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Encapsulation of sodium nimesulide and precursors in β-cyclodextrin

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Crystalline 1 : 1 inclusion complexes with β-cyclodextrin (β-CD) and the sodium salt of nimesulide (4-nitro-2-phenoxymethanesulfonanilide), and the sodium salt of the derivative 2-phenoxymethanesulfonanilide, have been prepared by co-precipitation from aqueous solution. The presence of true inclusion complexes was supported by elemental analysis, thermogravimetry and powder X-ray diffraction. FTIR and ^{13}C CP MAS NMR spectroscopy confirmed that no chemical modification of the guests occurred upon formation of inclusion complexes. The reaction of the precursors 2-phenoxynitrobenzene and 2-phenoxyaniline with β-CD was also studied and crystalline inclusion complexes with a 2 : 1 (host-to-guest) stoichiometry were isolated. The interaction of the different guest species with β-CD host molecules was studied theoretically by carrying out *ab initio* calculations. Favourable inclusion geometries were obtained for the four guests mentioned above. On the other hand, it was found that the inclusion of the neutral guests nimesulide and 2-phenoxymethanesulfonanilide was considerably less favourable. This is in agreement with the experimentally observed difficulty in isolating true inclusion complexes containing these guests and β-CD. The calculated lower stability is attributed to the different steric hindrance arising from the different conformational preferences of neutral and anionic forms.

Introduction

Nimesulide (4-nitro-2-phenoxymethanesulfonanilide) **4** is a non-steroidal anti-inflammatory drug (NSAID) that is particularly selective towards cyclooxygenase-2 inhibition.[1,2] This selectivity probably accounts for why the drug induces only a moderate incidence of gastric side effects. The main drawback of nimesulide is that, like many other NSAIDs, it has a very poor water solubility (about 0.01 mg mL^{-1}) that imposes bioavailability problems *in vivo*.[2] One technique for increasing the aqueous solubility of acidic drugs like nimesulide relies on the use of cyclodextrins (CDs), torus-shaped oligosaccharides that can form inclusion complexes by taking up the guest molecule into their central hydrophobic cavity.[3] In one patent application, an inclusion compound of nimesulide with β-cyclodextrin was obtained by spray-drying of an ammoniacal solution of nimesulide and CD.[4] The enhancement of nimesulide solubility by this method (to ~16 mg mL^{-1}) is due not only to the effect of cyclodextrin but also to the formation of a more soluble nimesulide salt. It was subsequently reported that complexation with β-CD of the sodium salt of nimesulide **6** can increase the aqueous solubility of nimesulide (5000 times) as well as the solubility in acidic medium (seven times) and at pH 6.8 (34 times).[5] The incorporation of a nimesulide–L-Lysine salt into β-CD further increased the water solubility of nimesulide across a wide pH range.[6]

Nimesulide–cyclodextrin drug formulations are available commercially and have been undergoing clinical trials. These studies indicate that the combination of nimesulide with cyclodextrin results in a faster onset of analgesic action.[7,8] The potential significance of these drug formulations makes it important to understand how nimesulide interacts with cyclodextrins, both in solution and in the solid state. In the case of the nimesulide–L-Lysine complex mentioned above, the inclusion was proven in the solid state by differential scanning calorimetry and in solution by ^{1}H NMR spectroscopy.[6] The NMR results suggest that, in solution, the nitrophenyl ring is included in the CD cavity. Miro and co-workers also investigated the interactions between nimesulide and cyclodextrin both in solution and in the solid state.[9] Two different methods in solution (phase solubility and UV spectrophotometry) indicated an apparent stability constant of ~550 M^{-1}, assuming the formation of a 1 : 1 complex. Nimesulide/β-cyclodextrin formulations were isolated by various methods (physical mixing, kneading, co-evaporation, freeze-drying and spray-drying) and characterised by DSC, powder X-ray diffraction (XRD) and FTIR spectroscopy.[9] In the present paper, we describe the synthesis, by co-precipitation from aqueous solution, of β-CD inclusion complexes containing the precursors 2-phenoxynitrobenzene **1** and 2-phenoxyaniline **2**, and the sodium salts of 2-phenoxymethanesulfonanilide **5** and nimesulide **6**. The products have been characterised in the solid state by elemental analysis, thermogravimetry (TG), powder XRD, FTIR and ^{13}C magic angle spinning (MAS) NMR spectroscopy. In addition, *ab initio* calculations have been performed in order to compare possible host–guest inclusion geometries for the different systems.

