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Fluorine-19 Nuclear Magnetic Resonance Study of the Inclusion of Fluoro- and Difluoro-*trans*-cinnamates by α-Cyclodextrin

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^{19}F n.m.r. studies of the inclusion of *o*-, *m*-, *p*- and α-fluoro-*trans*-cinnamates and *o*, *p*- and α,*p*-difluoro-*trans*-cinnamates by α-cyclodextrin (αCD) have shown that two inclusion equilibria

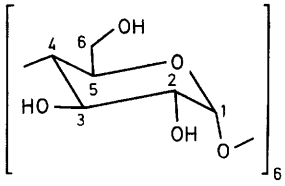
$$S + \alpha CD \overset{K_1}{\rightleftharpoons} S\cdot\alpha CD$$

$$S\cdot\alpha CD + \alpha CD \overset{K_2}{\rightleftharpoons} S\cdot(\alpha CD)_2$$

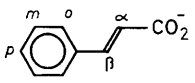
are established in D_2O solution at pD = 8.5 ± 0.1. Typically at 294 K, $K_1 = 111 \pm 13$ dm^3 mol^{-1} and $K_2 = 23 \pm 2$ dm^3 mol^{-1} for α,*p*-difluoro-*trans*-cinnamate. Chemical-shift and other data indicate that the predominant S·αCD complex is that in which the carboxylate group of the fluorocinnamate enters the wide end of the αCD cavity, delineated by twelve secondary hydroxy groups, first. The S·(αCD)$_2$ complex probably has a structure in which the fluoro-*trans*-cinnamate is encapsulated by two αCD with the wide ends of their cavities in close proximity.

α-Cyclodextrin (αCD) or cyclohexa-amylose is a six-membered α-1,4-linked cyclic oligomer of D-glucopyranose [structure (I)], which forms inclusion complexes with a variety of substrates in aqueous solution.[1–6] Usually the 1:1 complex S·αCD is readily formed and a 1:2 complex, S·(αCD)$_2$, has also been observed although there have been few studies of this latter species.[7,8] A knowledge of the stoichiometry of the cyclodextrin inclusion complexes and the environmental changes experienced by the substrate on inclusion is of intrinsic interest. This interest is increased by the use of cyclodextrin inclusion complexes as models for the host–guest interaction thought to be important in enzyme–substrate and drug–receptor systems, and also by the potential importance of cyclodextrin inclusion complexes in the design of controlled chemical syntheses.[1–6]

^{1}H and ^{13}C n.m.r. spectroscopy has proved to be a powerful tool in the study of cyclodextrin inclusion complexes[7,9,10] but has been hampered by the substantial number of resonances arising from both the cyclodextrin and the included substrates. The use of selectively fluorinated substrates and ^{19}F n.m.r. spectroscopy avoids such potential difficulties and has provided considerable insight into enzyme–substrate interactions.[11–16] Accordingly in this study ^{19}F n.m.r. spectroscopy is employed to



(I)



(II)

examine the inclusion of *o*-, *m*-, *p*- and α-fluoro-*trans*-cinnamates and the *o*, *p*- and α,*p*-difluoro-*trans*-cinnamates [structure (II)] by α-cyclodextrin. These selectively fluorinated substrates provide an opportunity to determine the stoichiometry of the inclusion complexes formed and to assess the environmental changes experienced by the substrate and thereby gain insight into the stereochemistry of the inclusion complex.

