Cyclodextrin Complexes of Substituted Perbenzoic and Benzoic Acids and Their Conjugate Bases: Free Energy Relationships Show the Interaction of Polar and Steric Factors

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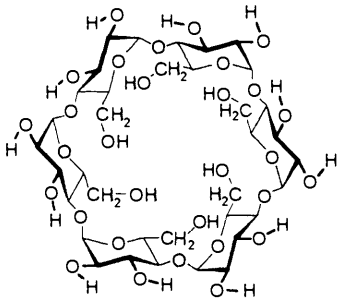
The stability constants of the complexes of α-cyclodextrin and 4-methyl-, 4-nitro-, 4-sulfonato- and 3-chloro-substituted perbenzoic acids, perbenzoates and benzoates, but not benzoic acids, show linear free energy relationships. In contrast to α-cyclodextrin, the stability constants of the β-cyclodextrin complexes of perbenzoic acid and benzoic acids do show the same trend. The stability constants are discussed in terms of the orientation of the guest species in the cyclodextrin cavity.

Cyclodextrins are torus-shaped macrocyclic glucose polymers containing six, seven or eight (α-, β- or γ-cyclodextrin) glucopyranose units, attached by α-(1,4)linkages. The primary hydroxy, O(6)H, groups project from one edge of the torus and the secondary hydroxy, O(2)H and O(3)H, groups constitute the other, wider rim,[1-3] as shown for α-cyclodextrin **1**. The



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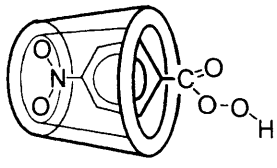

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different numbers of hydroxy groups at each end of the cavity endow the cyclodextrin with a dipolar character. A permanent dipole moment of 13.5 D has recently been calculated for α-cyclodextrin using the CNDO/2 MO method.[4] Cyclodextrins form inclusion complexes with guest species that can fit partly or wholly into the cavity. For example, the likely structure, *vide infra*, of the α-cyclodextrin-4-nitroperbenzoic acid complex is shown schematically as structure **2**. Despite extensive X-ray crystal[5-9] and solution NMR structural studies, and thermodynamic measurements on simple mononuclear benzene derivatives, the driving force for inclusion in aqueous solutions remains to be explained fully.[1-3] Gelb *et al.*, from their ^{13}C NMR structural studies, and thermodynamic measurements of the α-cyclodextrin complexes of substituted phenols and benzoic acids and their conjugate bases, show that binding is enthalpy, rather than entropy, driven. They conclude that dipolar or induced dipolar forces predominate over hydrophobic interactions.[10] Further evidence for the importance of dipolar interactions are the correlations between the logarithms of the stability constants of the cyclodextrin inclusion complexes of substituted- and 1,4-disubstituted-benzene derivatives and the Hammett σ-values of the substituents,[11,12] or the dipole moment of the derivative.[13] Size, or polarisability effects are also important since correlations are observed with the surface area,[14] molar volume[15] and molar refractivity[13] of the benzene derivatives. Bertrand *et al.* show that, in general, complex formation of a substituted phenol with α-cyclodextrin is more exothermic than with β-cyclodextrin with its larger cavity, but the entropy of complex formation is also more negative. These observations are compatible with the crystal structures and the accepted idea of α-cyclodextrin holding the guest molecule in the cavity with relatively large binding energy in one or two tightly bound configurations whereas complexes with β-cyclodextrin appear to be more loosely bound in the larger cavity but with several configurations.[15] The NMR study by Inoue *et al.* of inclusion complexes of β-cyclodextrin and *p*-substituted phenols shows the guest molecules completely penetrating the cavity of the cyclodextrin so that both the hydroxy group and the substituent could be largely in contact with the aqueous environment.[16]