Results and discussion

Synthesis and characterisation of inclusion compounds

The precursor compounds 2-phenoxynitrobenzene **1** and 2-phenoxyaniline **2** (Chart 1) are partially soluble in water and therefore a co-precipitation method from aqueous solution was used to prepare β-CD inclusion complexes **1a** and **2a**. Specifically, the solids **1** and **2** were added to a solution of β-CD in water at 80 °C. Slow cooling of the resulting solutions led to the precipitation of crystalline products. Elemental analysis indicated the formation of 2 : 1 (host-to-guest) inclusion com-

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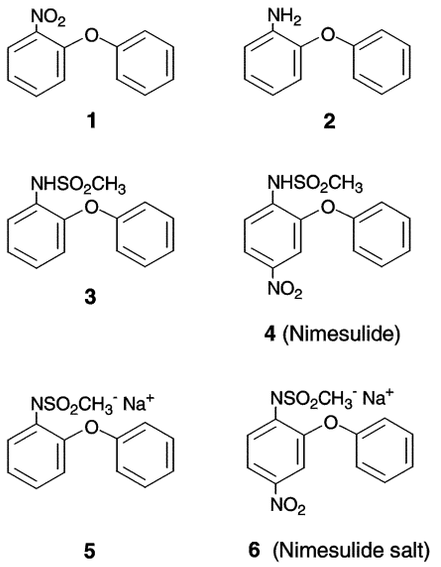

Chart 1

plexes, designated as 2β-CD·(2-phenoxynitrobenzene) **1a** and 2β-CD·(2-phenoxyaniline) **2a**. This method could not be used for the encapsulation of 2-phenoxymethanesulfonanilide **3** and nimesulide **4**, due to the poor solubility of the guest compounds in water. Co-precipitation from mixed solvent solutions (water/ethanol/1,4-dioxane) resulted only in the crystallisation of the pure components β-CD and **3** or **4**. The reaction of dichloromethane solutions of **3** or **4** with an aqueous solution of β-CD was also unsuccessful. On the other hand, inclusion compounds could readily be obtained by the addition of the sodium salts of either 2-phenoxymethanesulfonanilide **5** or nimesulide **6** to an aqueous solution of β-CD at 90 °C. This difference in behaviour is not surprising since it has already been reported that ionised forms of certain acidic drugs (e.g., indomethacin, acetazolamide, sulfamethoxazole) yield more stable complexes with cyclodextrins than the respective unionised form.[10,11] Elemental analysis indicated the formation of 1 : 1 (host-to-guest) inclusion complexes, designated as β-CD·(2-phenoxymethanesulfonanilide salt) **5a** and β-CD·(nimesulide salt) **6a**.

Thermal analysis of cyclodextrin–drug formulations can be useful for the recognition of inclusion complex formation.[12] TGA of plain β-CD hydrate shows loss of hydrated water up to 75 °C (15.2%, 11–12 water molecules per β-CD molecule) (Fig. 1). There is no further change until about 235 °C when the compound starts to melt and decompose, characterised by a peak in the differential thermogravimetric (DTG) profile at 294 °C. At 500 °C, 100% mass loss is complete. TG analysis of 2-phenoxyaniline **2** reveals that the compound starts to evaporate at 75 °C, slightly above the melting point of *ca.* 45 °C. Further heating to 190 °C results in complete mass loss (the boiling point is 172–173 °C). In the case of a physical mixture of β-CD and **2** (1 : 1 molar ratio), each component behaves independently, that is, well-defined steps are visible in the TG profile corresponding to the points where β-CD melts and decomposes, and 2-phenoxyaniline evaporates. The thermal behaviour of the inclusion compound **2a** is quite different, especially in the temperature range 25–240 °C. In this range, a protracted mass loss takes place (13.8%), attributed to removal of water molecules located in the β-CD cavities, and also in the interstices between the macrocycles. Removal of 2-phenoxyaniline molecules may also take place in this temperature range, although there is no well-defined step as observed for the pure non-included compound **2**. This is an early indication for the formation of a true inclusion complex. Decomposition of **2a** takes place in two steps above 240 °C, quite similar to pure β-CD hydrate, and mass loss is 96% at 500 °C. Very similar

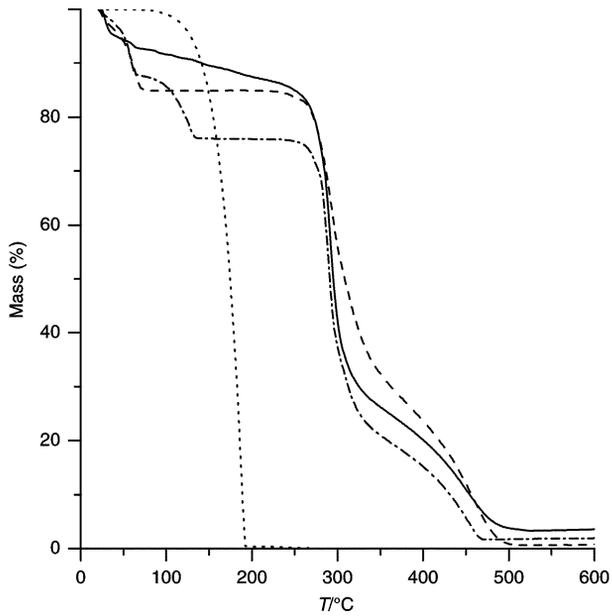

Fig. 1 TGA of 2β-CD·(2-phenoxyaniline) **2a** (—), 2-phenoxyaniline **2** (···), free β-CD hydrate (---), and a physical mixture of β-CD and **2** in a 1 : 1 molar ratio (-·-).

results to these were obtained for 2-phenoxynitrobenzene **1** and 2β-CD·(2-phenoxynitrobenzene) **1a** (not shown).