EXPERIMENTAL

α-Cyclodextrin (Sigma) was stored as the anhydrous material over P_2O_5 in a vacuum desiccator prior to use. The *o*-, *m*- and *p*-fluoro- and *o*,*p*-difluoro-*trans*-cinnamic acids were prepared by saponification of the corresponding ethyl esters obtained from a Wittig condensation of the appropriate fluorobenzaldehyde and carboxymethylidene triphenylphosphorane using a modification of a literature method.[17–22] α-Fluoro-*trans*-cinnamic acid was also prepared by a literature method.[23] α,*p*-Difluoro-*trans*-cinnamic acid was prepared as follows. *p*-Fluorobenzaldehyde (6.2 g, 0.05 mol) was reacted with ethyl fluoroacetate under literature conditions[23] to give ethyl-α,*p*-difluoro-*trans*-cinnamate (4.31 g, 41%), b.p. 78–80 °C, 0.15 mmHg. Calculated for $C_{11}H_{10}O_2F_2$ (%): C, 62.26; H, 4.75; F, 17.91. Found (%): C, 62.35; H, 5.02; F, 17.8. ν_{max} = 1730, 1665, 1605 and 1510 cm^{-1}. ^1H n.m.r. (CCl_4): δ 1.37 (3H, t, J = 7 Hz, OCH_2CH_3), 4.25 (2H, d, J = 7 Hz, OCH_2CH_3), 6.77 (1H, d, $J_{H\text{-}F}$ = 41 Hz, C*H*=CF) and 6.8–7.6 (4H, m, C_6H_4); m/e = 212 (M^+, 100%), 184(30), 167(44) and 139(25). Concentrated hydrochloric acid (15 cm^3) was added dropwise to the ester (2.0 g, 0.009 mol) and the crude product was filtered off and recrystallised from aqueous acetic acid to give α,*p*-difluoro-*trans*-cinnamic acid (1.51 g, 87%), m.p. 205–206 °C. ν_{max} (nujol) = 1680, 1650 and 1595 cm^{-1}. ^1H n.m.r. ([$^2H_6$]acetone): δ 7.00 (1H, d, $J_{F\text{-}H}$ = 37 Hz, CH=CF) and 7.02–7.83 (4H, m, C_6H_4). m/e = 184 (M^+, 100%), 164(19) and 120(28). The fluoro-*trans*-cinnamic acids are almost insoluble in water and in consequence only the water-soluble sodium fluorocinnamates were studied by ^{19}F n.m.r. These salts were prepared by stoichiometric neutralisation of the acid with sodium hydroxide and the solid product was obtained by freeze drying.

The solutions for ^{19}F n.m.r. study were made up in D_2O and the pD was adjusted to 8.5 ± 0.1 with DCl + D_2O. The total α-cyclodextrin concentration, [αCD], varied in the range 0–0.130 mol dm^{-3}, the fluoro-*trans*-cinnamate concentration was constant at 10^{-3} mol dm^{-3} and all solutions were 0.10 mol dm^{-3} in sodium chloride.

^{19}F n.m.r. spectra were recorded on a Bruker CXP300 n.m.r. spectrometer at 282.35 MHz locked on the D_2O deuterium frequency. An average of 5000 transients was collected for each spectrum into a 8192 point data base. The samples in 5 mm n.m.r. tubes were thermostatted at 294.0 ± 0.3 K. Chemical shifts were measured relative to a 2% sodium trifluoroacetate + D_2O solution sealed in a capillary. The use of such an external reference introduces the possibility of the incorporation of bulk susceptibility effects into the observed ^{19}F chemical shifts. Accordingly the bulk susceptibility variation introduced through the variation of [αCD] was simulated by preparing a series of D_2O solutions containing D-glucose at up to six times the maximum [αCD] employed in the fluorocinnamate inclusion studies. These solutions were also 0.10 mol dm^{-3} in sodium chloride and 2% in sodium trifluoroacetate. The ^{19}F shifts of the latter

from the ^{19}F frequency of a 2% sodium trifluoroacetate + D_2O solution sealed in a capillary were then plotted against [αCD] to produce a bulk susceptibility correction chart for the ^{19}F shifts observed in the fluoro-*trans*-cinnamate solutions. The shift difference between the internal and external trifluoroacetate resonances increased smoothly to a maximum of 0.07 ppm at [D-glucose] = 0.78 mol dm^{-3}. Thus the bulk susceptibility corrections required were very small compared with the shift variation observed for fluoro-*trans*-cinnamate as [αCD] varied (fig. 1–3, *vide infra*). (Trifluoroacetate is included by αCD and consequently cannot be used as an internal reference.) No significant shift or linewidth variation of the α- and *p*-^{19}F resonances of α,*p*-difluoro-*trans*-cinnamate were induced by up to 0.78 mol dm^{-3} D-glucose in D_2O solution in the presence of 0.10 mol dm^{-3} sodium chloride, and similar behaviour is assumed for the other fluoro-*trans*-cinnamates.

