Cooperativity and steric hindrance: important factors in the binding of α-cyclodextrin with *para*-substituted aryl alkyl sulfides, sulfoxides and sulfones

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Binding constants for 22 *para*-substituted aryl alkyl sulfides, sulfoxides and sulfones have been determined spectrophotometrically. It was found that the presence of sulfur containing substituents generally results in destabilisation of complex formation, and it is postulated that the angle of the sulfur bond in these compounds results in steric hindrance with the 5-H protons at the rear of the cyclodextrin cavity, causing it to be displaced from its optimal position or orientation. Additionally, the observation, for several sulfides, of cooperativity in the binding of a second molecule of cyclodextrin is discussed in terms of binding induced changes in electrical potential within the cyclodextrin cavity.

Introduction

The subject of cyclodextrin chemistry has experienced an enormous amount of interest over the last two decades, with over 7000 papers published[1] on the subject in the intervening period between the last two major reviews of the area.[1,2] Nevertheless, as Inoue points out in his recent review of NMR studies of cyclodextrins,[3] there still remains no clear agreement on the major driving force behind the inclusion of guest species within the cyclodextrin cavity. Indeed, in view of the wide variety of guest types which can complex with cyclodextrin there are likely to be several different types of driving force acting in various combinations. Inoue[3] lists the main factors influencing complexation as, Van der Waals interactions between cyclodextrin and guest; hydrophobic interactions; release of high energy water or ring strain energy upon binding; hydrogen bonding between guest and hydroxy groups of the cyclodextrin; and effects of solvent surface tension.

The binding of 1,4-di-substituted benzenes within α-cyclodextrin offers a good system in which to investigate factors influencing complexation; this is due to the effect of the tightly fitting benzene ring which ensures that guest molecules can only take up a limited number of conformations within the cavity.[4] For larger cyclodextrins or smaller guests the number of conformations is much larger and, as a consequence, the predictability of the system suffers as we have seen in our recently proposed model of complex formation for 1,4-di-substituted benzenes;[5] a reasonable correlation was obtained for binding constants for α-cyclodextrin, yet for β-cyclodextrin the binding constants for the same compounds correlated poorly. For α-cyclodextrin the results of crystallographic[6] and NMR[7] studies as well as our own model[5] indicate that the principal factor affecting orientation is dipole–dipole interactions (although the results are not always interpreted as such). CNDO calculations have shown that α-cyclodextrin has a large dipole moment (*ca.* 13 D) running from the secondary hydroxy to the primary hydroxy end of the molecule when complexed with aromatic guests such as *p*-nitrophenol.[3] Guests orientate within the cyclodextrin cavity so that their dipole moment is antiparallel to the large dipole moment of the cyclodextrin. Moreover, computer modelling studies of the electrical potential along the longitudinal axis of α-cyclodextrin show that conformational changes in the cyclodextrin upon binding, and induced dipole–dipole interactions, maximise the electrostatic interaction between host and guest.[4,8]

We have recently studied the binding of substituted perbenzoic acids and their anions with cyclodextrins[9] and the effect of α-cyclodextrin on the stability of the transition state of the peracid–iodide reaction.[10] The present study concerns a specific group of 1,4-disubstituted benzenes, namely those possessing an alkyl sulfide, sulfoxide or sulfone group as one of the substituents. These represent an independent test set of 17 substituted benzene derivatives against the original 48 derivatives, none of which contained a sulfur atom, used to develop our model.[5] The results suggest that the shape of the sulfur containing group is an important determining factor of binding strength and orientation. Binding constants for the 2:1 cyclodextrin–substrate complexes were also studied and these revealed a high incidence of cooperativity in the binding of a second molecule of cyclodextrin for these substrates. Substrate promoted dipole–dipole interactions between opposite dipoles of the two cyclodextrin molecules are postulated as a possible mechanism for cooperative binding.

Experimental

Materials

Analytical grade reagents were used in all cases. Solutions of α-cyclodextrin (Aldrich) were made up in distilled water or acetate buffer and were filtered through a 10 μm scinter funnel prior to use. 1 mmol dm^{-3} solutions of the sulfoxides, sulfones and the more soluble sulfides (all obtained from Aldrich) were prepared by dissolving in distilled water over a period of several hours. For the majority of sulfides, which were considerably less soluble than the sulfoxides and sulfones, solutions were prepared by stirring an amount of compound sufficient to give an approximately 1 mmol dm^{-3} solution in distilled water for about 4–6 h after which it was filtered through a scintered glass funnel (10 μm) to remove the undissolved material. Standardisation of the solutions was carried out by following the loss in peroxide concentration upon mixing with a 1 mmol dm^{-3} solution of *m*-chloroperbenzoic acid (MCPBA) in distilled water. Under these conditions only oxidation of the sulfide to

Table 1 λ_{max} values, molar absorptivities and stability constants for a range of aryl alkyl sulfides, sulfoxides and sulfones. λ_{max} values and molar absorptivities are also shown for the 1:1 and 2:1 (where present) α-cyclodextrin–guest complexes. Molar absorptivities in parentheses for the 2:1 complexes indicate values which are uncertain due to the large standard deviations of the K_{12} stability constant. Stability constants were measured spectrophotometrically at 25 °C in the buffer system indicated.