Fig. 2 shows the results of TG analysis of β-CD·(nimesulide salt) **6a**, the sodium salt of nimesulide **6**, pure β-CD hydrate and a physical mixture of β-CD and **6** in a 1 : 1 molar ratio. Compound **6** exhibits two abrupt mass losses in the temperature range 25–300 °C. The first of these occurs between 83 and 100 °C (4.6%) and is attributed to the removal of water of crystallisation. The compound then starts to melt at 240 °C, and a well-defined mass loss occurs between 250 and 300 °C (24.8%), possibly associated with the decomposition of the methanesulfonamide functional group. Further heating to 540 °C leaves a residual mass of 22.3%. The thermal behaviour of compound **6a** is comparable with that of pure β-CD hydrate except that the amount of easily removed water is less (7.8% mass loss between 23 and 90 °C) and melting/decomposition occurs at a slightly lower temperature (onset at 190 °C, DTG_{max}

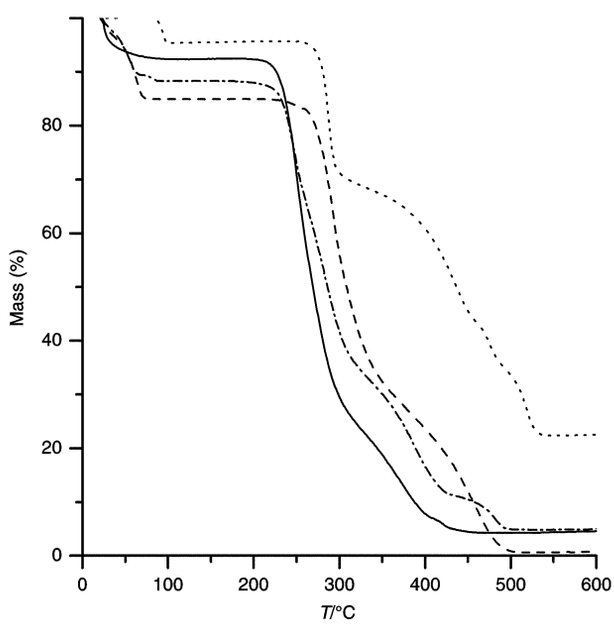

Fig. 2 TGA of β-CD·(nimesulide salt) **6a** (—), nimesulide sodium salt **6** (···), free β-CD hydrate (---), and a physical mixture of β-CD and **6** in a 1 : 1 molar ratio (-·-).

= 260 °C). The residual mass at 450 °C is 5%. As found for the other systems discussed above, the TG behaviour of the physical mixture of pure β-CD hydrate and compound **6a** can be interpreted in terms of the individual components. One apparent difference is that β-CD in the mixture melts and decomposes at a slightly lower temperature than pure β-CD hydrate. This may be due to the promoting effect of the nimesulide salt on the decomposition of cyclodextrin. The inclusion complex **5a** exhibits a similar TG profile to that of **6a** (onset at 190 °C, DTG_{max} = 260 °C), except that the mass loss in the range 23 to 100 °C was 9.3% (not shown).

The X-ray powder diffraction patterns of pure β-CD hydrate, compounds **2**, **5** and **6**, and the resulting inclusion complexes **2a**,**5a** and **6a**, are shown in Fig. 3. The product 2β-CD·(2-phenoxyaniline) **2a** is crystalline and its powder XRD pattern is very distinct from those of either compound **2** or pure β-CD hydrate, suggesting the formation of a new phase corresponding to a true inclusion complex.[13] The pattern is characterised by low angle peaks at 15.02, 12.48, 9.18, 7.44, 6.18, 5.89, 5.04 and 4.83 Å. It is known that cyclodextrin inclusion compounds usually crystallise from water to give "channel" or "cage" structures in which the cyclodextrin molecules are stacked like coins in a roll or arranged in a herring-bone pattern.[13] Caira established the existence of a series of distinct isostructural CD inclusion complexes,[14] and showed that the type of packing mode present in a given complex can be determined by comparison of its experimental powder diffraction pattern with simulated patterns calculated from known crystal structures. Fig. 3 also shows a simulated powder diffraction pattern calculated from the crystal structure data for the 1 : 1 (host : guest) β-CD inclusion