RESULTS

The ^{19}F resonances of the ring substituent fluorines (multiplets with J_{F-H} = 7–9 Hz for *o*-, *p*- and *m*-fluoro- and J_{F-F} = 15.7 for *o*,*p*-difluoro-*trans*-cinnamate) and the α-fluorines (doublets with J_{F-H} = 36.2 and 37.6 Hz for α-fluoro- and α,*p*-difluoro-*trans*-cinnamate, respectively) are characterised by chemical shifts upfield from the ^{19}F resonance of CF_3COO^- (table 1). The hyperfine splitting of these resonances is lost as the concentration of αCD is increased and a systematic variation of the chemical shift occurs. The magnitude and direction of the chemical-shift variation depends on the site of the fluorine atom in the fluoro-*trans*-cinnamate as does the systematic broadening of the ^{19}F resonances, as exemplified by α,*p*-difluoro-*trans*-cinnamate (fig. 1). Over the total [αCD] range examined for all six fluoro-*trans*-cinnamates only one resonance was observed for each fluorine in the fluoro-*trans*-cinnamate, consistent with site exchange of the fluoro-*trans*-cinnamate occurring rapidly on the n.m.r. timescale. With the possible exception of *m*-fluoro-*trans*-cinnamate the ^{19}F chemical-shift variations are biphasic (fig. 2 and 3), consistent with the formation of two inclusion complexes:

$$S + \alpha CD \overset{K_1}{\rightleftharpoons} S\cdot\alpha CD \tag{1}$$

$$S\cdot\alpha CD + \alpha CD \overset{K_2}{\rightleftharpoons} S\cdot(\alpha CD)_2. \tag{2}$$

Using the non-linear least-squares program DATAFIT, these chemical shifts were fitted to

$$\delta = \frac{\delta_0[S] + \delta_1[S\cdot\alpha CD] + \delta_2[S\cdot(\alpha CD)_2]}{[S] + [S\cdot\alpha CD] + [S\cdot(\alpha CD)_2]} \tag{3}$$

which describes the variation of the observed chemical shift, δ with the variation of [αCD], where δ_0, δ_1, and δ_2 are the chemical shifts of S, S·αCD and S·$(\alpha CD)_2$, respectively. In the case of the two difluoro-*trans*-cinnamates both chemical-shift variations were fitted simultaneously to eqn (3). The curves in fig. 2 and 3 represent the best fits of the data to eqn (3) and the best-fit values of K_1, K_2, δ_1 and δ_2 are given in table 1. Qualitatively the variation of δ with [αCD] for the two *o*-, three *p*- and two α- ^{19}F resonances are seen to represent three distinct families of curves, which implies a correlation between the stereochemistry of the inclusion complexes and the ^{19}F chemical-shift variation. Similar trends are observed in the δ_1 and δ_2 data of table 1. In the case of the *m*-fluoro-*trans*-cinnamate the ^{19}F chemical-shift variation is relatively small and does not exhibit a noticeable biphasic variation. By analogy with the other fluoro-*trans*-cinnamates it is reasonable to assume that both S·αCD and

Table 1. Equilibrium constants and ^{19}F chemical shifts[a]

trans-cinnamate	K_1 /dm^3 mol^{-1}	K_2 /dm^3 mol^{-1}	δ_0[b] (ppm)	δ_1 (ppm)	δ_2 (ppm)	$\delta_1-\delta_0$ (ppm)	$\delta_2-\delta_0$ (ppm)	$\delta_2-\delta_1$ (ppm)
α-fluoro-	184 ± 16	7.8 ± 1.0	−42.82	−39.44 ± 0.17	−32.00 ± 0.01	3.38	10.81	7.43
p-fluoro-	109 ± 10	35 ± 1	−36.72	−35.66 ± 0.05	−40.78 ± 0.03	1.06	−4.06	−5.1
α,*p*-difluoro-	111 ± 13	23 ± 2	(α) −44.11	−39.75 ± 0.39	−32.54 ± 0.15	4.36	11.57	7.21
			(*p*) −36.80	−35.54 ± 0.10	−41.68 ± 0.13	1.26	−4.89	−6.15
o-fluoro-	49 ± 2	39 ± 2	−41.43	−39.51 ± 0.08	−42.75 ± 0.01	1.92	−1.33	−3.25
o,*p*-difluoro-	32 ± 3	94 ± 5	(*o*) −37.13	−35.03 ± 0.14	−37.32 ± 0.01	2.10	−0.19	−2.29
			(*p*) −33.14	−33.09 ± 0.09	−36.55 ± 0.02	0.06	−3.41	−3.47
cinnamate[c]	110	15						
cinnamic acid[c]	2260	60						

[a] Shifts are relative to CF_3COO^- and are corrected for bulk susceptibility variations. A negative sign signifies an upfield shift. The experimental temperature was 294.0 ± 0.3 K. [b] Error is 0.01 ppm. [c] Ref. (8).