Name/structure	Buffer	λ_{max}/nm	ε/dm^3 mol^{-1} cm^{-1}	K_{11}/dm^3 mol^{-1}	**1:1** λ_{max}/nm	**1:1** ε/dm^3 mol^{-1} cm^{-1}	K_{12}/dm^3 mol^{-1}	**2:1** λ_{max}/nm	**2:1** ε/dm^3 mol^{-1} cm^{-1}
4-Methoxyphenyl methyl sulfide CH_3O–C_6H_4–SCH_3	Acetate	254	10 300	110 ± 18	256	8 200	200 ± 40	262	10 400
4-(Methylsulfanyl)benzyl alcohol $HOCH_2$–C_6H_4–SCH_3	Acetate	256	12 200	85 ± 11	258	10 100	32 ± 9	262	11 300
4-Bromophenyl methyl sulfide Br–C_6H_4–SCH_3	Acetate	260	13 900	310 ± 50	264	12 700	430 ± 130	266	13 800
Methyl 4-nitrophenyl sulfide[a,b] NO_2–C_6H_4–SCH_3	Acetate	352	13 100	123 ± 7	372	12 600	153 ± 17	368	15 700
2-Chloroethyl 4-tolyl sulfide CH_3–C_6H_4–SCH_2CH_2Cl	Acetate	254	8 100	71 ± 10	256	7 000	23 ± 4	260	12 200
4-Chlorophenyl methyl sulfide Cl–C_6H_4–SCH_3	Acetate	258	13 100	154 ± 27	260	12 400	390 ± 100	264	13 900
Methyl methylsulfanylphenyl ketone[b] $CH_3(O)C$–C_6H_4–SCH_3	Acetate	310	17 500	9 ± 5	314	15 900	0.4 ± 19	316	(33 600)
Methyl *p*-tolyl sulfide CH_3–C_6H_4–SCH_3	Acetate	254	10 600	41 ± 25	254	8 200	1 000 ± 700	260	10 200
2-(*p*-Tolylsulfanyl)ethanol CH_3–C_6H_4–SCH_2CH_2OH	Acetate	254	10 600	147 ± 31	256	9 200	42 ± 14	262	9 228
4-Chlorophenyl 3-chloropropyl sulfide Cl–C_6H_4–$SCH_2CH_2CH_2Cl$	Acetate	260	7 700	135 ± 21	262	6 300	0.9 ± 6	268	(20 200)
4-Methylsulfanylphenylacetic acid HO_2CCH_2–C_6H_4–SCH_3	H_2SO_4, pH 1.71	256	11 800	520 ± 260	256	11 400	90 ± 70	260	10 700
4-Methylsulfanylphenylacetate $^-O_2CCH_2$–C_6H_4–SCH_3	Carbonate	256	12 100	68 ± 3	260	10 100	—	—	—
4-Methylsulfanylaniline[b] NH_2–C_6H_4–SCH_3	Carbonate	260	13 000	102 ± 10	262	11 000	9 ± 4	268	11 800
4-Methylsulfanylanilinium NH_3^+–C_6H_4–SCH_3	H_2SO_4, pH 1.96	256	11 300	52 ± 3	258	9 400	—	—	—
4-Bromophenyl methyl sulfone Br–C_6H_4–SO_2CH_3	H_2O	236	17 100	139 ± 9	236	15 000	—	—	—
4-Bromophenyl methyl sulfoxide Br–C_6H_4–$S(O)CH_3$	H_2O	238	11 200	337 ± 8	240	9 000	—	—	—
Ethyl 4-nitrophenyl sulfone NO_2–C_6H_4–$SO_2CH_2CH_3$	Acetate	254	10 000	18 ± 6	254	9 300	—	—	—
4-Aminophenyl methyl sulfone[b] NH_2–C_6H_4–SO_2CH_3	Carbonate	264	16 700	41 ± 7	266	16 100	—	—	—
4-Fluorophenyl methyl sulfone F–C_6H_4–SO_2CH_3	H_2O	220	8 300	17 ± 7	220	7 800	—	—	—
4-Methoxyphenyl methyl sulfone[b] CH_3O–C_6H_4–SO_2CH_3	H_2O	242	15 153	4 ± 3	242	12 200	—	—	—
(*S*)-(−)-Methyl *p*-tolyl sulfoxide CH_3–C_6H_4–$S(O)CH_3$	H_2O	230	7 667	29 ± 5	230	6 500	—	—	—
Methyl *p*-tolyl sulfone CH_3–C_6H_4–SO_2CH_3	H_2O	228	11 800	2.8 ± 2.4	228	6 600	—	—	—

[a] Data taken from ref. 13. [b] Compounds displaying through-resonance.