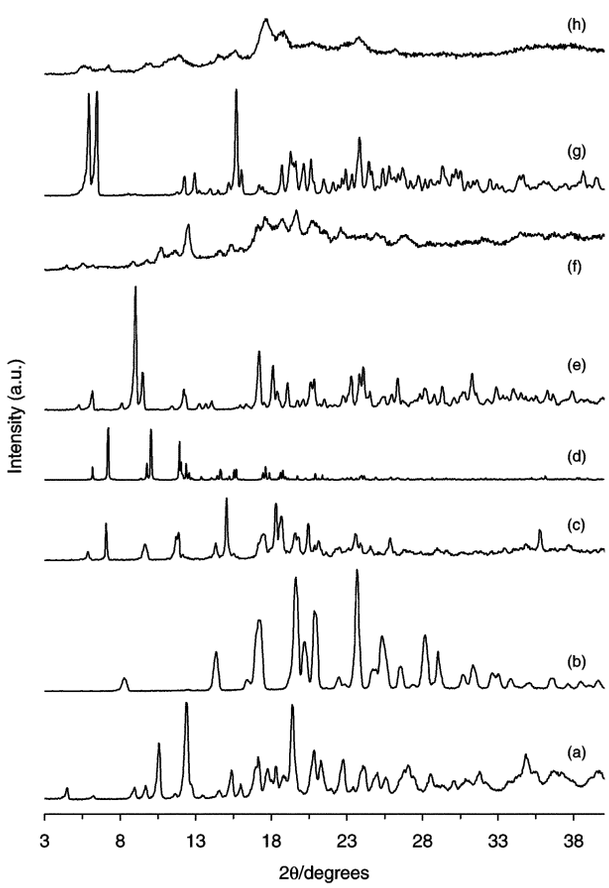

Fig. 3 Powder XRD patterns of (a) plain β-CD hydrate, (b) 2-phenoxyaniline **2**, (c) β-CD inclusion complex **2a**, (d) the 1 : 1 complex of β-CD with benzocaine (calculated), (e) 2-phenoxymethanesulfonanilide sodium salt **5**, (f) β-CD inclusion complex **5a**, (g) nimesulide sodium salt **6**, and (h) β-CD inclusion complex **6a**. The program PowderCell[16] was used to produce the calculated pattern (d) using the crystal structure data reported in the literature[14] (guest molecules were omitted from the calculations for simplicity).

compound of benzocaine (ethyl 4-aminobenzoate).[15] This compound exhibits the typical channel-type structure consisting of head-to-head dimers of β-CD molecules stacked along the crystallographic *c* axis. The coincidence of the calculated pattern with the experimental pattern of compound **2a**, especially at low angles (2θ = 3–20°), indicates that the crystal packing of the β-CD host molecules in **2a** is very similar. Compound **5a**, on the other hand, exhibits a different powder XRD pattern that resembles that of pure β-CD hydrate, although there are substantial changes in the intensities of certain peaks with slight changes in the 2θ values. This suggests that the major phase in **5a** comprises β-CD molecules arranged in a herring-bone-type pattern, as found in either pure β-CD hydrate or β-CD inclusion compounds with small alcohols.[17] Additional weak reflections at 15.30, 7.51, 5.00 and 4.72 Å may be indicative of a minor phase consisting of a channel-type inclusion compound as described above. Compound **6a** appears to be the least crystalline of the four inclusion complexes prepared in this work. However, the powder XRD pattern matches quite well with that of compound **2a**, suggesting the presence of a channel-type inclusion compound. It is surprising that the structurally similar sodium salts **5** and **6** give rise to β-CD inclusion complexes with identical stoichiometries (1 : 1) but different structures, as evidenced by powder X-ray diffraction.

Fig. 4 shows the ^{13}C CP MAS NMR spectra of pure β-CD hydrate, compounds **2**, **5** and **6**, and the resulting inclusion complexes **2a**,**5a** and **6a**. The spectrum of β-CD hydrate is similar to that previously reported and exhibits multiple resonances for each type of carbon atom.[18–20] This has been mainly correlated with different torsion angles about the (1 → 4) linkages for C-1 and C-4,[18,19] and with torsion angles describing the orientation of the hydroxyl groups.[20] The different carbon resonances are assigned to C-1 (101–104 ppm), C-4 (78–84 ppm), C-2,3,5 (71–76 ppm) and C-6 (57–65 ppm). By contrast, the corresponding β-CD carbons for the inclusion complexes are generally observed as single broad peaks at 103.4, 81.0, 72.9 and 59.9 ppm, respectively. This can tentatively be attributed to inclusion complexation, assuming that inclusion of guest molecules in the β-CD cavities will be accompanied by the host molecule adopting a more symmetrical conformation, with each glucose unit in a similar environment.[21] In addition to the resonances for the β-CD carbons, the spectra of **2a**, **5a** and **6a** exhibit several relatively weak, broad lines that can be assigned to the carbon atoms of the guest molecules. These are weakly shifted compared with the corresponding lines for the non-included compounds, confirming that no chemical modification of the guests occurs upon formation of inclusion complexes.

Ab initio calculations

Fig. 5 shows a typical inclusion geometry found for β-CD and 2-phenoxyaniline **2**. Within the resolution of the scheme it can also be used to describe the results with 2-phenoxynitrobenzene **1** as the guest species. The inclusion of the non-substituted ring leaves the substituted ring in a nearly up-right position, allowing the approach of a second host molecule and the formation of a head-to-head dimer (*i.e.*, 2 : 1 host-to-guest geometry). This seems to fit very well with the characterisation data for compound **2a**.