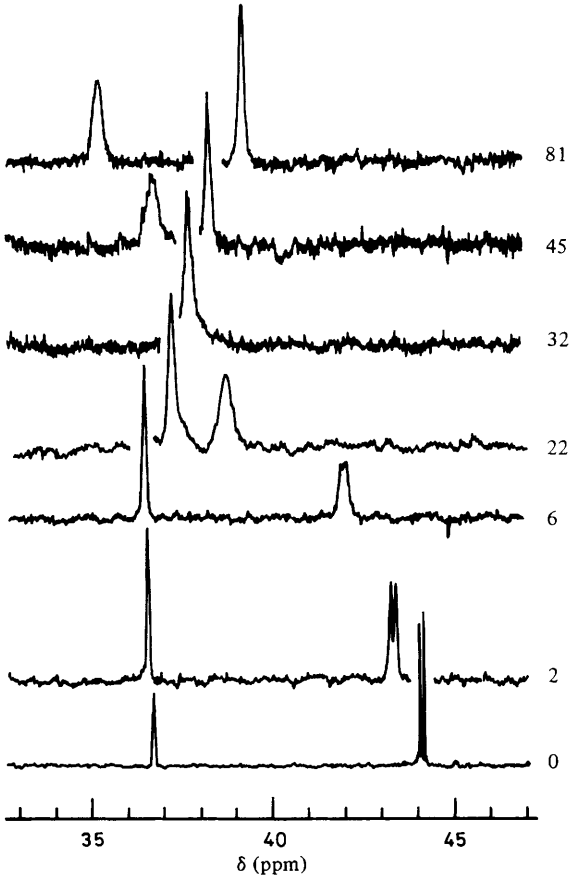


Fig. 1. Variation of the ^{19}F (282.35 MHz) spectrum of α,*p*-difluoro-*trans*-cinnamate in the presence of αCD in D_2O at pD 8.5±0.1 in the presence of 0.1 mol dm^{-3} NaCl at 294.0 K. In the bottom spectrum the doublet (−44.11 ppm) arises from α-F and the unresolved multiplet (−36.80 ppm) arises from *p*-F. [difluoro-*trans*-cinnamate] = 10^{-3} mol dm^{-3} and [αCD]/10^{-3} mol dm^3 are shown on the spectra.

$S\cdot(\alpha CD)_2$ are also formed in this case. Nevertheless a unique fit of the *m*-fluoro-*trans*-cinnamate data to eqn (3) could not be obtained and the reason for this may be that a fortuitous combination of δ_1, δ_2, K_1 and K_2 values eliminates the biphasic chemical-shift variation observed in the other data sets. [A fit of the *m*-fluoro-*trans*-cinnamate data to the appropriate equation for the equilibrium shown in eqn (1) yields $K_1 = 31.0 \pm 0.4$ dm^3 mol^{-1} and $\delta_1 - \delta_0$ (apparent) = 1.50±0.01 ppm; the best fit is shown in fig. 2.]

The variation of the ^1H decoupled fluoro-*trans*-cinnamate ^{19}F linewidth with [αCD] is also markedly biphasic with the exception of the *m*-fluoro-*trans*-cinnamate system, which exhibits no significant broadening. In the absence of αCD the ^{19}F linewidths are 3–5 Hz (1.6 Hz digital resolution) and the maximum broadening observed for the α,*p*-difluoro-*trans*-cinnamate system is 120 and 45 Hz for the α- and *p*-^{19}F resonances, respectively. As [αCD] increases the line broadening increases systematically to a maximum coincident with the maximum [S·αCD] as calculated from K_1 and K_2 (table

