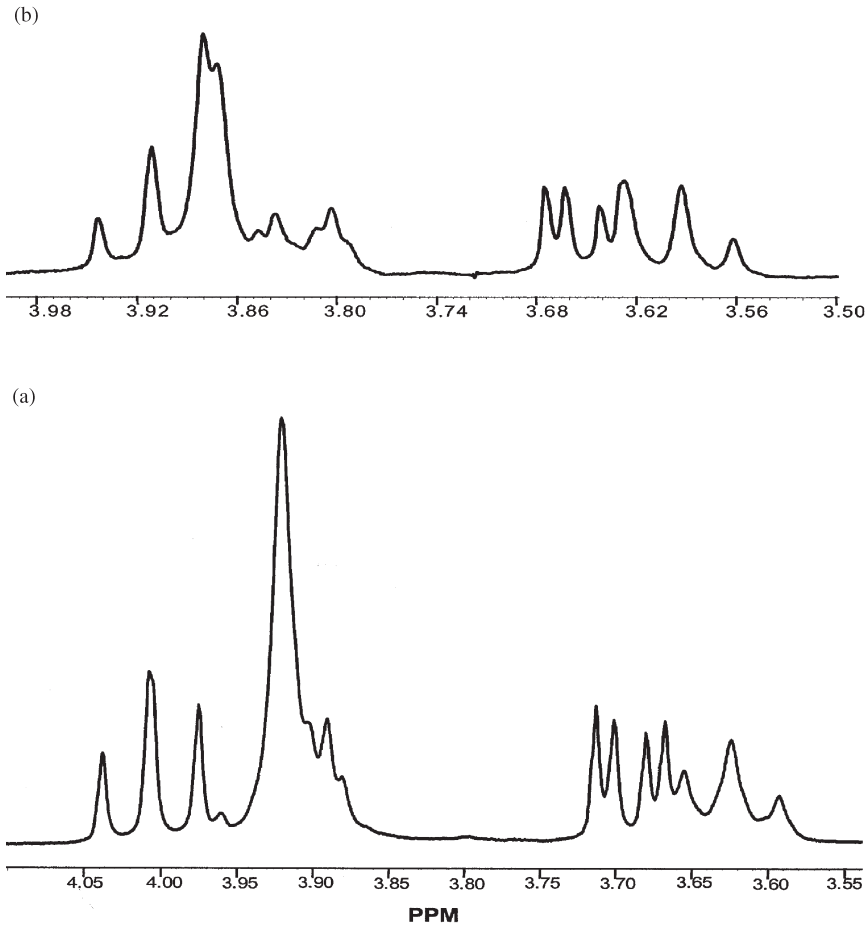

FIGURE 3 Partial 300 MHz spectra of (a) 10 mM β-CD and (b) 5 mM Na niflumate and 5 mM β-CD. Only the spectral region for protons H-2 to H-6 of β-CD is displayed.

chemical shift, $\Delta\delta_{obs}^{(X)}$. We developed a computer program written in C^{++} based on an iteration procedure following specific algorithms in order to fit the experimental values of $\Delta\delta_{obs}^{(X)}$ to the appropriate equation. Each iteration sets up a quadratic program to determine the direction of search and the loss function (ΔY^2, defined as the sum of the squared deviation about the predicted values), until the search converges. The program produces one single K value for the entire process and a set of calculated $\Delta\delta_C^{(X)}$ values. The program is quite flexible since both the guest and host can be observed for spectroscopic perturbations as a function of variable guest or host concentrations.

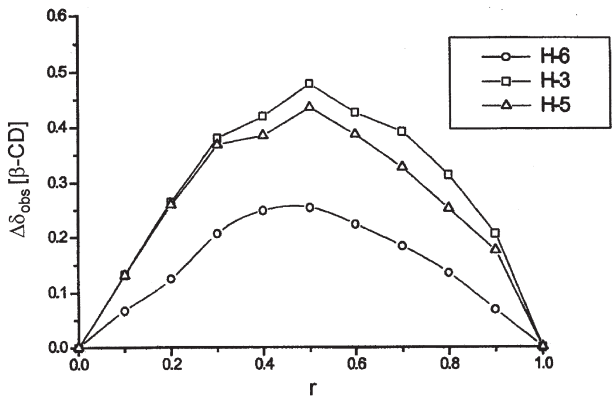

FIGURE 4 Job plots for protons H-3, H-5 and H-6 of β-CD in the presence of different concentrations of NIF.