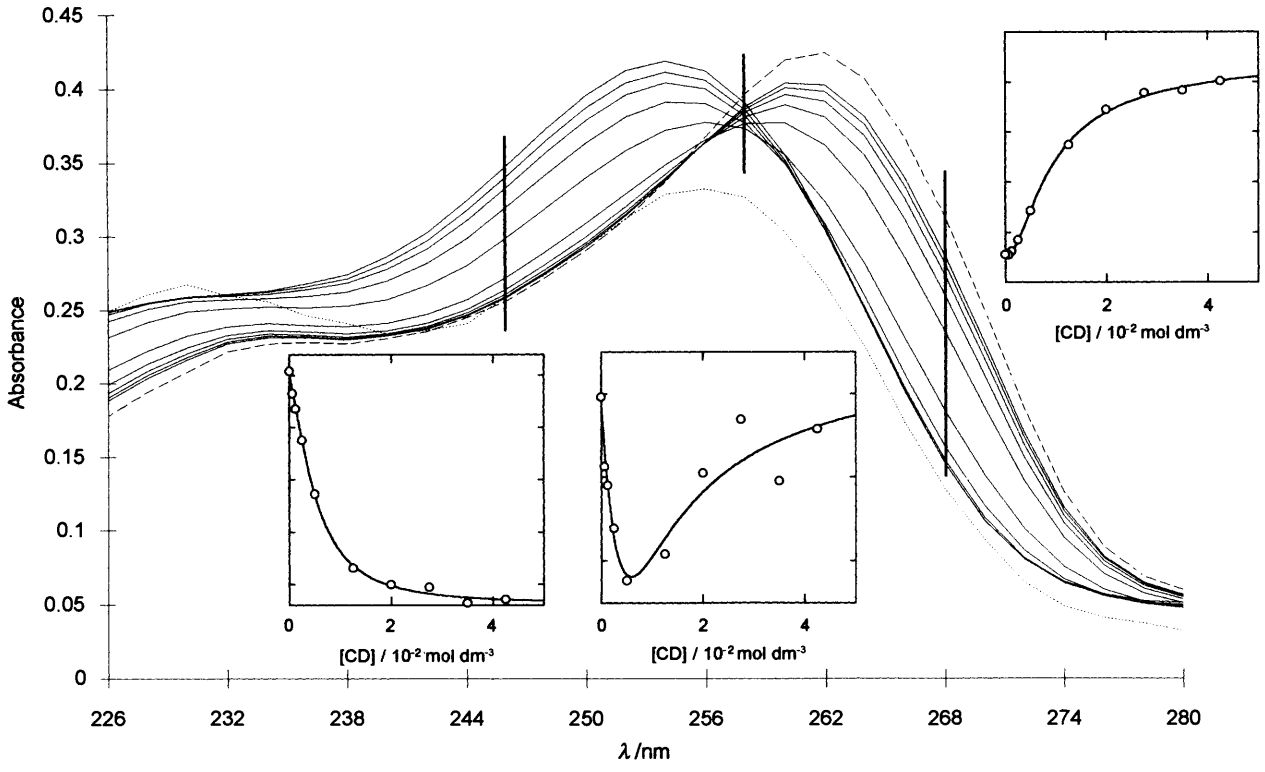


Fig. 1 Effect of α-cyclodextrin concentration on the spectrum of 5.1 × 10^{-5} mol dm^{-3} 4-methoxyphenyl methyl sulfide at 25 °C in acetate buffer, pH 4.6, ionic strength 0.05 mol dm^{-3}. The dotted and broken lines are, respectively, the calculated spectra of the 1:1 and 2:1 cyclodextrin–guest complexes. The insets are examples of the best fits to eqn. (3) at 246, 258 and 268 nm.

sulfoxide occurs and the reaction is over in minutes. Peroxide concentrations were determined spectrophotometrically by measuring triiodide formation at 352 nm in a solution containing 3.1 g dm^{-3} potassium iodide in phthalate buffer and using a molar absorptivity of 24 100 dm^3 mol^{-1} cm^{-1}.[11] Molar absorptivities for the sulfides, sulfoxides and sulfones at the main absorbance band are given in Table 1.

Methods

Binding constant determinations were made using a spectrophotometric titration procedure[12] on a Hewlet Packard HP8451A diode array spectrophotometer at 25 °C. In all cases the α-cyclodextrin concentration was in ten-fold excess over the substrate concentration, which was generally about 5 × 10^{-5} mol dm^{-3}. Cyclodextrin concentrations ranged from 0 to 0.05 mol dm^{-3}. Binding constant determinations for the majority of the sulfides and some sulfoxides and sulfones were carried out in 0.05 mol dm^{-3} ionic strength acetate buffer at pH 4.6. Background spectra were obtained prior to addition of the substrate and subtracted from the cyclodextrin/substrate spectrum. With 4-methylsulfanylphenylacetic acid and 4-methylsulfanylaniline, determinations were carried out for both the conjugate acid and conjugate base in 0.02 mol dm^{-3} sulfuric acid and carbonate buffer (pH 9.92, I = 0.05 mol dm^{-3}), respectively. For the majority of sulfoxides and sulfones, which generally absorb quite far down into the UV and for which the binding constants are fairly small, determinations were carried out in distilled water. This minimised errors occurring as a result of the subtraction of background spectra; such errors would be more pronounced at lower wavelengths. An important consideration in measuring binding constants of aryl alkyl sulfides is their volatility; an open flask of the solution will rapidly lose sulfide to the atmosphere. Measures to alleviate this problem include: determining the sulfide concentration regularly (spectrophotometrically); taking aliquots from a completely full flask; ensuring that the flask is shaken before removal of an aliquot and positioning the pipette tip as far below the surface as possible when removing an aliquot.

Results

We have recently found that methyl *p*-nitrophenyl sulfide binds with both one and two molecules of α-cyclodextrin,[13] as defined by the equilibria in eqns. (1) and (2), in which K_{11} and K_{12} are stepwise binding constants, CD is α-cyclodextrin and S is the sulfide. This system is described by eqn. (3) in which $A(\lambda_i)$ is the absorbance at i nm and $\varepsilon_0(\lambda_i)$, $\varepsilon_{11}(\lambda_i)$ and $\varepsilon_{12}(\lambda_i)$ are the molar absorptivities for free S, S,CD and S,$(CD)_2$, respectively. The majority of sulfides in this study were also described by this equation. Two sulfides, however, together with all of the sulfoxides and sulfones, did not show any 2:1 complexation and eqn. (4) describes this simplified situation in which only a 1:1 complex is formed.

$$S + CD \rightleftharpoons^{K_{11}} S,CD \quad (1)$$

$$S,CD + CD \rightleftharpoons^{K_{12}} S,(CD)_2 \quad (2)$$

$$\frac{A(\lambda_i)}{[S]_0} = \frac{\varepsilon_0(\lambda_i) + \varepsilon_{11}(\lambda_i)K_{11}[CD]_0 + \varepsilon_{12}(\lambda_i)K_{11}K_{12}[CD]_0^2}{1 + K_{11}[CD]_0 + K_{11}K_{12}[CD]_0^2} \quad (3)$$

$$\frac{A(\lambda_i)}{[S]_0} = \frac{\varepsilon_0(\lambda_i) + \varepsilon_{11}(\lambda_i)K_{11}[CD]_0}{1 + K_{11}[CD]_0} \quad (4)$$