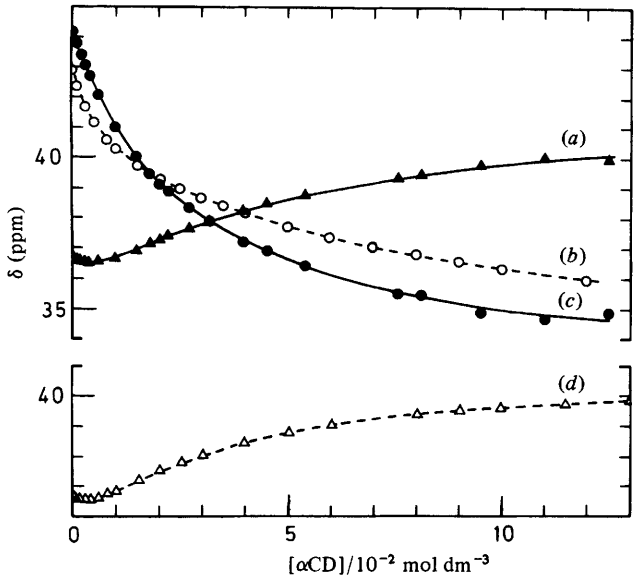


Fig. 2. Variation of the ^{19}F chemical shifts (δ) of fluoro- and difluoro-*trans*-cinnamate with α-cyclodextrin concentration, [αCD]. The experimental data are shown as individual points and the best fits of these data to eqn (3) are shown as curves. Curves (*a*) and (*c*) pertain to *p*- and α-F, respectively, of α,*p*-difluoro-*trans*-cinnamate and curves (*b*) and (*d*) pertain to α- and *p*-fluoro-*trans*-cinnamate, respectively. The chemical shifts are upfield from the CF_3COO^- reference and are corrected for bulk susceptibility variation.

1) and thereafter decreases. Similar but smaller systematic line broadenings are observed for the other fluoro-*trans*-cinnamates with the exception of *m*-fluoro-*trans*-cinnamate. N.m.r. studies[7, 24] show that the tumbling or correlation time, τ_c, of $S\cdot(\alpha CD)_2$ as an entity (where S = *p*-methyl-*trans*-cinnamate) is 6×10^{-10} s at 306 K in water and it may be assumed that similar and smaller τ_c values apply for $S\cdot(\alpha CD)_2$ and $S\cdot\alpha CD$ when S = fluoro-*trans*-cinnamate. Such τ_c values appear to be too small to produce significant longitudinal ^{19}F relaxation through dipole–dipole, chemical-shift anisotropy or related relaxation processes,[25, 26] and hence it is likely that the observed ^{19}F line broadening occurs predominantly through transverse relaxation. This transverse relaxation is probably a consequence of fluoro-*trans*-cinnamate exchange occurring between the S, $S\cdot\alpha CD$ and $S\cdot(\alpha CD)_2$ environments. These three species co-exist in significant temperature-dependent concentrations over the [αCD] range studied and as only a single ^{19}F resonance is observed even down to 273 K it is clear that chemical exchange between these species is occurring sufficiently rapidly to coalesce the three resonances to a broad singlet. Computer simulation of chemical exchange between two sites characterised by two singlets of equal intensity of 3 Hz width at half maximum amplitude, $W_{\frac{1}{2}}$, and separated by 3.45 ppm shows that single Lorentzian resonances of $W_{\frac{1}{2}} = 560$ and 50 Hz are observed when the site exchange rate constants are 5×10^3 and 5×10^4 s^{-1}, respectively. Qualitatively this indicates that the observed α-F line broadening is consistent with transverse relaxation being induced by chemical exchange occurring at rates within the range reported for a temperature-jump spectrophotometric study[1] in which, amongst other included species, the dissociation of *p*-nitrophenolate from $S\cdot\alpha CD$ was characterised by a