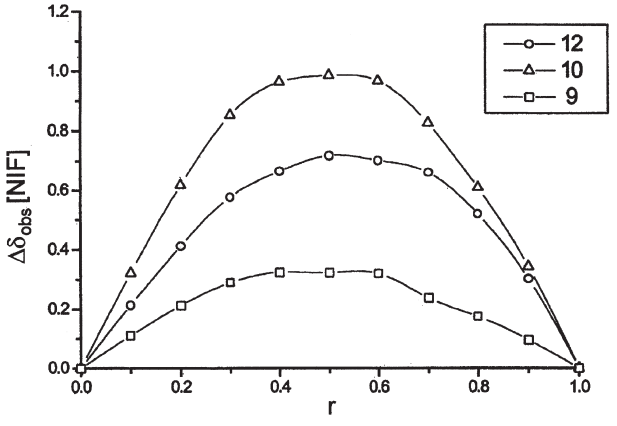

FIGURE 5 Job plots for protons 9, 10 and 12 of the NIF in the presence of different concentrations of β-CD.

TABLE I Chemical shifts (ppm) of the niflumic acid anions and β-cyclodextrin protons in the free (experimental values) and complexed states (fitted values)

Proton	δ_{free}	$\Delta\delta_C$
Niflumic acid anion		
2	8.182 (dd)	–
3	6.948 (dd)	–
4	8.246 (dd)	–
8	7.429 (d)	–
9	7.560 (t)	−0.148
10	7.685 (d)	−0.438
12	7.977 (s)	0.302
β-cyclodextrin		
H1	5.111	–
H2	3.690	–
H3	4.007	0.192
H4	3.624	–
H5	3.907	0.183
H6	3.921	0.0981

The overall K obtained from this procedure was $336\,M^{-1}$ at 298 K, with $\Delta Y^2 = 1.38 \times 10^{-3}$ and the correlation factor $r = 0.9992$. The complete set of chemical shifts in the free state and pure complex are reported in Table I. Binding constants for the inclusion of niflumic acid in β-CD based on microcalorimetric and chromatographic (HPLC) data at 298 K have been determined in Ref. [5]. The reported values are $1131\,M^{-1}$ at pH 6.0 and $520\,M^{-1}$ at pH 7.0, indicating a lower tendency of the ionised form of the drug to bind to the host than the unionised form. The value of $336\,M^{-1}$ at pH ~ 12 obtained in this study is consistent with these data.

TABLE II Crystal data and structure refinement

Molecular formula	$(C_{42}H_{70}O_{35})_2 \cdot (C_{13}H_8F_3N_2O_2^-)_4 \cdot (Cs^+)_4 \cdot 22H_2O$
Formula weight	4322.8
Temperature	173 K
Radiation/wavelength	0.71069 Å
Space group	$P2_1$
a, α	$a = 11.6837(1)$ Å, $\alpha = 90.0°$
b, β	$b = 52.4496(7)$ Å, $\beta = 105.67(3)°$
c, γ	$c = 15.0628(1)$ Å, $\gamma = 90.0°$
Volume/Z	8887.5(2) Å^3/2
Density (calculated)	1.615 g/cm^3
Crystal dimensions	0.40 × 0.30 × 0.20 mm
θ-range for data collection	1.85–27.88°
Index ranges	$-14 \le h \le 15$, $-48 \le k \le 66$, $-19 \le l \le 19$
Reflections collected/independent	26724/26695
Solution method	Direct methods [13]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	26695/1/1476
Goodness of fit on F^2	1.026
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.098$, $wR_2 = 0.264$
R indices (all data)	$R1 = 0.124$, $wR_2 = 0.290$
Largest diffraction peak and hole	1.50 and −2.05 eÅ^{-3}

Solid State Structure

Overall Description of the Structure

Crystallographic data for the complex (β-CD)$_2$·(Cs^+ niflumate$^-$)$_4$·22H_2O are listed in Table II and Fig. 6 shows the asymmetric unit in the crystal. This unit