Consideration of the crystal and solution structures and the trends in the stability constants of the cyclodextrin complexes that are described above led us, recently, to attempt to identify the properties of a substituent or pair of substituents in the 1,4-positions on the benzene ring that, firstly, determine the orientation of the guest in the cyclodextrin cavity, and, secondly, that confer stability to the complex. To this end, we proposed[17] that charged substituents protrude from the wider side of the cavity because of their high degree of solvation and the large energy that would be required to desolvate them substantially in order that they penetrate the cavity, whilst for uncharged derivatives the atom or group with the highest Hammett σ-value is bound in the narrower end of the cavity because of the favourable host–guest dipole–dipole interaction energy. We were then able to show that the logarithm of the stability constant showed a good correlation (for 46 derivatives, with one outlier) with an expression that contains a constant corresponding to the stability of unsubstituted benzene, the σ-value of, and the molar refractivity of the substituent located at the narrower end of the cyclodextrin cavity, the product of the σ-values of the substituents, and the charge of the substituent. Thus, we were able to account for the stability of the inclusion complexes simply by considering the overall charge, the charge distribution and the polarisability, or size, of the substituents. The success of this approach may be attributed to the limited number of tightly-packed configurations available to the α-cyclodextrin complexes.[15] A similar analysis of β-cyclodextrin complexes gave a very poor correlation.[17] The larger number of possible configurations of the latter complexes[15] in which the substituents on the benzene may protrude to a greater or lesser extent from either end of the host cavity[16] and in which the alignment of the axis of the guest with respect to that of the host may be up to 36°[9] means that more interaction effects between the various forces are likely to be in play than is the case with α-cyclodextrin.

Notwithstanding the success of the correlation with α-

cyclodextrin, the standard deviation of the correlation line is about twice that expected from consideration of the within-group standard deviation of replicate measurements.[17] This indicates that an important factor influencing the stability of the inclusion complexes has been omitted from the correlation analysis. This factor is likely to be associated with steric effects involving the substituent included in the narrow end of the cyclodextrin cavity, since the molar refractivity accounts for the size, but not the shape, of the substituent. Indeed, examination of the correlation data[17b] shows that the observed stability constant for 1,4-diethoxybenzene (the derivative with the longest substituent used in the correlation analysis), after correction for the statistical effect for a symmetrical guest, is an order of magnitude less than that predicted from the correlation equation. The present results show that lengthening the substituent by one oxygen atom, in going from benzoic acids and their conjugate bases to perbenzoic acids and their conjugate bases, can have seemingly bewildering effects on the stability constants. These unexpected results are satisfactorily explained by consideration of the interaction of polar and steric factors.

Apparent Stability Constants and Competitive Binding

The equilibria shown in eqns. (1)–(4) are for the interaction of an acid, HA, and its conjugate base, A^-, with cyclodextrin, C, in a solution of $NaNO_3$, whose anion competes for the cyclodextrin.[18–20] The mixed acid dissociation constant K_a, is

$$AH \overset{K_a}{\rightleftharpoons} A^- + H^+ \quad (1)$$

$$C + AH \overset{K_{AH}}{\rightleftharpoons} C,AH \quad (2)$$

$$C + A^- \overset{K_A}{\rightleftharpoons} C,A^- \quad (3)$$

$$C + NO_3^- \overset{K_{NO_3}}{\rightleftharpoons} C,NO_3^- \quad (4)$$

defined in eqn. (5), where $\{H^+\}$ is the hydrogen ion activity measured with the glass electrode, and the stability constants of the cyclodextrin complexes of the acid, its conjugate base, and nitrate are defined in eqns. (6)–(8), respectively.

$$K_a = \frac{\{H^+\}[A^-]}{[HA]} \quad (5)$$

$$K_{HA} = \frac{[C,HA]}{[HA][C]} \quad (6)$$

$$K_A = \frac{[C,A^-]}{[A^-][C]} \quad (7)$$

$$K_{NO_3} = \frac{[C,NO_3^-]}{[NO_3^-][C]} \quad (8)$$

Defining the apparent acid dissociation constant, in the presence of cyclodextrin, K_a^{app}, eqn. (9), and applying the mass balance eqn. (10) and the electroneutrality principle (neglecting OH^-), eqn. (11), where $[Na^+]_t$ is obtained from the amount of sodium hydroxide added during the titration, and y, the activity coefficient, is approximated by eqn. (12), in which I is the ionic strength,[21] yields the expression shown in eqn. (13).

$$K_a^{app} = \frac{\{H^+\}([A^-] + [C,A^-])}{[HA] + [C,HA]} \quad (9)$$

$$[HA]_0 = [HA] + [C,HA] + [A^-] + [C,A^-] \quad (10)$$

$$[Na^+]_t + \{H^+\}/y = [A^-] + [C,A^-] \quad (11)$$

$$\log_{10} y = \frac{-0.509\sqrt{I}}{1 + 1.5\sqrt{I}} \quad (12)$$

$$K_a^{app} = \frac{\{H^+\}([Na^+]_t + \{H^+\}/y)}{[HA]_0 - ([Na^+]_t + \{H^+\}/y)} \quad (13)$$

Eqn. (13) is used to calculate K_a^{app} from $\{H^+\}$ and $[Na^+]_t$, using the end point of the pH titration to obtain $[HA]_0$.