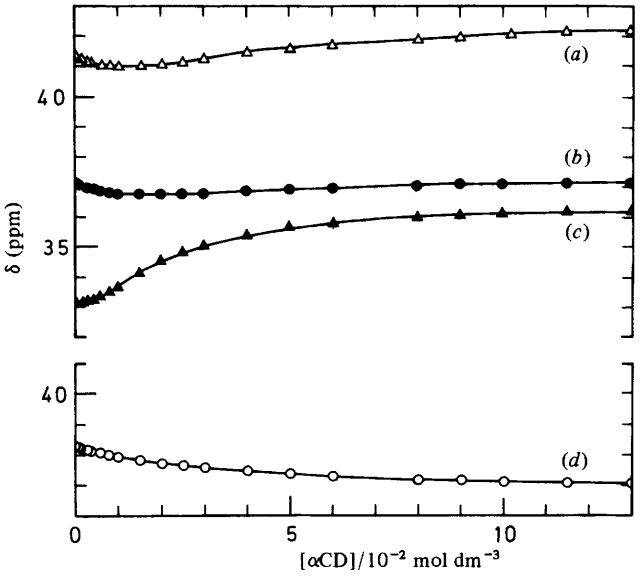


Fig. 3. Variation of the ^{19}F chemical shifts (δ) of fluoro- and difluoro-*trans*-cinnamate with α-cyclodextrin concentration, [αCD]. The experimental data are shown as individual points and the best fits of these data to eqn (3) are shown as curves (*a*)–(*c*). Curves (*b*) and (*c*) pertain to *o*- and *p*-F, respectively, of *o*,*p*-difluoro-*trans*-cinnamate and curve (*a*) pertains to *o*-fluoro-*trans*-cinnamate. Curve (*d*) for *m*-fluoro-*trans*-cinnamate represents the best fit of the data points to the single equilibrium shown in eqn (1). The chemical shifts are upfield from the CF_3COO^- reference and are corrected for bulk susceptibility variations.

dissociation rate constant k_d (287 K) = 3.1×10^4 s^{-1}. However, as for all of the fluoro-*trans*-cinnamate systems studied only a single chemical exchange averaged resonance was observed for each fluorine substituent at 273 K it proved impossible to make a quantitative analysis of the exchange kinetics.

DISCUSSION

The ^{19}F chemical-shift data (table 1) show that S·αCD and S·$(αCD)_2$ are readily formed when S = fluoro-*trans*-cinnamate. However, four different structures potentially exist for S·αCD if the possibilities of either end of S entering either the narrow end of the αCD cavity, delineated by the six primary hydroxy groups, OH(6), or the wide end, delineated by the twelve secondary hydroxy groups, OH(2 and 3), are considered. An examination of space-filling models indicates that entry of the fluoro-*trans*-cinnamate through the wider end of the αCD cavity is favoured on steric grounds over entry through the narrow end. Consistent with this a ^{13}C n.m.r. solution study[7] indicates that *p*-methyl-*trans*-cinnamate enters through the wider end of the αCD cavity and X-ray diffraction studies[27,28] of crystalline S·αCD, where S = *p*- and *m*-nitrophenol and *p*-hydroxybenzoic acid, reveal molecular structures in which the nitro and carboxylic acid substituent ends of S are inserted into the wide end of the αCD cavity. It appears therefore that the two S.αCD species most likely to be produced in this study are those in which either end of fluoro-*trans*-cinnamate is inserted into the wide end of the αCD cavity. This steric restriction requires that

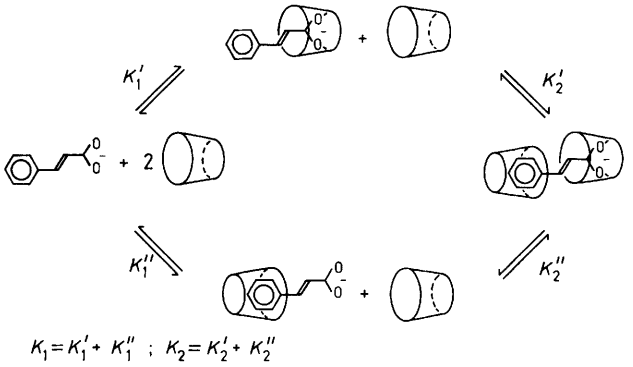


Fig. 4. Representation of the inclusion equilibria possible in the fluoro- and the difluoro-*trans*-cinnamate/α-cyclodextrin systems. The truncated cone represents the α-cyclodextrin cavity.

$S\cdot(\alpha CD)_2$ consist of the fluoro-*trans*-cinnamate encapsulated by two αCD with the wide ends of their cavities in close proximity, consistent with deductions made from ^{13}C n.m.r. spectroscopic studies of the inclusion of *p*-methyl-*trans*-cinnamate.[7] In consequence of these considerations the four possible environments for a given fluoro-*trans*-cinnamate are encompassed by the four equilibria characterised by the constants K_1', K_1'', K_2' and K_2'', as shown in fig. 4. The ratio of the concentration of the two $S\cdot\alpha CD$ species is constant but the ^{19}F data do not permit a determination of these concentrations separately. It is readily shown, however, that the equilibrium constants in table 1 and fig. 1 are related through the equalities: $K_1 = K_1' + K_1''$ and $K_2 = K_2' + K_2''$. It is seen from table 1 that the magnitudes of K_1 and K_2 vary significantly with the fluoro-*trans*-cinnamate, which probably reflects a combination of the electronic, solvational and stereochemical changes caused by fluorination of cinnamate in the *o*, *p* and α positions. However, the variation of K_1 and K_2 with the fluoro-*trans*-cinnamate is modest and encompasses the K_1 and K_2 values reported for cinnamate,[8] which indicates that fluorination of cinnamate does not have a major effect on the cinnamate–αCD inclusion interaction. (Coincidentally this further demonstrates the utility of specific substitution of hydrogen by fluorine in ^{19}F n.m.r. studies of systems in which ^1H and ^{13}C studies are hampered by a plethora of resonances.[11–16, 26]) However, the K_1 value for cinnamic acid[8] is substantially outside the range exhibited by the fluoro-*trans*-cinnamates and probably reflects the effect of substrate charge on the inclusion process.