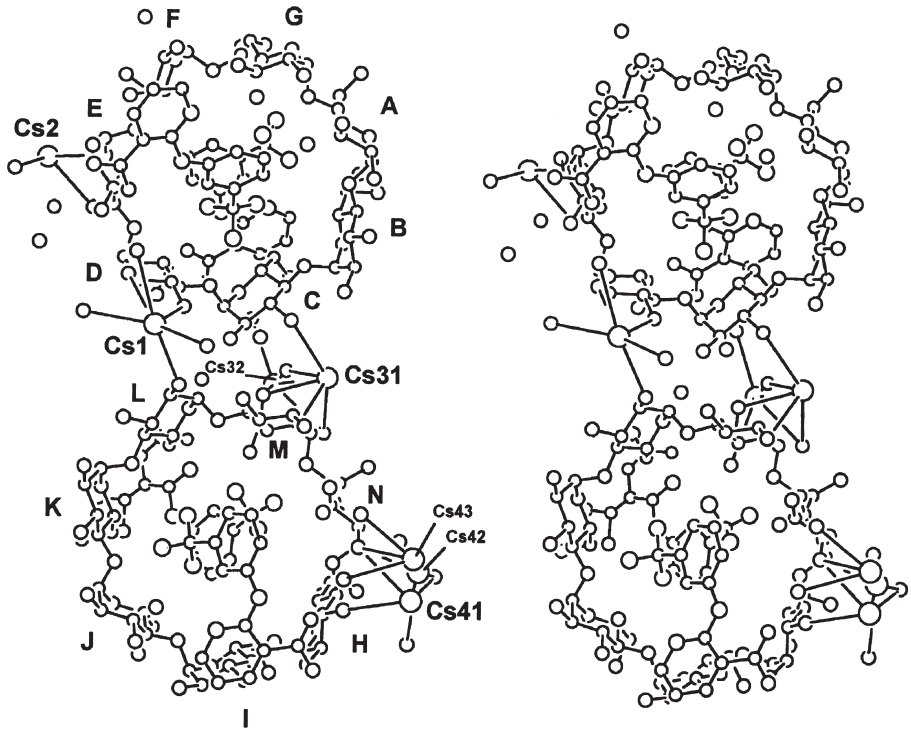

FIGURE 6 Stereo view of the asymmetric unit showing non-hydrogen atoms only in ball-and-stick mode. The β-CD molecules are viewed from their secondary sides. Isolated spheres are O atoms of water molecules not bound to metal ions.