Concerning the interaction of phenoxymethanesulfonanilide **3**, nimesulide **4**, and the corresponding sodium salts **5** and **6**, with β-CD, particular attention was paid to the preferred fragment for inclusion and to a comparison between the inclusion of neutral (**3**, **4**) and anionic (**5**, **6**) forms (Fig. 6). For the sodium salt of nimesulide, the best inclusion geometry was found to be the one where the SO_2CH_3 fragment is encapsulated (see the graphical abstract), resulting in a stabilisation energy of *ca.* 10 kJ mol^{-1} [Fig. 6(a)]. The corresponding energy for the inclusion of the non-substituted aromatic ring is only slightly less (*ca.* 7 kJ mol^{-1}). Therefore it is difficult to draw any firm

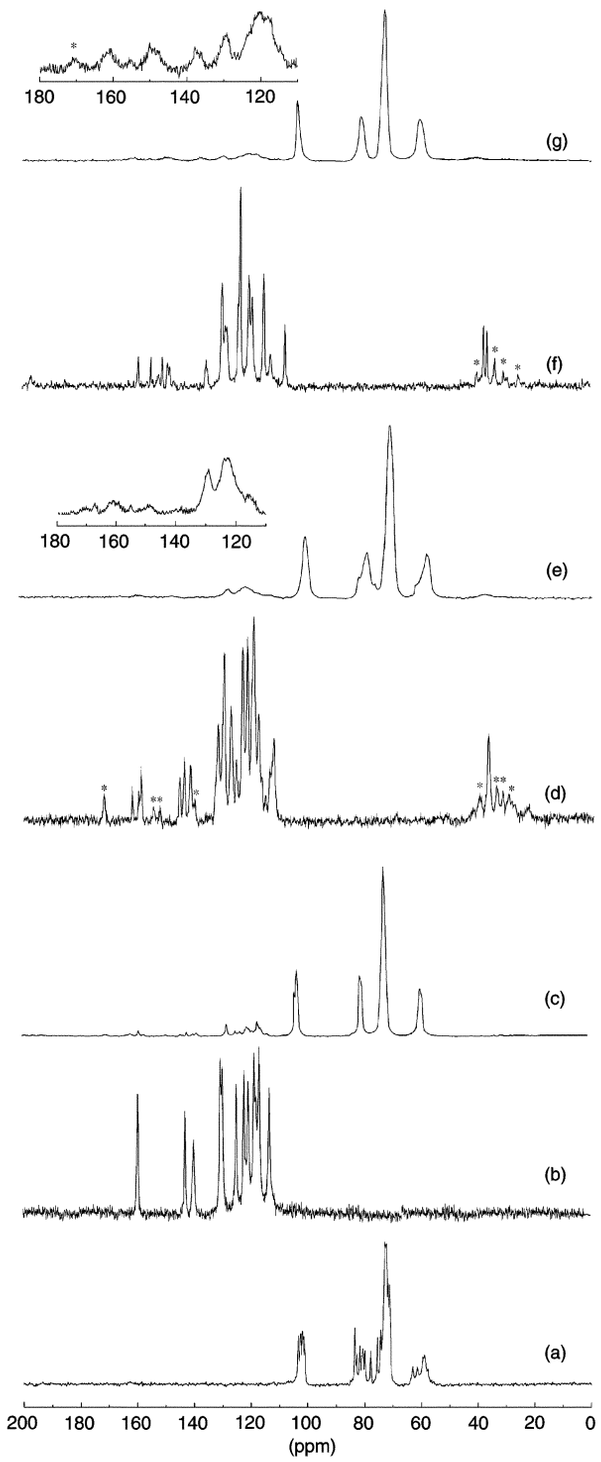

Fig. 4 Solid-state ^{13}C CP MAS NMR spectra of (a) plain β-CD hydrate, (b) 2-phenoxyaniline **2**, (c) β-CD inclusion complex **2a**, (d) 2-phenoxymethanesulfonanilide sodium salt **5**, (e) β-CD inclusion complex **5a**, (f) nimesulide sodium salt **6**, and (g) β-CD inclusion complex **6a**. Spinning sidebands are denoted by *.

conclusions about which form is likely to dominate in the solid-state for compound **6a**. In either case, the spatial orientation of the non-included fragments prevents the approach of further CD hosts, which suggests that the formation of head-to-head dimers with 2 : 1 host-to-guest geometry is not possible. Piel *et al.* reported the preparation (by co-precipitation from aqueous solution) of a nimesulide–L-lysine–β-cyclodextrin complex with 1 : 1 : 1 stoichiometry.[6] The solution ^1H NMR results for this complex indicated that the nitrophenyl ring is included in the β-CD cavity, rather than the non-substituted ring, in agreement with the *ab initio* calculations reported here.

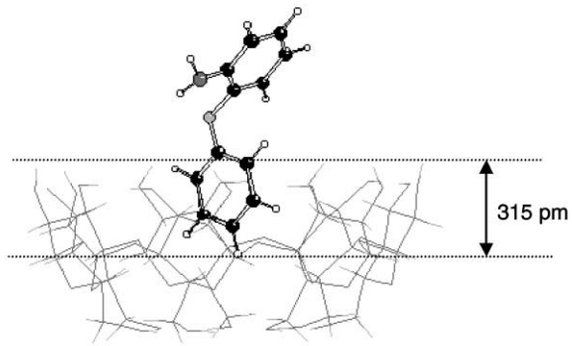

Fig. 5 Schematic view of the lowest energy structure for the inclusion of 2-phenoxyaniline **2** in β-cyclodextrin.