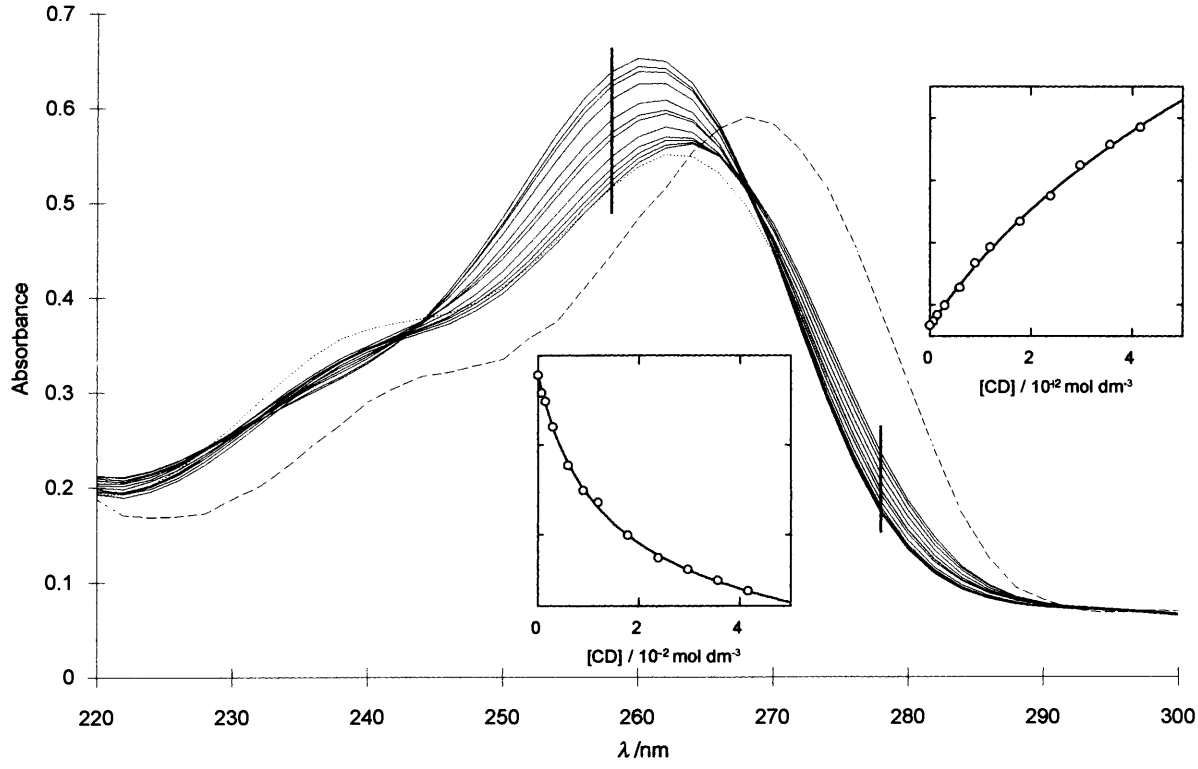


Fig. 2 Effect of α-cyclodextrin concentration on the spectrum of 5.03×10^{-5} mol dm^{-3} 4-methylsulfanylaniline at 25 °C in carbonate buffer, pH 9.92, ionic strength 0.05 mol dm^{-3}. The dotted and broken lines are, respectively, the calculated spectra of the 1:1 and 2:1 cyclodextrin–guest complexes. The insets are examples of the best fits to eqn. (3) at 258 and 278 nm.

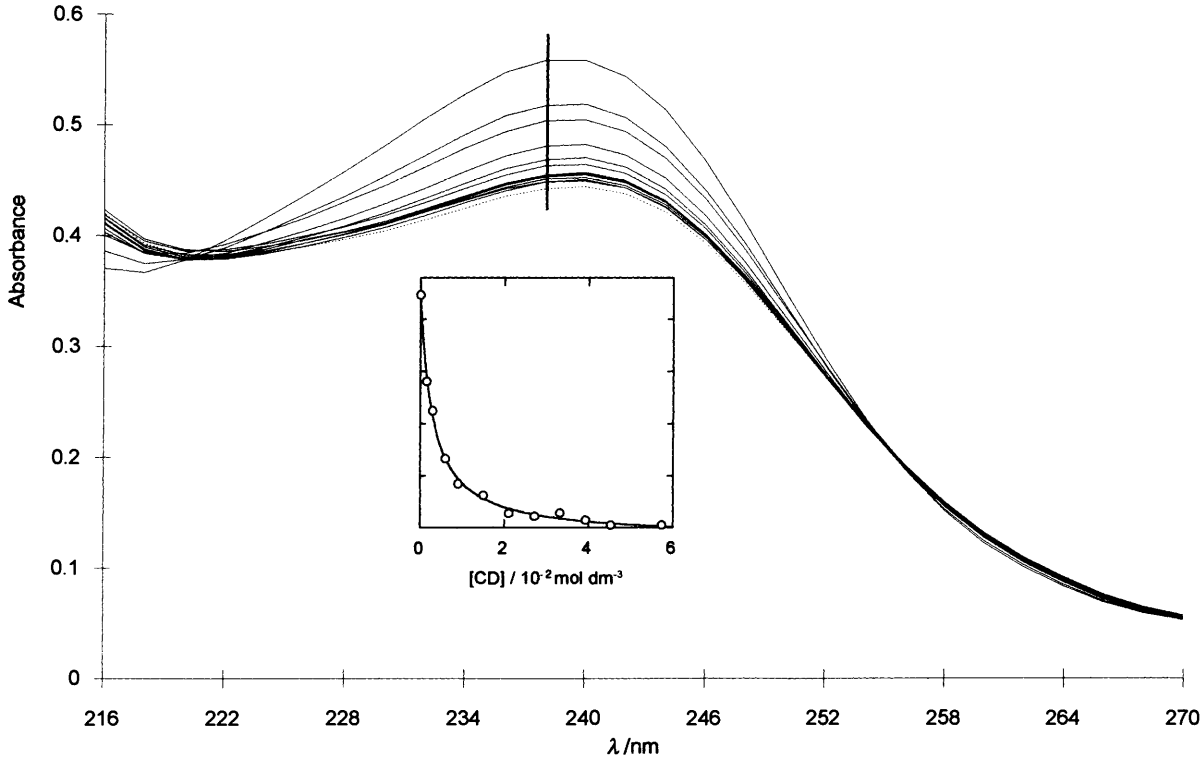


Fig. 3 Effect of α-cyclodextrin concentration on the spectrum of 4.98×10^{-5} mol dm^{-3} 4-bromophenyl methyl sulfoxide at 25 °C in water. The dotted line is the calculated spectrum of the 1:1 cyclodextrin–guest complex. The inset is an example of the best fit to eqn. (4) at 238 nm.