The ^{19}F chemical-shift data in table 1 show that: (i) the formation of $S\cdot(\alpha CD)_2$ from $S\cdot\alpha CD$ induces a greater shift change ($\delta_2 - \delta_1$) than does the formation of $S\cdot\alpha CD$ ($\delta_1 - \delta_0$) and (ii) the shift for α-F is downfield for $S\cdot\alpha CD$ and $S\cdot(\alpha CD)_2$ whereas the shifts for *o*-F and *p*-F are downfield and upfield for $S\cdot\alpha CD$ and $S\cdot(\alpha CD)_2$, respectively. In interpreting these shifts it must be remembered that whilst a given segment of the fluoro-*trans*-cinnamate may be in close proximity to a particular segment of αCD and will experience a strong local solvational and electronic variation the effects of this variation will be transmitted throughout the conjugated fluoro-*trans*-cinnamate and will modify all ^{19}F chemical shifts to some extent. The greatest environmental change experienced by the fluoro-*trans*-cinnamates is in $S\cdot(\alpha CD)_2$, in which space filling models show fluoro-*trans*-cinnamate to be completely encapsulated and where it appears that the fluoro-*trans*-cinnamate hydration shell is probably totally lost. The polar carboxylate group of fluoro-*trans*-cinnamate interacts more

strongly with water than does the phenyl group and accordingly the solvational change experienced by the carboxylate group on transfer from water to the largely hydrophobic αCD cavities of S·(αCD)$_2$ will be greater than that experienced by the phenyl group. Thus α-F, which is adjacent to the carboxylate group, should reflect solvational changes in $\delta_2-\delta_0$ more than *o*- and *p*-F. In contrast the $\delta_2-\delta_0$ of *o*- and *p*-F are expected to reflect more strongly the dispersion-force interactions established between the π system of the phenyl group and the interior of the αCD cavity, which are considered to be a major factor stabilising cyclodextrin inclusion complexes.[29]

In the S·αCD complex one end of the fluoro-*trans*-cinnamate is in a water environment whilst the other resides in the αCD cavity. The *p*-F is furthest removed from the carboxylate group and exhibits the smallest values for $\delta_1-\delta_0$ and the most negative values for $\delta_2-\delta_1$. Thus of *o*- and *p*-F the latter is least affected by the formation of S·αCD and most affected by the formation of S·(αCD)$_2$. This suggests that the predominant S·αCD species formed is that in which the carboxylate group of fluoro-*trans*-cinnamate enters the αCD cavity as shown in the equilibrium characterised by K_1' in fig. 4. This deduction is reinforced by the observation that the fluoro-*trans*-cinnamate carboxylate substituent bears substantial stereochemical and electronic similarities to the nitro and carboxylic acid groups of *p*- and *m*-nitrophenol and *p*-hydroxybenzoic acid, which were found to be inserted first into the αCD cavity in S·αCD complexes in the previously discussed X-ray studies.[27,28] That the alternative S·αCD complex characterised by K_1'' in fig. 4 may well exist as a minor species is suggested by the formation of S·(αCD)$_2$. The formation of this complex indicates that the energetics of the inclusion of either end of fluorocinnamate in S·αCD in solution are probably not substantially different. The existence of S·(αCD)$_2$ in solution, in the absence of any evidence for the dimerisation of αCD in the absence of S, is a demonstration of the substantial magnitude of the interaction established between the fluoro-*trans*-cinnamate and αCD. The stability of the cyclodextrin inclusion complexes arising out of such interactions has been variously attributed to modification of torsional forces in the αCD structure,[30] solvational changes of αCD and S[31] and the establishment of dispersion-force interactions between αCD and S.[29] It seems probable that the importance of these stabilising factors will vary with the nature of S for αCD and for a given S with the nature of the cyclodextrin.

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