The variation of K_a^{app} with cyclodextrin concentration gives the stability constants, as follows. Now, because of uncertainty[18–20] in the value of K_{NO_3}, it is convenient to define apparent stability constants for C,HA and C,A^- in terms of the sum of [C] and $[C,NO_3^-]$, as in eqns. (14) and (15).

$$K_{HA}^{app} = \frac{[C,HA]}{[HA]([C] + [C,NO_3^-])} \quad (14)$$

$$K_A^{app} = \frac{[C,A^-]}{[A^-]([C] + [C,NO_3^-])} \quad (15)$$

From eqns. (5), (9), (14) and (15), after taking logs, eqn. (16) is obtained, and the mass balance eqn. (17) and eqns. (5), (10), (14) and (15) yield the expression shown in eqn. (18).

$$\Delta pK_a \equiv pK_a^{app} - pK_a = \log\left\{\frac{1 + K_{HA}^{app}([C] + [C,NO_3^-])}{1 + K_A^{app}([C] + [C,NO_3^-])}\right\} \quad (16)$$

$$[C]_0 = [C] + [C,NO_3^-] + [C,HA] + [C,A^-] \quad (17)$$

$$[C]_0 = [C] + [C,NO_3^-] + \left\{\frac{K_{HA}^{app}\{H^+\}([C] + [C,NO_3^-]) + K_A^{app}K_a([C] + [C,NO_3^-])}{\{H^+\}[1 + K_{HA}^{app}([C] + [C,NO_3^-])] + K_a[1 + K_A^{app}([C] + [C,NO_3^-])]}\right\}[HA]_0 \quad (18)$$

Eqns. (16) and (18) yield K_{HA}^{app} and K_A^{app} from the variation of K_a^{app} with $[C]_0$. Finally, applying the mass balance eqn. (19) to eqns. (8) and (14) gives eqn. (20), and when $K_{NO_3}[C] \ll 1$, eqn. (21) results, and similarly for eqns. (8) and (15) the expression shown in eqn. (22) is obtained.

$$[NO_3^-]_0 = [NO_3^-] + [C,NO_3^-] \quad (19)$$

$$K_{HA} = K_{HA}^{app}\left\{1 + \frac{K_{NO_3}[NO_3^-]_0}{1 + K_{NO_3}[C]}\right\} \quad (20)$$

$$K_{HA} = K_{HA}^{app}(1 + K_{NO_3}[NO_3^-]_0) \quad (21)$$

$$K_A = K_A^{app}(1 + K_{NO_3}[NO_3^-]_0) \quad (22)$$

Experimental

Materials.—The α-cyclodextrin·4H_2O and β-cyclodextrin·7H_2O were purchased from Sigma. The substituted perbenzoic acids contain the parent acid, up to 30%, as the only significant impurity; 4-methyl, 4-sulfonato- and 4-nitro-perbenzoic acid were provided by Interox Chemicals and 3-chloroperbenzoic acid was purchased from BDH. Removal of the parent acids from the samples of the perbenzoic acids and manipulation of the pure compounds are hazardous procedures and Interox supplied the peracids on condition that we did not attempt to do so. Other reagents were of the best available grade and solutions were made up in distilled water.