Typical spectral changes in the presence of α-cyclodextrin are shown in Figs. 1–4, respectively, for 4-methoxyphenyl methyl sulfide, 4-methylsulfanylaniline, 4-bromophenyl methyl sulfoxide and 4-bromophenyl methyl sulfone; also shown are the calculated spectra for 1:1 and 2:1 (where present) cyclodextrin–guest complexes. The insets show absorbance changes at

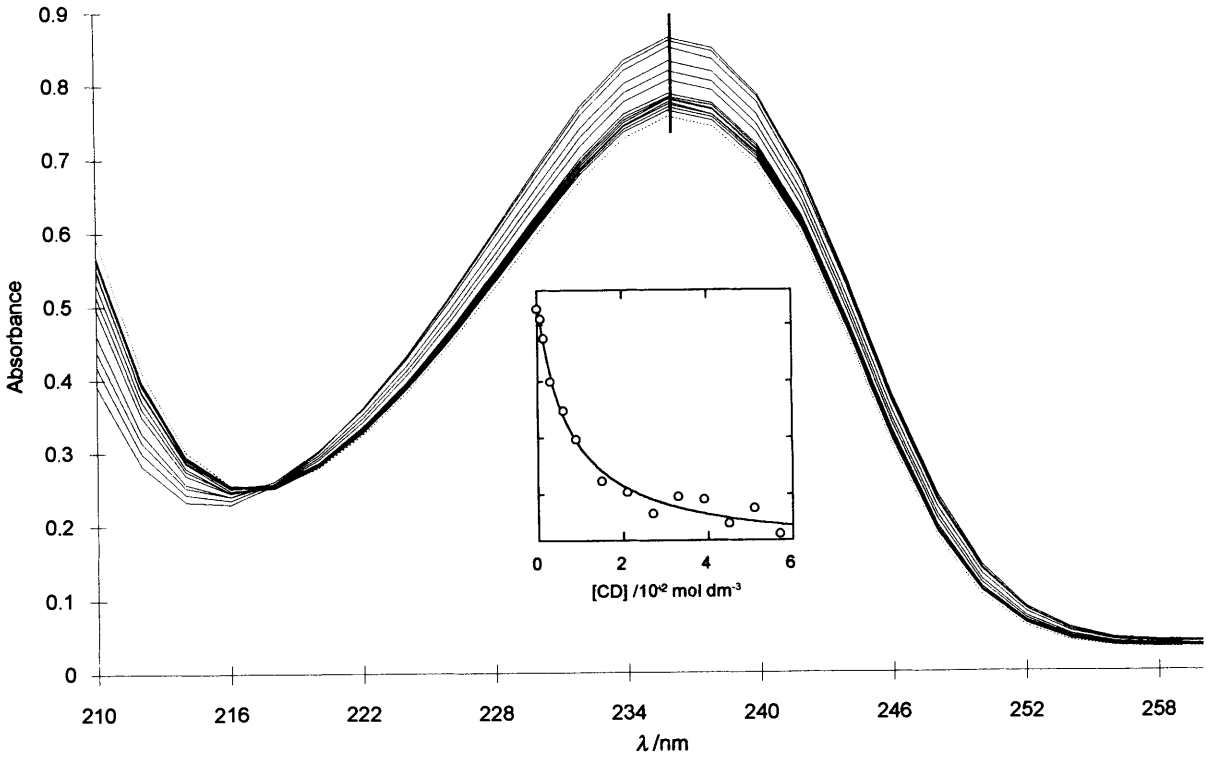


Fig. 4 Effect of α-cyclodextrin concentration on the spectrum of 5.1 × 10^{-5} mol dm^{-3} 4-bromophenyl methyl sulfone at 25 °C in water. The dotted line is the calculated spectrum of the 1:1 cyclodextrin–guest complex. The inset is an example of the best fit to eqn. (4) at 236 nm.

individual wavelengths; the solid lines represent the best fit curves according to either eqn. (3) or (4) using non-linear regression at multiple wavelengths. The binding constants for all of the substrates studied are given in Table 1, together with λ_{max} values and molar absorptivities for the calculated spectra of the 1:1 and 2:1 cyclodextrin–guest complexes. Cooperative binding is displayed in five of the cases for which 2:1 complexes are observed, most notably for methyl *p*-tolyl sulfide where K_{12} is over 20 times greater than K_{11}.

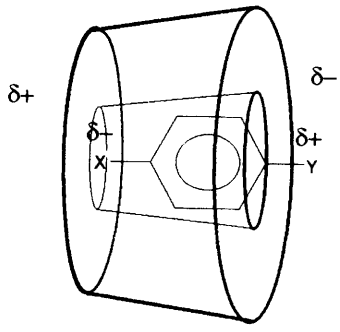
Fig. 1 is typical of the spectral changes observed in this study for aryl alkyl sulfides in the presence of α-cyclodextrin. The binding of one molecule of cyclodextrin results in a red shift together with a decrease in absorbance at λ_{max} and the subsequent binding of a second cyclodextrin molecule results in a further red shift and an increase in absorbance at λ_{max}. There is also an isosbestic point formed at low cyclodextrin concentration, which gradually decays, although unlike our recent study of methyl *p*-nitrophenyl sulfide,[13] no clearly defined isosbestic points are formed at higher cyclodextrin concentrations. Fig. 2 shows the case where a small K_{12} value is obtained; clearly, from the calculated spectrum for the 2:1 complex, if it were possible to carry out the determination over a much higher cyclodextrin concentration range, the spectral changes would resemble those in Fig. 1. Similar spectra were obtained for several of the substrates capable of hydrogen bonding interactions with the solvent 4-(methylsulfanyl)benzyl alcohol, 2-(4-tolylsulfanyl)ethanol and 4-methylsulfanylphenylacetic acid). Those sulfides having charged *para*-substituents, *i.e.* 4-methylsulfanylphenylacetate (pH 10) and 4-methylsulfanylanilinium do not show any detectable 2:1 binding under the conditions used. Whilst K_{12} values were obtained for all of the neutral sulfides, the standard deviations of K_{12} for two sulfides, 4-chlorophenyl propyl sulfide and methyl 4-methylsulfanylphenyl ketone, include zero. The spectral changes for these compounds (not shown), do, however, show that there are two processes occurring.