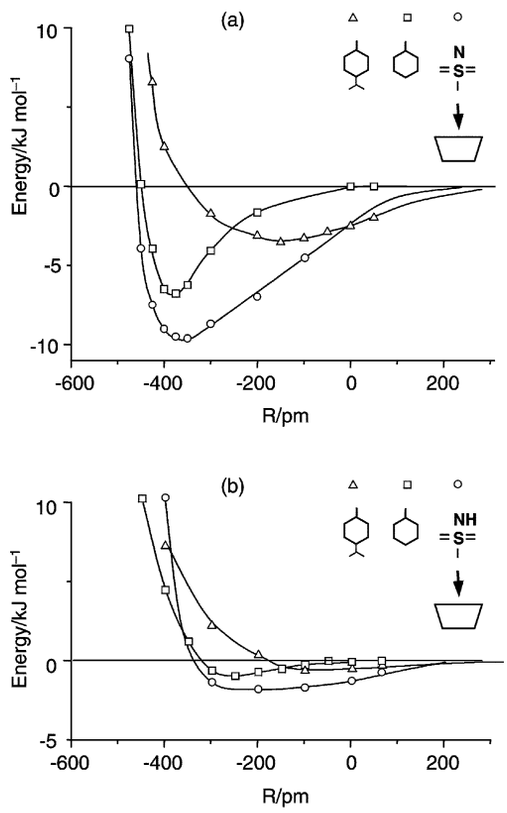

Fig. 6 Calculated energy *vs.* host–guest distance plot for the interaction of the sodium salt of nimesulide **6** (a) and nimesulide **4** (b) with β-cyclodextrin. *R* is defined as the distance between the plane of the outer hydrogen atoms in the secondary hydroxyl groups of β-CD and the nearest hydrogen atom of the approaching guest. Negative *R* values refer to inclusion.

The interaction of β-CD with nimesulide **4** presents a much lower stability (<2 kJ mol^{-1}) regardless of which fragment is encapsulated [Fig. 6(b)], in agreement with the observed experimental difficulties in preparing the inclusion complexes **3a** and **4a**. This lower stability must be related with the different steric hindrance arising from the different conformational preferences of neutral and anionic forms. For instance, the extended *trans* geometry adopted by the C–N–S–CH_3 fragment in **6** is more favourable to inclusion than the preferred *gauche* geometry of the same fragment in the neutral form **4** (Fig. 7).

Conclusions

In this study, experimental and theoretical methods have successfully been combined to study the formation of stable inclusion compounds between β-cyclodextrin and four derivatives of diphenyl ether. The inclusion compounds were

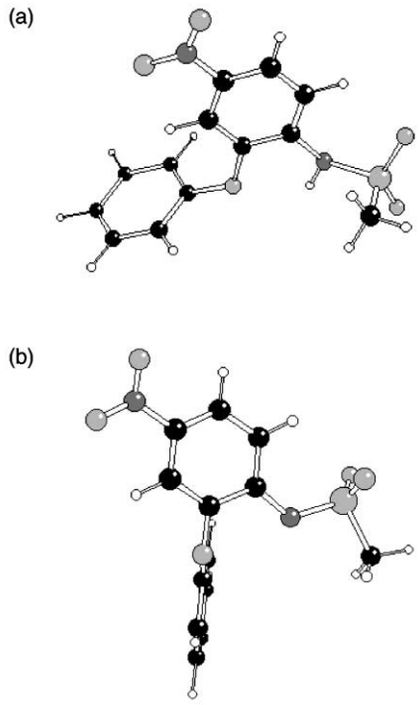

Fig. 7 Optimised structure of the lowest energy conformation for nimesulide in neutral (a) and anionic (b) forms.

prepared by co-precipitation from aqueous solution, leading to 2 : 1 complexes in the case of 2-phenoxynitrobenzene and 2-phenoxyaniline, and 1 : 1 complexes in the case of the sodium salts of 2-phenoxymethanesulfonanilide and nimesulide. The inclusion of the guest species was proved in the solid state by thermogravimetry, powder X-ray diffraction and ^{13}C MAS NMR spectroscopy. In accordance with these results, *ab initio* calculations predict the existence of stable inclusion geometries for these four host–guest systems. The calculations also predict that the formation of stable inclusion geometries for the neutral compounds 2-phenoxymethanesulfonanilide and nimesulide is considerably less favourable. This may explain, at least in part, the experimentally observed difficulty in isolating true inclusion compounds containing these guest species.

Experimental

Materials and methods

Powder XRD data were collected on a Philips X'pert diffractometer using Cu Kα radiation filtered by Ni (λ = 1.5418 Å). TGA studies were performed using a Shimadzu TGA-50 thermogravimetric analyser at a heating rate of 1 °C min^{-1} under air, with a flow rate of 30 mL min^{-1}. Infrared spectra were recorded on a Mattson Mod 7000 FTIR spectrophotometer using KBr pellets. Solid state ^{13}C CP MAS NMR spectra were recorded at 100.62 MHz, on a 9.4 T Bruker Avance 400 spectrometer (25 °C, 4.5 μs ^{1}H 90° pulses, 2.0 ms contact time, 9 kHz spinning rate and 4 s recycle delays). Chemical shifts are quoted in parts per million from TMS.