Methods.—Solutions of the mixtures of peracid and parent acid, about 4×10^{-3} mol dm^{-3} in peracid, containing the required amount of cyclodextrin and 0.1 mol dm^{-3} $NaNO_3$ were titrated with 0.1 mol dm^{-3} NaOH in a thermostatted vessel at 25 °C as described previously.[22]

Results

Iodometric determinations, prior to, and immediately after the pH titration, showed that less than 7% of the peracid decomposed during the course of the titration. The extent of decomposition, although small, is larger than expected over the pH range of the titration and so is probably due to the high local pH in the vicinity of the added NaOH. The nature of the peracid and the concentration of cyclodextrin had no systematic effect on the extent of decomposition. The decomposition causes a small systematic change in the value of K_a^{app} calculated for different $[Na^+]_t$ and so, as previously,[22] acid dissociation constants are calculated from the pH of half neutralisation, *i.e.* when $[Na^+]_t = [HA]_0/2$ in eqn. (13). The measured pK_a values of the peracids are virtually identical to those reported previously,[22] the value for 4-methylperbenzoic acid was determined in the present work as 7.86. The data are fitted simultaneously to eqns. (16) and (18); however, since the peracid was titrated in the presence of the parent acid (or *vice versa*), eqn. (18) is modified to include an additional term that is identical to the last term on the right hand side of the equation but referring to the amount of cyclodextrin complexed by the parent acid (or peracid). The experimental results and best-fit lines are shown in Figs. 1–4, and the best-fit values of the apparent stability constants in Table 1, the subscripts P and PH refer to peracids whilst A and AH refer to the parent acids.

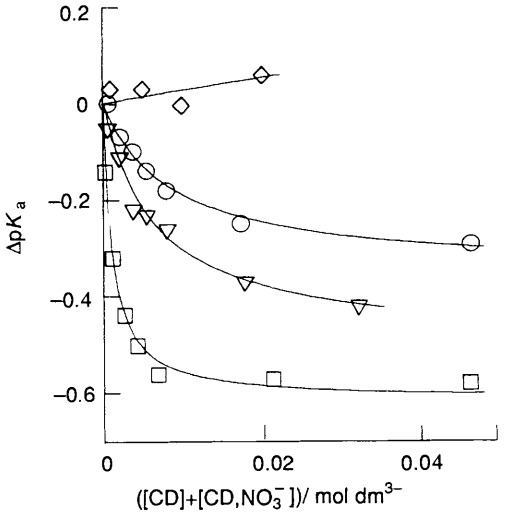

Fig. 1 Effect of α-cyclodextrin on the pK_a of substituted perbenzoic acids in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C: ◇, 4-Me; ○, 4-NO_2; ▽, 4-SO_3^-; □, 3-Cl

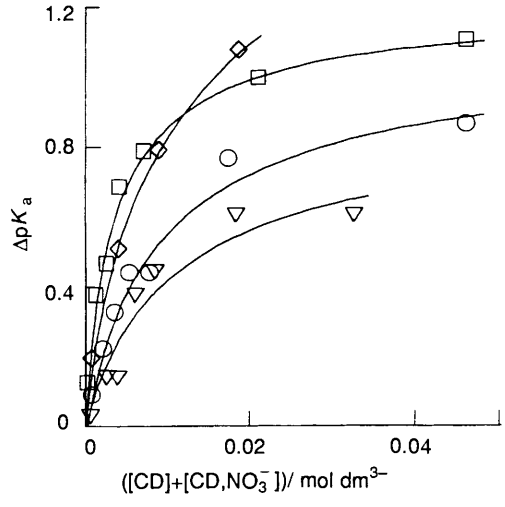

Fig. 2 Effect of α-cyclodextrin on the pK_a of substituted benzoic acids in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C (see Fig. 1 for key to symbols)

Discussion

The peracids used in this work oxidise chloride and so the apparent stability constants were determined in nitrate medium.

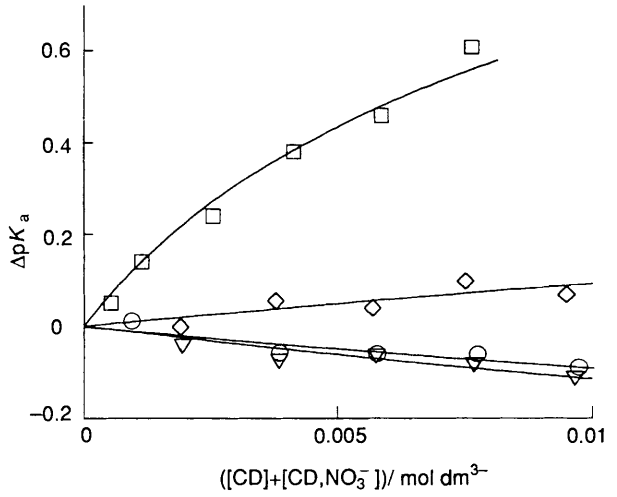

Fig. 3 Effect of β-cyclodextrin on the pK_a of substituted perbenzoic acids in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C (see Fig. 1 for key to symbols)