Typical spectral changes for the sulfoxides and sulfones are shown in Figs. 3 and 4, respectively. The absorbance decreases with increasing cyclodextrin concentration, although unlike the sulfides there is no red shift. It should be noted that the quoted binding constants for all the sulfoxides except methyl *p*-tolyl sulfoxide, for which the (*S*)-isomer was available, are composite values for solutions containing 50% each of the (*R*)- and (*S*)-isomers.

Discussion

K_{11} binding constants

In an attempt to gain some insight into the mechanism of binding for the range of substrates investigated in this study, the K_{11} values were fitted to the model of inclusion compound formation for α-cyclodextrin with 1,4-disubstituted benzenes, recently proposed by us,[5] in which dipole–dipole and induced-dipole–dipole interactions are the predominant factors with respect to the substituents. The model, which only applies to those compounds which do not display through-resonance (arbitrarily defined as those derivatives in which $\sigma_p^+ - \sigma_p$ is less than −0.14 for one substituent and $\sigma_p^- - \sigma_p$ is greater than 0.09 for the second substituent),[5] proposes that for neutral guests, alignment within the cavity will be so as to form a favourable dipole–dipole interaction with the cyclodextrin (**1**). Thus, the negative end of the guest molecule dipole [designated X in structure (**1**)] will be positioned at the narrow end of the cavity, with the positive end of the guest dipole (designated Y in structure (**1**)] protruding. Additionally, guests with charged substituents will have the charged substituent protruding from the wide end of the cavity. The model is described by eqn. (6) in which σ_x and σ_y are the Hammett σ_p values for the x and



[1]

y-substituents respectively, R_{m_x} is the x-substituent molar refractivity, $\sigma_x\sigma_y$ is an interaction term, Y_{sub^-} is an indicator variable for negatively charged substituents and $Carb^-$ is a specific indicator variable for benzoates.

$$\log K_{11} = 1.28\,(0.11) + 1.38\,(0.16)\,\sigma_x - 2.35\,(0.33)\sigma_x\sigma_y + 0.120\,(0.013)(1 - Carb^-)R_{m_x} - 0.27\,(0.12)\,Y_{sub^-} \quad (6)$$
$$(n = 48, r = 0.923, s = 0.345)$$

In Fig. 5(*a*) the observed K_{11} values listed in Table 1 have been plotted against values predicted using our model, omitting those compounds which display through-resonance. Hammett σ_p values for the substituents were taken from the recent compilation of Hansch *et al.*[14] and values for substituent molar refractivity were obtained from the compilation of Hansch and Leo.[15] For several sulfides (2-chloroethyl 4-tolyl sulfide, 4-chlorophenyl 3-chloropropyl sulfide and 2-(*p*-tolylsulfanyl)-ethanol) substituent R_{m_x} values were interpolated from published values[15] since no values were available. The filled squares are those compounds which, on the basis of their respective σ_p values, *i.e.* with regard to giving favourable host–guest dipole–dipole interactions, would be predicted to have the sulfide substituent at the Y position, whereas the open squares are those in which the sulfur containing substituent is predicted to be at the X position. Clearly the former are predicted reasonably well by the model, whereas the latter show large systematic deviations between observed and predicted. Quite remarkably, if the assumption is made that the sulfur containing groups are always located at the secondary hydroxy rim, regardless of the respective σ-values of the two substituents then the correlation shown in Fig. 5(*b*) is obtained using our model. It should be noted that where, as a result of applying this revised rule, the guest is oriented such that both substituents experience unfavourable dipole–dipole interactions with the cyclodextrin, the sign of the $\sigma_x\sigma_y$ interaction term in eqn. (6) is reversed. The sums of the squares of deviation decreases from 44.6 using the original model to 3.7 for the revised model. We suggest that the improved correlation obtained by applying the revised rule is a manifestation of steric hindrance when the sulfide, sulfoxide or sulfone groups are located within the cavity. According to Inoue,[3] the extent to which a benzene ring can penetrate the α-cyclodextrin cavity is limited by the interaction between the benzene ring protons *meta* to the X substituent (using our terminology) and the 5-H protons of the cyclodextrin which are directed into the cavity [structure (**2**)]. The radius of the circle formed by the six 3-H protons is about 3.6 Å, whereas that formed by the 5-H protons is only 3.2 Å. This idea of limited penetration due to steric hindrance is supported in the literature by both molecular modelling studies[16] and