Distilled water, and analytical grade ethanol, tetrahydrofuran and dichloromethane were used as solvents. β-CD, kindly donated by Wacker-Chemie (Munich), was re-crystallised prior to use. The precursors 2-phenoxynitrobenzene **1**,[22,23] 2-phenoxyaniline **2**,[24] 2-phenoxymethanesulfonanilide **3**,[24] and nimesulide **4**[24] were prepared according to published procedures. ^{13}C CP MAS NMR of **2**: δ = 160.3, 143.7, 140.5, 131.4, 130.8, 125.7, 122.9, 121.6, 119.4, 118.7, 117.7, 114.2. ^{13}C CP MAS NMR of **3**: δ = 154.2, 152.2, 132.9, 130.6, 127.7, 124.8, 121.9, 115.1, 39.4.

2-Phenoxymethanesulfonanilide sodium salt 5

A solution of 2-phenoxymethanesulfonanilide **3** (3.10 g, 0.012 mol) in tetrahydrofuran (20 cm^3) was added to a stirred solution of sodium metal (0.30 g, 0.014 mol) in tetrahydrofuran (20 cm^3). The mixture was heated under reflux for 6 h, after which the solution was cooled to ambient temperature, ethanol (2 cm^3) carefully added and stirring continued for 1 h. The solvents were removed under reduced pressure and the solid residue re-suspended in dichloromethane, filtered and washed several times with dichloromethane to give the sodium salt **5** (2.70 g, 80%) (Found: C, 54.7; H, 4.1; N, 4.85; S, 11.35%. Calc. for $C_{13}H_{12}O_3NSNa$: C, 54.75; H, 4.25; N, 4.9; S, 11.25%); ν_{max}/cm^{-1} 3594s, 3460vs, 3243s, 3073s, 3065s, 3018sh, 2936m, 2926m, 2095w, 2015w, 1941w, 1894w, 1858w, 1786w, 1641sh, 1622s, 1601s, 1586s, 1564m, 1487vs, 1450s, 1411m, 1321s, 1297s, 1257s, 1226vs, 1209s, 1192sh, 1167m, 1158m, 1146m, 1111vs, 1098vs, 1074sh, 1042m, 1024m, 996s, 965m, 958m, 927m, 896m, 869m, 853m, 805s, 789s, 756s, 747vs, 692s, 552m, 519s, 468s, 457s; ^{13}C CP MAS NMR: δ = 161.9, 159.6, 158.8, 145.1, 143.7, 141.4, 131.7, 129.7, 127.4, 125.3, 123.2, 121.5, 119.2, 117.5, 112.2, 37.0, 34.3.

Nimesulide sodium salt 6

Sodium metal (0.28 g, 0.012 mol) was added to a stirred solution of nimesulide **4** (3.10 g, 0.01 mol) in tetrahydrofuran (20 cm^3). After heating under reflux for 4 h, the solution was cooled to ambient temperature, ethanol carefully added and stirring continued for 1 h. The solvents were removed under reduced pressure and the solid residue re-suspended in dichloromethane (200 cm^3), filtered and washed several times with dichloromethane to give the sodium salt **6** (2.60 g, 79 %) (Found: C, 46.9; H, 3.35; N, 8.5; S, 9.85%. Calc. for $C_{13}H_{11}O_5N_2SNa$: C, 47.25; H, 3.35; N, 8.5; S, 9.7%); ν_{max}/cm^{-1} 2927m, 1648m, 1584m, 1493s, 1328vs, 1301vs, 1262m, 1245s, 1221s, 1107s, 1083s, 981s, 959m, 800m, 747m, 690m, 527m; ^{13}C CP MAS NMR: δ = 159.1, 154.6, 151.8, 150.6, 148.7, 147.9, 135.0, 129.5, 128.5, 127.8, 123.7, 120.1, 118.9, 114.8, 112.5, 107.3, 37.5, 36.3.

2β-CD·(2-phenoxynitrobenzene) 1a

2-Phenoxynitrobenzene **1** (26.2 μl, 0.15 mmol) was added to a stirred solution of β-CD (0.200 g, 0.15 mmol) in water (10 cm^3) at 80 °C. The mixture was maintained at this temperature for 2 h, after which it was cooled slowly over 48 h to give the inclusion complex **1a** (0.150 g, 75% relative to β-CD) as small (0.1–0.2 mm) crystals (Found: C, 43.5; H, 6.2; N, 0.45%. Calc. for $2(C_{42}H_{70}O_{35})\cdot(C_{12}H_9NO_3)\cdot10H_2O$: C, 43.25; H, 6.45; N, 0.55%); ν_{max}/cm^{-1} 3377vs, 2925s, 1744m, 1638m, 1612m, 1589m, 1531s, 1492m, 1480m, 1411m, 1368m, 1348m, 1334m, 1302m, 1244m, 1198m, 1157s, 1100sh, 1079s, 1055s, 1028vs, 1003sh, 945m, 938sh, 756m, 704m, 692sh, 650w, 607m, 577m, 529m; ^{13}C CP MAS NMR: δ = 154.0, 152.5, 148.6, 140.2, 134.1, 129.2, 125.4, 123.0, 117.3 (all guest aryl–C), 103.5 (br, β-CD, C-1), 81.0 (br, β-CD, C-4), 72.6 (br, β-CD, C-2,3,5), 60.2 (br, β-CD, C-6).