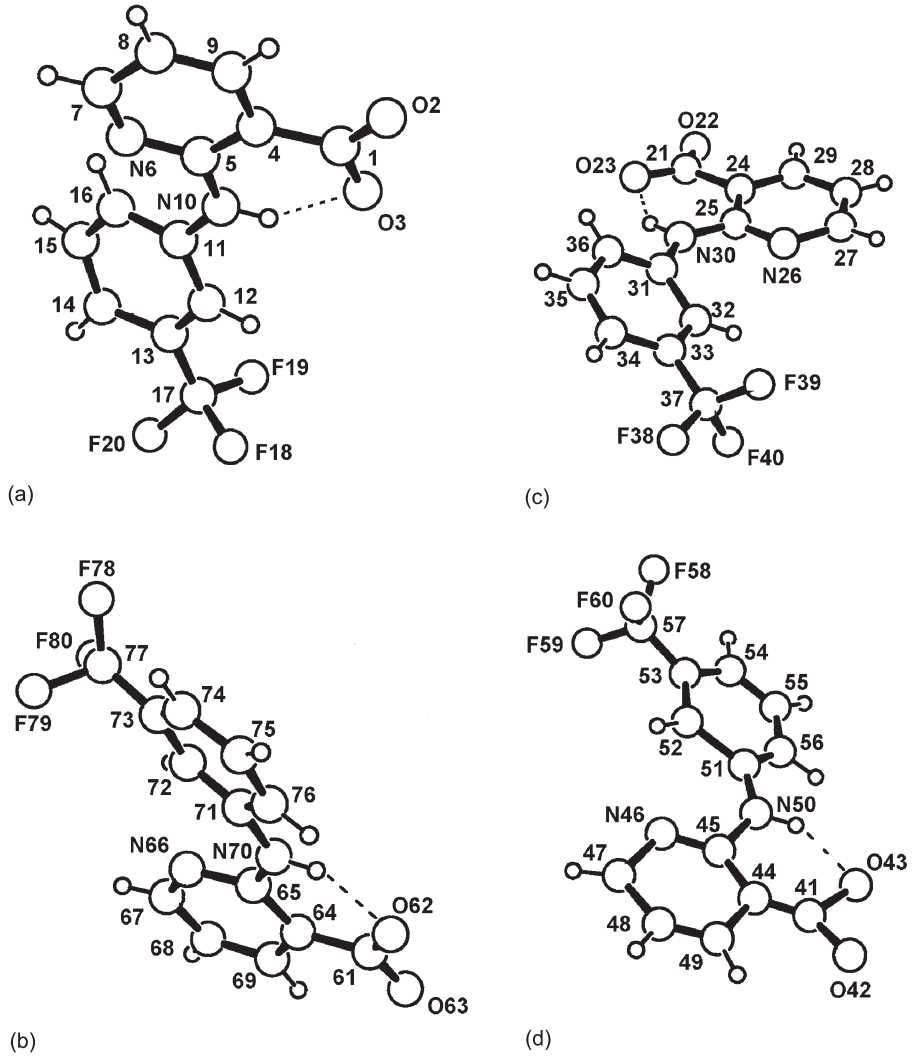

FIGURE 7 Conformations of the four independent niflumate anions in the crystal. The dotted lines indicate the intramolecular hydrogen bonds.

comprises two β-CD molecules (CD1, residues A–G and CD2, H–N), four Cs^+ ions, four niflumate ions and 22 water molecules. Positions of the components of the two disordered metal ions are also indicated. Cation disorder in crystals of such complexes is not uncommon. Cs^+ ion disorder has been observed in the α-CD complex of a metallacarborane [6] and we have reported Na^+ ion disorder in the β-CD complex of the NSAID sodium meclofenamate [7]. The Cs^+ ions have mixed environments, being coordinated to water molecules, drug carboxylate oxygen atoms and to oxygen atoms of the β-CD molecules. All four Cs^+ ions act as bridges linking adjacent β-CD molecules by coordination to various combinations of O2, O3 (secondary hydroxyl), O5 (pyranose) and O6 (primary hydroxyl) host atoms. The mode of guest inclusion is analogous in each of the independent host molecules and involves insertion of the guest trifluoromethylphenyl residue from both the primary and the secondary host sides.

Guest Conformations and Mode of Inclusion

Figure 7 shows the conformations of the four independent niflumate anions, A and B being associated with host molecule CD1 and C and D with host CD2. In each anion, the pyridine ring with its attached carboxylate and amine residues form a planar system stabilised by intramolecular hydrogen bonds N–H···O with N···O 2.62(1)–2.67(1) Å. This plane is twisted significantly with respect to the phenyl ring plane, as indicated by the torsion angle C5–N10–C11–C16 (anion A) and its analogues in the anions B, C and D, with values 30, −22, −32, 22°, respectively, with average estimated standard deviation (e.s.d.) 2°.

Details of the inclusion mode are shown in Fig. 8. The trifluoromethylphenyl residues of niflumate anions A and B insert from the secondary and primary sides, respectively, of one of the independent β-CD molecules. An analogous inclusion mode is observed for the guest anions C and D in the

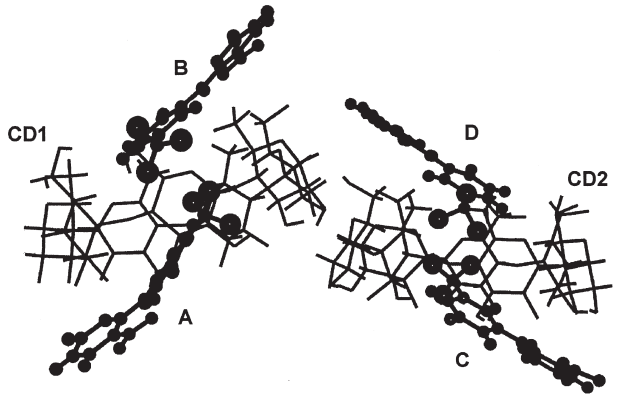

FIGURE 8 Details of the guest inclusion mode in the independent host molecules.