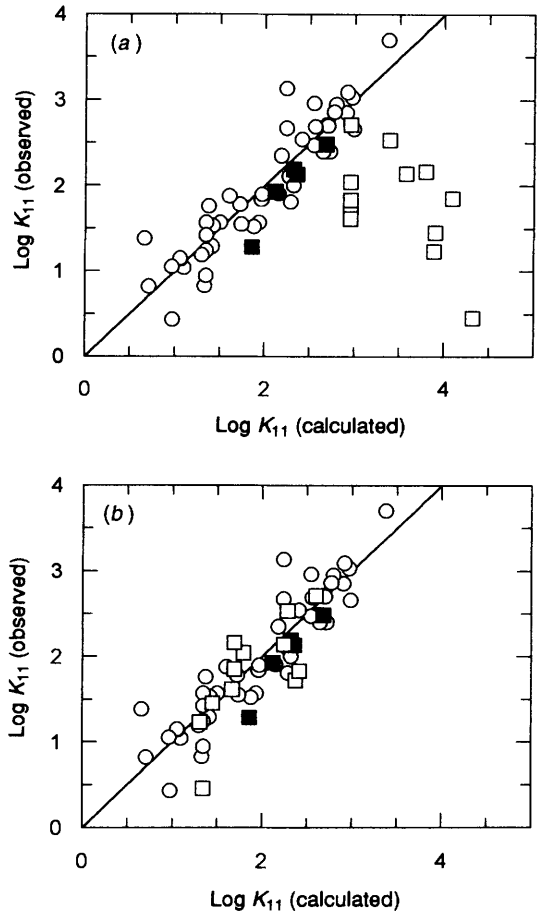
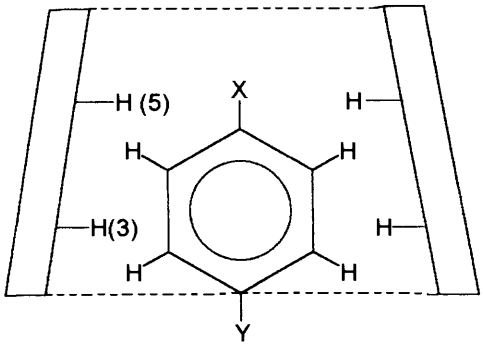


Fig. 5 Plot of observed values of log K_{11} *vs.* the values calculated according to eqn. (6) for cases where (*a*) the orientation of the compounds within the cavity is determined using the rules described in ref. 5 and (*b*) a revised model in which the sulfur containing group is always located at the wide end of the cavity: (○), best fit values from ref. 5; (■), compounds in which the sulfur containing substituent is predicted from the rules proposed in ref. 5 to be located at the wide end of the cavity; (□), compounds in which the sulfur containing substituent is predicted from the rules proposed in ref. 5 to be located at the narrow end of the cavity.

experimental data from crystallographic[6] and NMR[3,7] studies of the inclusion of substituted phenols and benzoic acids in α-cyclodextrin, which show that the degree of penetration by the benzene ring is relatively constant.

In the case of complex formation between α-cyclodextrin and a *para*-substituted thioanisole, as in structure (**3**), in which the sulfur containing substituent is directed into the cavity, the angle of the sulfur bond is likely to cause steric hindrance between the CH_3 and the 5-H protons, resulting in the benzene ring being displaced from its optimal position in the cavity. This is confirmed by STERIMOL B5 parameters, which are based on van der Waals radii and molecular geometries[17] and describe the maximum width of substituents.[18,19] These parameters indicate that the methyl sulfide (3.26 Å), methyl sulfoxide (3.17 Å) and methyl sulfone (3.17 Å) substituents are all likely to experience steric hindrance with the 5-H protons. The effect of this will be to reduce the van der Waals attractive interactions between the benzene ring and the cavity and it will also mean that the full potential of the interaction between the bulky sulfur group and the cavity is not realised. Two possibilities then exist: (*a*) the reduced interactions caused by steric hindrance still result in a greater binding energy than if the molecule were to orientate in the opposite direction within the cavity (in which case there may be unfavourable dipole–dipole interactions) or



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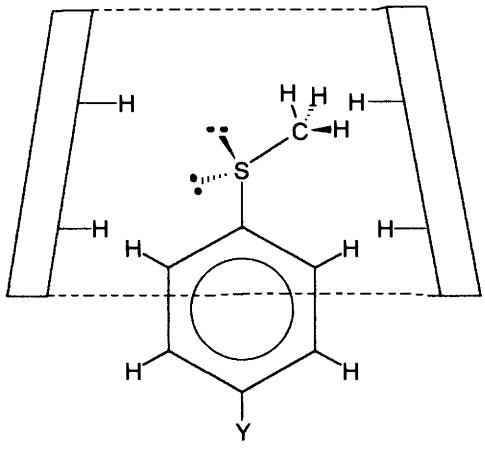

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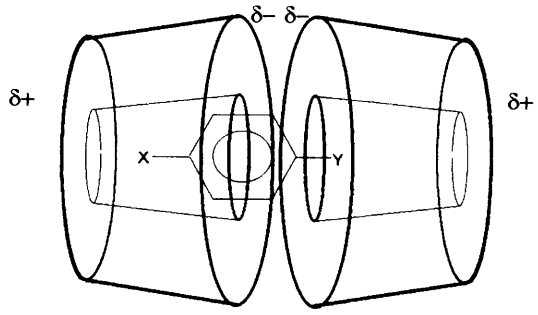
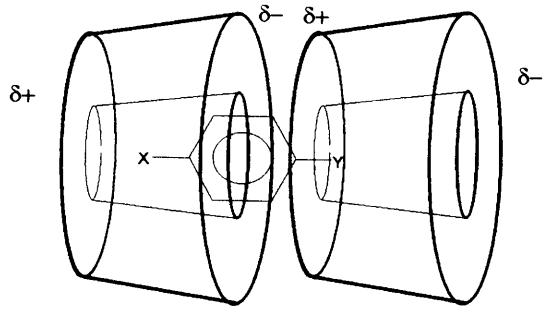


2:1 'head to head' [4]



2:1 'head to tail' [5]

(*b*) the conformation with the guest molecule oriented in the opposite direction gives a stronger binding energy. We cannot tell from the results of the improved correlation shown in Fig. 5(*b*) which of the possibilities is more likely since both will result in binding constants which will be lower than predicted from our model. Indeed both situations may occur, depending on the nature of the substituent. It is also interesting to note that in our original model diacetylbenzene was rejected as an outlier since the observed binding constant (log K_{obs} = 1.01, ref. 20) was significantly lower than predicted (log K_{pred} = 2.72). STERIMOL B5 parameters indicate that the methyl group of the acetyl substituent (3.13 Å) is likely to interact with the 5-H protons of α-cyclodextrin in an analogous way to the sulfide, sulfoxide or sulfone substituents in the present study. With two such groups on the same molecule then a considerable loss in binding energy is likely.