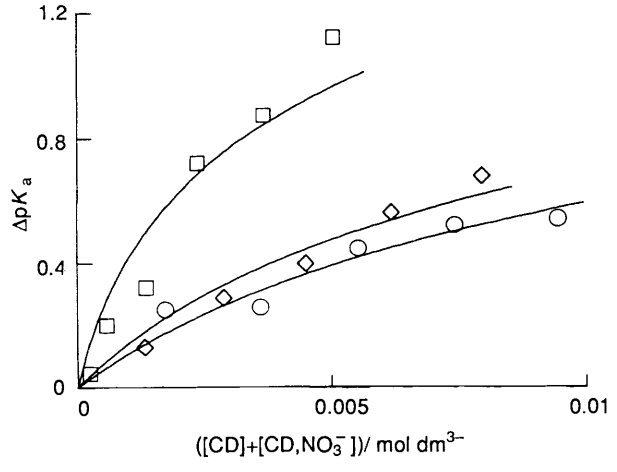

Fig. 4 Effect of β-cyclodextrin on the pK_a of substituted benzoic acids in 0.1 mol dm^{-3} $NaNO_3$ at 25 °C (see Fig. 1 for key to symbols)

Table 1 Apparent stability constants (dm^3 mol^{-1}; ± standard deviation), in 0.1 mol dm^{-3} $NaNO_3$, of the cyclodextrin complexes of substituted-perbenzoic (PH) and -benzoic (AH) acids and their conjugate bases (P and A) at 25 °C

Substituent	K_A^{app}	K_{AH}^{app}	K_P^{app}	K_{PH}^{app}
α-Cyclodextrin				
4-Me	< 5	598 ± 29	< 5	6.4 ± 2.4
4-NO_2	30 ± 10	383 ± 50	176 ± 24	78 ± 14
4-SO_3^-	32 ± 22	255 ± 73	278 ± 34	87 ± 16
3-Cl	69 ± 8	1150 ± 70	2000 ± 180	482 ± 52
β-Cyclodextrin				
4-Me	< 5	396 ± 30	< 5	24 ± 4
4-NO_2	< 5	292 ± 24	23 ± 3	< 5
4-SO_3^-	*a*	*a*	30 ± 3	< 5
3-Cl	< 5	1620 ± 240	< 5	343 ± 17

[a] Not determined, systematic deviations were observed in the results, which we are presently unable to account for.

The stability constant of the α-cyclodextrin nitrate complex is reported to be 1.4 dm^3 mol^{-1}, from conductivity measurements.[18] Hence the approximation required for eqns. (21) and (22) holds under the conditions of the experiments, and the true stability constants are a factor of 1.14 greater than the apparent stability constants shown in Table 1. The stability constant of the β-cyclodextrin nitrate complex is variously reported as 5.5 and 0.2 dm^3 mol^{-1}, from spectrophotometric measurements of competitive dye-binding.[19,20] Hence a significant correction according to eqns. (21) and (22) may or may not need to be applied, although the approximation required for the equations holds under the conditions of the experiments in both cases. The uncertainty in the correction is irrelevant to the discussion of the present results since this largely involves comparisons of the binding constants of various guests with the same cyclodextrin under the same conditions.