second host molecule. In all cases, the sense of the twisting between the principal residues of the anions referred to above favours maximum penetration of the $-CF_3$ groups into the centre of the β-CD cavities. Space-filling models show that the $-CF_3$ moieties of the two anions entering a β-CD molecule are nearly in van der Waals contact, with closest F···F contacts of 3.04 and 3.16 Å (sum of van der Waals radii 2.7 Å). As a measure of the extent of penetration of the four $-CF_3$ moieties, the distances of the respective C atoms from the least-squares planes through the seven glycosidic oxygen atoms of each independent host molecule were calculated. These distances are 2.95 and 2.69 Å for guest entry from the β-CD primary sides (C77, C57, Fig. 7) but only 0.47 and 1.02 Å for entry from the secondary sides (C17, C37). The phenyl rings enter the β-CD cavities at shallow angles. Phenyl rings of anions A and B make dihedral angles of 41.9(4) and 30.2(4)°, respectively, with their β-CD glycosidic oxygen mean plane. The corresponding data for anions C and D are 34.7(4) and 31.7(5)°.

Despite the difference in host–guest stoichiometry in the two phases (1:1 in solution vs. 1:2 in the crystal), the modes of guest inclusion are analogous. The two important features revealed by the X-ray analysis, viz. (a) preference for inclusion of the trifluoromethylphenyl residue of the niflumate anion (rather than the pyridinecarboxylato residue) and (b) equal facility of entry of the trifluoromethylphenyl residue from the primary or secondary sides of the β-CD molecule, are in accord with the results from the solution study. The latter revealed large shifts for the guest phenyl ring protons while the pyridine rings protons were unaffected. In addition, almost identical shifts for the host H3 and H5 signals were observed.

TABLE III Geometrical parameters for the β-cyclodextrin molecules

Residue	D* (Å)	ϕ† (°)	d‡ (Å)	α¶ (°)	D_3§ (Å)	τ‖ (°)
CD1						
A	4.40	129.5	−0.235	87.5	2.73	51
B	4.35	127.9	−0.102	82.4	2.71	58
C	4.33	127.8	0.244	71.9	2.83	52
D	4.43	128.7	0.080	87.2	3.03	58
E	4.35	127.4	−0.401	85.9	2.75	54
F	4.37	127.9	0.228	74.9	2.81	57
G	4.37	127.3	0.186	86.8	2.74	−176
CD2						
H	4.37	127.4	−0.015	76.9	2.83	67 160
I	4.32	127.4	−0.092	78.3	2.79	54
J	4.45	129.1	0.035	88.5	2.73	52
K	4.35	130.9	0.126	87.8	2.73	54
L	4.37	125.8	−0.156	73.9	2.98	69
M	4.41	128.0	0.016	78.5	2.87	54
N	4.43	130.8	0.087	86.2	2.85	61

*Glycosidic O4n···O4($n+1$) distance. †O4($n-1$)···O4n···O4($n+1$) angle. ‡Deviations of atoms O4n from their least-squares planes (mean e.s.d. 0.006 Å). ¶Dihedral angle between the mean O4n plane and the mean C2n, C3n, C5n, O5n plane of each residue (mean e.s.d. 0.5°). §Inter-ring hydrogen bond O(2n)···O3($n-1$) distances (mean e.s.d. 0.005 Å). ‖Torsion angle C4n–C5n–C6n–O6n (mean e.s.d. 1.5°).