2β-CD·(2-phenoxyaniline) 2a

2-phenoxyaniline **2** (0.028 g, 0.15 mmol) was added to a stirred solution of β-CD (0.200 g, 0.15 mmol) in water (10 cm^3) at 80 °C. The mixture was maintained at this temperature for 2 h, after which it was cooled slowly over 48 h to give the inclusion complex **2a** (0.130 g, 65% relative to β-CD) as small (0.3–0.5 mm) crystals (Found: C, 41.7; H, 6.4; N, 0.5%. Calc. for $2(C_{42}H_{70}O_{35})\cdot(C_{12}H_{11}ON)\cdot18H_2O$: C, 41.5; H, 6.8; N, 0.5%); ν_{max}/cm^{-1} 3385vs, 2931m, 1623m, 1587m, 1504m, 1489m, 1462m, 1418m, 1370m, 1334m, 1302m, 1222m, 1157s, 1011sh, 1079s, 1054s, 1027vs, 1004sh, 945m, 938sh, 862w, 755m, 746sh, 704m, 691m, 608m, 578m, 529w; ^{13}C CP MAS NMR: δ = 162.0,

158.9, 157.1, 144.2, 142.3, 140.1, 138.6, 129.4, 128.2, 125.0, 123.5, 121.1, 120.4, 119.0, 117.2, 116.2, 113.9 (all guest aryl–C), 104.1 (sh, β-CD, C-1), 103.3 (br, β-CD, C-1), 81.2 (br, β-CD, C-4), 72.6 (br, β-CD, C-2,3,5), 59.9 (br, β-CD, C-6).

β-CD·(2-phenoxymethanesulfonanilide salt) 5a

The sodium salt **5** (0.142 g, 0.502 mmol) was added to a stirred solution of β-CD (0.660 g, 0.502 mmol) in water (1 cm^3) at 90 °C. Stirring was continued at this temperature and the solution concentrated to give the inclusion complex **5a** (0.740 g, 92.3%) as a pale pink precipitate (Found: C, 40.6; H 6.65; N, 0.7; S, 1.4%. Calc. for $(C_{42}H_{70}O_{35})\cdot(C_{13}H_{12}O_3NSNa)\cdot 12H_2O$: C, 40.3; H, 6.5; N, 0.85; S, 1.95%); ν_{max}/cm^{-1} 3367vs, 2923m, 1649m, 1588m, 1491m, 1414m, 1370m, 1336m, 1305m, 1251m, 1205m, 1158s, 1103m, 1080s, 1053sh, 1028vs, 1003s, 946m, 937m, 860m, 793sh, 756m, 704m, 609m, 574m, 529m, 513sh; ^{13}C CP MAS NMR: δ = 155.4, 149.9, 129.6, 123.4, 116.0 (br, all guest aryl–C), 102.9 (sh, β-CD, C-1), 102.5 (br, β-CD, C-1), 80.8, 78.2 (β-CD, C-4), 72.8 (br, β-CD, C-2,3,5), 59.9 (β-CD, C-6), 38.8 (guest–SO_2CH_3).

β-CD·(nimesulide salt) 6a

The sodium salt **6** (0.166 g, 0.502 mmol) was added to a stirred solution of β-CD (0.660 g, 0.502 mmol) in water (1 cm^3) at 90 °C. Stirring was continued at this temperature and the solution concentrated to give the inclusion complex **6a** (0.760 g, 92%) as a bright yellow precipitate (Found: C, 40.5; H, 6.25; N, 1.8; S, 1.95%. Calc. for $(C_{42}H_{70}O_{35})\cdot(C_{13}H_{11}O_5N_2SNa)\cdot 9H_2O$: C, 40.6; H, 6.15; N, 1.7; S, 2.0%); ν_{max}/cm^{-1} 3383vs, 2927m, 1640m, 1601m, 1591sh, 1581m, 1490s, 1455m, 1415m, 1367m, 1324m, 1291s, 1220m, 1156s, 1101s, 1078s, 1054s, 1027vs, 1004sh, 945m, 862m, 839m, 796m, 755m, 704m, 654w, 578m, 530m; ^{13}C CP MAS NMR: δ = 170.8, 161.2, 155.5, 150.1, 137.2, 129.5, 120.1, 118.0 (br, all guest aryl–C), 103.3 (br, β-CD, C-1), 80.9 (br, β-CD, C-4), 72.6 (br, β-CD, C-2,3,5), 60.1 (br, β-CD, C-6), 40.0 (br, guest –SO_2CH_3).

Computational details

All *ab initio* calculations were performed using the GAUSSIAN 98w package.[25] Molecular structures were fully optimised at the HF/6-31G* standard levels,[26] starting from several distinct geometries. Harmonic vibrational wavenumbers were calculated at the same level using analytical second derivatives. Concerning the inclusion compounds, the possible inclusion geometries were evaluated by a set of single point calculations, using the two-layer approximation of Morokuma and co-workers (ONIOM keyword of GAUSSIAN 98).[27–29] Nimesulide was treated as high layer (6-31G*), while β-CD was set as low layer (Stevens/Basch/Krauss ECP minimal basis set [30,31]).

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