K_{12} values

Whilst much discussion has centred on binding mechanisms for 1:1 complexes between cyclodextrin and various guests in solution the same cannot be said for complexes with two molecules of cyclodextrin. Many instances of such complexes with substituted benzenes have been reported in the literature, including those for sym-1,4-dihalobenzenes,[21] 1,4-dihalobenzenes,[22] halobenzenes[23] and sym-1,4-disubstituted benzenes.[20] However, it is also notable that for *para*-substituted phenols,[24] phenolates,[24] benzoic acids,[25] benzoates[25] and anilines[26] the K_{12} values are very small or zero. The present study shows that 12 out of the 14 sulfides studied showed 2:1 binding, whilst for the remaining sulfides and all of the sulfoxides and sulfones no K_{12} term could be detected. From these results and those of the literature it appears that where a charged substituent is present, or a neutral one which is capable of hydrogen bonding interactions, the K_{12} term will generally be absent or very small.

Where K_{12} values could be detected for the sulfides, the most striking feature was the presence of cooperative binding in five out of twelve cases. Cooperative binding is also evident in Connors' work on sym-1,4-disubstituted benzenes[20] where he notes the possibility that facing secondary hydroxy rims of α-cyclodextrin may interact attractively; he terms this a 'substrate promoted ligand dimerization'. In other studies both 'head-to-head' structures,[27,28] as favoured by Connors [structure (**4**)] and the alternative 'head-to-tail' complex[29] [structure (**5**)] have been suggested. Both structures could be stabilised by hydrogen-bonding between hydroxy groups of the two molecules. As far as we are aware there is no firm evidence to favour either structure in solution.

We prefer the head-to-tail structure and suggest a possible mechanism for cooperative binding in which the driving force is interaction between opposite dipoles of the cyclodextrin, possibly stabilised by hydrogen bonding. Using crystallographic data for cyclodextrin (α, β and γ) complexes with various guests, Sakurai *et al.*[4,8] have generated CNDO electrical potential maps and dipole moments for cyclodextrin and have shown that electrostatic properties within the cavity are highly dependent on the conformation of the macrocyclic ring. For cyclodextrin–water complexes the water molecules are hydrogen-bonded between the primary hydroxy groups,[30] causing one of the glucosidic residues to be tilted. The consequent distortion to the macrocyclic ring results in a dipole moment (*ca.* 8 D)[4] which is not only reduced compared to other inclusion compounds, but which is also directed away from the axis of the cyclodextrin

cavity. The inclusion of a tight fitting disubstituted benzene within the cavity, however, changes the conformation of the cyclodextrin in such a way as to maximise the electrostatic interaction between the host and guest. The dipole moment of the cyclodextrin increases markedly and the direction of the dipole becomes almost parallel with the longitudinal axis (13.5 D for *p*-nitrophenol, 16 D for *p*-iodoaniline).[4] Whilst induced dipole effects undoubtedly play a part in this change, the fact that the inclusion of krypton (no dipole) within the cavity gives a similar directional and magnitudinal change in dipole (*ca.* 18 D) implies that conformational changes alone are highly significant.[4]

Whilst these molecular modelling studies were based on crystallographic data, we suggest that similar conformational and electrostatic changes may occur in solution and that the driving force in the formation of a 2:1 complex is the enhanced interaction between the opposite dipoles of the primary and secondary hydroxy rims as a result of substrate inclusion. For this to occur the Y-substituent of the guest in the 1:1 complex must penetrate the primary hydroxy rim of a second 'empty' cyclodextrin molecule, breaking the hydrogen bonded interaction between water molecules and the primary hydroxys, thus reducing the distortion of the macrocycle. The dipole moment of the second cyclodextrin molecule is then likely to approach the magnitude and direction of the first. Depending on the orientation of the second molecule of cyclodextrin, hydrogen bonding interactions may also occur. Clearly, this substrate promoted dipole–dipole interaction between cyclodextrins affords a mechanism whereby cooperative binding could occur.

Our ideas are supported by the correlation to eqn. (7) of K_{12} values for our sulfide series (with sulfide substituent assumed to be occupying the Y-position) and for sym-1,4-dihalobenzenes,[21] 1,4-dihalobenzenes,[22] halobenzenes,[23] and sym-1,4-disubstituted benzenes.[20] The independent variables, log K_{11} and R_{m_y}, the molar refractivity of the Y-substituent, are very significant, as shown by the relatively small standard deviations of the regression coefficients, given in brackets. No other parameters, including a constant parameter yielded significant regression coefficients. The significance of the R_{m_y} term is of no surprise, *i.e.* hydrogen and fluoro groups at the Y-position will not allow significant penetration at the primary hydroxy end of a second cyclodextrin molecule, whereas bromo, iodo or sulfide, groups will. The significance of the log K_{11} term is also to be expected since, generally, the factors favouring high K_{11} values are also those likely to induce a larger dipole in the cyclodextrin, thus increasing the dipole–dipole interaction between cyclodextrin molecules. The correlation is very significant at the 0.005 level, notwithstanding the low correlation coefficient that is not unexpected since the number of conformations in which the second cyclodextrin molecule can interact is much larger than in the more restricted case of 1:1 complexes. In the latter case the tight fit of the benzene ring in the α-cyclodextrin cavity gives only a limited number of conformations.[4]

$$\log K_{12} = 0.33\ (0.08) \log K_{11} + 0.096\ (0.018) R_{m_y} \quad (7)$$
$$(n = 32, r = 0.746, s = 0.70)$$

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