Geometries of the Host Molecules

Table III lists the parameters defining the conformations of the two independent β-CD molecules [8]. All of the D-glucose units adopt the usual $^4C_1$ conformation (Fig. 6) with the majority of the primary hydroxyl groups in a gauche–gauche orientation (torsion angle τ). Exceptions occur for residues G (CD1) and H (CD2, disordered site). Values of the O4n···O4($n+1$) distances (D) and O4($n-1$)···O4n···O4($n+1$) angles (ϕ) indicate that there is little deviation from seven-fold rotational symmetry for the glycosidic oxygen atoms in either host molecule. However, host distortion resulting from two factors, namely coordination of Cs^+ ions to CD hydroxyl oxygen atoms and inclusion of the guest anions, is evident from the deviations (d) and tilt angles (α). The rms values for d are 0.233 (CD1) and 0.091 Å (CD2), indicating slight puckering of the O4 mean planes. More severe, however, are the irregular tilts (α) of the glucopyranose rings relative to the O4 mean planes. Table III shows that in host CD1, five of the glucose residues adopt "normal" tilts (mean 86°) towards the seven-fold axis of the macrocycle [8] but residues C and F show significantly larger tilts of the host primary sides towards the axis. From Fig. 6, it is evident that these abnormal tilts are partly due to Cs^+ ion coordination in these regions as well as steric effects from guest pyridinecarboxylate residues, which are in van der Waals contact with the primary and secondary sides of residues C and F, respectively. Similar distortions occur for residues H, I, L and M for analogous reasons. Irregular tilts of the glucopyranose residues are also responsible for some variation in parameter D, measuring the O2n···O3($n-1$) hydrogen bonded

TABLE IV Principal Cs^+–O distances (<3.5 Å) involving fully occupied ions (Cs1, Cs2) and the major components (Cs31, Cs41) of the disordered ions

Cs^+–O (carboxylate)	Cs^+–O (water)
Cs1–O62[a] 3.44(1)	Cs1–OW1 3.35(1)
Cs1–O63[a] 3.30(1)	Cs1–OW2 3.38(1)
Cs2–O2[b] 3.35(1)	Cs1–OW3 3.31(1)
Cs2–O22[c] 3.31(1)	Cs2–OW4 3.22(2)
Cs31–O42[d] 3.21(2)	Cs31–OW6 3.48(1)
Cs31–O43[d] 3.05(1)	Cs31–OW8 3.05(2)
	Cs41–OW4[e] 3.43(2)
	Cs41–OW15 3.05(2)
Cs–O (cyclodextrin)	
Cs1–O2L 3.15(1)	Cs31–O3C 3.49(2)
Cs1–O2D 3.39(1)	Cs31–O5M 3.26(1)
Cs1–O3D 3.40(1)	Cs31–O6M 3.02(2)
Cs1–O6B[f] 3.05(1)	Cs31–O6K[d] 3.23(1)
Cs2–O5H[g] 3.13(1)	Cs41–O2N 3.36(1)
Cs2–O6I[g] 3.04(1)	Cs41–O3H 3.37(1)
Cs2–O6H2[g]* 3.40(4)	Cs41–O2F[h] 3.28(1)
Cs2–O5E 3.30(1)	Cs41–O3G[h] 3.46(2)
Cs2–O6E 3.09(1)	

*Disordered component of atom O6H. Symmetry code: (a) $-1+x, y, z$; (b) $1+x, y, z$; (c) $-x, 1/2+y, 1-z$; (d) $x, y, 1+z$; (e) $-x, -1/2+y, 1-z$; (f) $-1+x, y, -1+z$; (g) $1-x, 1/2+y, 1-z$; (h) $-x, -1/2+y, 2-z$.

distances (2.71(1)–3.03(1) Å) between contiguous glucosidic units.

Metal Ion Coordination and Crystal Hydration

The caesium ions play multiple roles in the crystal, being co-ordinated to guest carboxylate oxygen atoms and water molecules, as well as bridging β-CD molecules by co-ordination to host hydroxyl and pyranose oxygen atoms. Table IV lists the principal Cs^+–O distances. Each Cs^+ ion has a co-ordination sphere with unique geometry. Since this is the first structurally well-characterised β-CD complex containing caesium ions [9], a summary of the co-ordination environments is given here. As shown in Fig. 6 and Table IV, Cs1 bridges the two independent β-CD molecules by co-ordination to O2 and O3 of residue D (CD1) and to O2 of residue L (CD2). There is further bridging by Cs1–O6 of residue B of a symmetry-related CD1 molecule. The co-ordination sphere is completed by three terminal water molecules and the two carboxylate O atoms of symmetry-related anion B (not shown). CD1 and CD2 are also bridged by Cs31 which co-ordinates to O3 of residue C (CD1) and atoms O5 and O6 of residue M (CD2). Further bridging by Cs31–O6K of symmetry-related CD2 occurs; the co-ordination of Cs31 is completed by bonding to two carboxylate O atoms and two water molecules. Cs2 bridges CD1 and symmetry-related CD2 by co-ordination to O5 and O6 on the primary side of residue E (CD1) and to atoms O5H, O6I and O6H2 of symmetry-related CD2. In this case, the co-ordination sphere is completed by a single water molecule (OW4) and one carboxylate O atom from each of anions A and C. Cs41 has no links to carboxylate O atoms and instead achieves six co-ordination by bridging CD2 (atoms O2N, O3H) and symmetry-related CD1 (O2F, O3G) and bonding to two water molecules. The Cs^+–O distances in Table IV span a wide range. For comparison, Cs^+–O (hydroxyl) and Cs^+–O (water) distances of 2.99 and 3.22 Å, respectively, occur in the α-CD complex of a metallacarborane [6].

The 22 water molecules in the asymmetric unit are distributed over 24 sites, 19 with site-occupancy factors (sof's) 1.0 and the remainder with sof's in the range 0.4–0.6. Those which do not co-ordinate to Cs^+ ions engage in a complex network of hydrogen bonds to one another and to atoms of the host molecules and guest anions.

Crystal Packing

As shown in the stereo view of Fig. 9, stacking of the two independent β-CD molecules with their respective pairs of guest anions results in parallel, infinite columns along the short cell *a*-axis. The host molecules within a column are thus successively interleaved by two guest anions which are in close contact. This arrangement represents a novel stacking mode for β-CD inclusion complexes.

Materials and Methods

NMR Experiments

The β-CD (water content 8 mol/mol) was purchased from Sigma Chemie GmbH (Germany) and D_2O (deuterium content 99.7%) from the Institute of Cryogenics and Isotope Separations (Rm. Vălcea, Romania). Niflumic acid was purchased from Sigma Chemical Company (MO, USA). Proton NMR spectra were performed at 300 MHz using a Varian Gemini spectrometer. The NMR spectra were recorded in D_2O solution at 298 ± 0.5 K and all chemical shifts were measured relative to external TMS. Typical conditions were as follows: 32 K data points; sweep width 4500 Hz giving a digital resolution of 0.28 Hz/point. The pulse width was 5 μs (45°) and the spectra were collected by co-addition of 32 or 64 scans. Due to the extremely low solubility of niflumic acid in water, it was converted to its sodium salt by titration with NaOD in D_2O to a final pH = 12 (uncorrected metre reading). At this pH value the niflumic acid is practically completely ionised and two stock solutions (both 10 mM) of sodium niflumate and β-CD were prepared in D_2O. The stoichiometry of the complex was determined by the continuous variation method. The overall concentration of the two species was kept constant ($[H]+[G]=M=$ 10 mM) and the ratio $r=[H]/([H]+[G])$ was varied from 0 to 1. This was accomplished using the

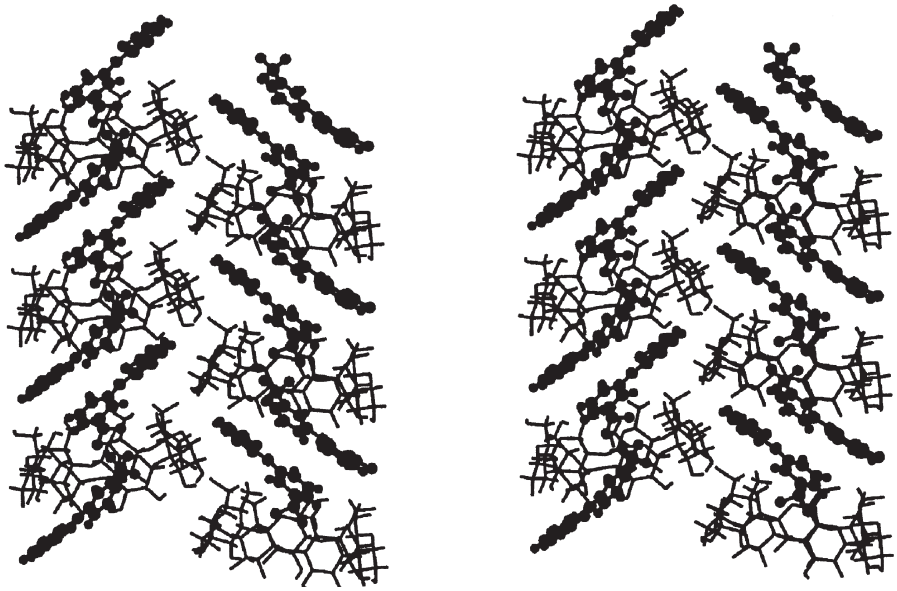

FIGURE 9 Stereo view illustrating the stacking of the complex units which generates crystallographically independent columns parallel to the crystal *a*-axis.

equimolar solutions of H and G and mixing them to constant volume to the desired ratio *r*. [*H*] and [*G*] are the total concentrations of the host and guest, respectively. The quantity $\Delta\delta_{obs}^{(X)}[X]$ where X = H or G was plotted against *r*. $\Delta\delta_{obs}^{(X)}$ is the difference between the chemical shift of free X and the observed value for a given ratio *r*.

For determination of the association constant (*K*), the same set of samples as that for the determination of stoichiometry was used. The data were evaluated according to Eq. (1):

$$\Delta\delta_{obs}^{(X)} = \left\{ M + \frac{1}{K} - \left[\left(M + \frac{1}{K} \right)^2 - 4[H][G] \right]^{1/2} \right\} \times \frac{\Delta\delta_C^{(X)}}{2[X]} \quad (1)$$

in which $\Delta\delta_C^{(X)}$ represents the chemical shift difference (for a given proton) between the free molecule and the pure complex [10].

X-ray Diffraction

Equimolar amounts of CsOH and niflumic acid were reacted by adding 0.1 M CsOH dropwise to a suspension of 100 mg niflumic acid (0.35 mmol) in 1 ml distilled water. After neutralisation (pH = 10), the solution was added to an aqueous solution of β-CD at 45°C containing 356 mg (0.31 mmol) of the host. Filtration of the solution (0.45 μm) and slow evaporation over several months yielded colourless prismatic crystals. Elemental analysis yielded C 37.72%, H 4.76%, N 2.43%, in agreement with the calculated values of C 37.79%, H 5.04%, N 2.59% for $C_{136}H_{172}N_8O_{78}Cs_4{\cdot}22H_2O$ corresponding to $(\beta\text{-CD})_2{\cdot}(Cs^+niflumate^-)_4{\cdot}22H_2O$, and also consistent with the structural analysis. Preliminary X-ray photography indicated Laue $2/m$ symmetry and the space group $P2_1$ was deduced from systematic absences ($0k0$: $k = 2n + 1$ only). Intensity data were collected on a Nonius Kappa CCD diffractometer from a crystal coated with Paratone N oil (Exxon) and cooled to 173 ± 1 K using a Cryostream cooler (Oxford Cryosystems). Data collection (COLLECT software [11]) involved a combination of ϕ- and ω-scans of 0.3° each with a crystal to detector distance of 71.0 mm. Program DENZO-SMN [12] was used for cell refinement and data reduction. For the specimen used, absorption was negligible (μR range 0.1–0.2). The structure was solved by direct methods (SHELXS97 [13]) and refined by full-matrix least-squares against F^2 (SHELXL97 [14]). One of the β-CD primary O atoms was disordered over two sites and modelled accordingly. Of the four unique Cs^+ ions, two were ordered while the other two were disordered over two and three major sites, respectively. Owing to the relatively large number (260) of non-H atoms in the asymmetric unit, anisotropic refinement was confined to the ordered Cs^+ ions, and the oxygen atoms of the two independent β-CD molecules and those of the four drug anions. The remaining atoms refined isotropically. H atoms were added in idealized positions to the host and guest atoms in a riding model with $U_{iso} = 1.2$ times those of the parent atoms but water H atoms were not included. Significant residual electron density peaks (max 1.5 eÅ^{-3}) were found close to the disordered Cs^+ ions as a result of their being treated isotropically.

In the final refinement, 30 low-angle reflections were omitted as their observed intensities were significantly less than their calculated values due to beam-stop truncation.

The CIF file for the structure has been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 176683).

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