α-Cyclodextrin Complexes of Benzoates.—The stability constant of the 4-nitrobenzoate complex is larger than that of the 4-methylbenzoate. This is consistent with the argument,[17] outlined in the Introduction, that the carboxylate group, because of its charge, protrudes from the wider rim of the cyclodextrin cavity and, hence, electron-withdrawing substituents in the 4-position favour binding because of the attractive host–guest dipole–dipole interaction. The Hammett σ-values[23] of the 4-methyl- and 4-nitro-substituents are −0.17 and 0.78, respectively. The 3-chlorobenzoate complex has the highest stability of the benzoates. A relatively high stability is expected for the latter since the σ-value of the 3-chloro substituent is 0.35. In addition, however, a substituent in the 3-position to benzoate is oriented differently in the cyclodextrin cavity to one in the 4-position because of the tight fit of the benzene ring in the cyclodextrin cavity, and this results in a favourable interaction in the case of the α-cyclodextrin 3-chlorobenzoate complex. It is interesting that the 4-sulfobenzoate complex exhibits a stability constant similar to that of the 4-nitrobenzoate, despite the negative charges at each end of the former derivative. The 4-sulfo group has a fairly large σ-value, 0.35, and by far the largest substituent molar refractivity,[24] 13.68, compared to 5.65, 7.36 and 6.03, for the methyl, nitro and chloro substituents, respectively. So, in this case, the favourable guest–host ion–dipole, dipole–dipole and induced dipole–dipole interactions are sufficient to overcome the unfavourable desolvation energy of the sulfonato group. This is consistent with the X-ray crystal structure of the α-cyclodextrin benzenesulfonate complex, in which the sulfonato group is located at the narrow end of the cyclodextrin cavity.[7] Our original postulate that charged substituents must protrude from the wider end of the cyclodextrin cavity[17] clearly needs qualifying in the case of negatively charged substituents of higher polarisability that are less strongly solvated because of a lower charge density.

α-Cyclodextrin Complexes of Benzoic Acids.—The stability constants of the benzoic acid complexes are considerably larger than those of the benzoates, consistent with our proposal,[17] of a repulsive interaction between the negative charge on the benzoate and the negatively charged end of the cyclodextrin dipole, which is located at the wider end of the cavity. In contrast to the benzoates, the stability constant of 4-methylbenzoic acid is somewhat larger than that of 4-nitrobenzoic acid, in agreement with the work of Connors.[11] The 4-nitro substituent has a larger σ-value than that of carboxylic acid, 0.45, and following our proposal,[17] should be located at the narrower end of the cyclodextrin cavity in the 4-nitrobenzoic acid cyclodextrin complex. In this orientation, the favourable dipole–dipole interaction between the host and guest is modulated by the electron-withdrawing carboxylic acid substituent. In the case of the 4-methylbenzoic acid complex the carboxylic acid substituent is located at the narrow end of the cavity, and, although the host–guest dipole interaction with this substituent is less than that with the nitro group, in this case the electron-donating methyl group reinforces the favourable dipole–dipole interaction resulting in a more stable complex than with the 4-nitrobenzoic acid. The balance of forces favouring one or other of the possible orientations of 4-sulfonato- and 3-chlorobenzoic-acids is difficult to decide because of the similarity of the substituent σ-values to that of carboxylic acid and because of the uncertainties introduced by the negatively charged, but highly polarisable, substituent in the former case and substitution at the 3-position in the latter. This will be discussed further when the results as a whole are examined in the light of the free energy relationships.

α-Cyclodextrin Complexes of Perbenzoates and Perbenzoic Acids.—The pattern of stability constants (Table 1) here is different to that seen with the parent benzoic acids and their conjugate bases. The differences are shown as free energy relationships in Fig. 5, in which the logarithms of the stability constants are compared with those of the perbenzoic acid complexes. The stability constants of the perbenzoate complexes are larger and more dependent, albeit in the same sense, on the nature of the substituent, than those of the benzoates. This is explained as follows. First, when the perbenzoate derivatives take the same orientation as the benzoates in the cyclodextrin cavity, they experience less repulsive interaction between the charge on the percarboxylate group and the negative end of the cyclodextrin dipole because of the greater separation of the latter than that between the end of the cavity

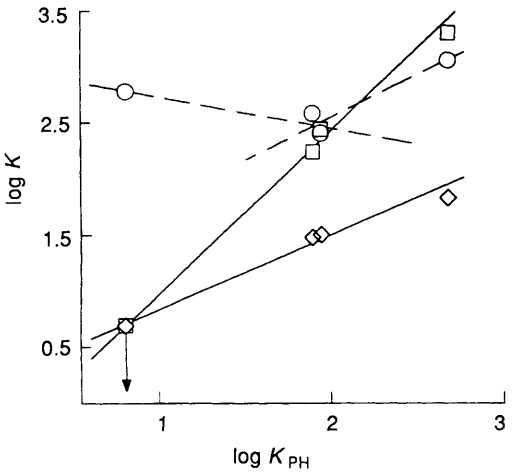

Fig. 5 Relationship between the logarithm of the stability constants of the α-cyclodextrin complexes of benzoates, ◇; benzoic acids, ○; perbenzoates, □; and those of the perbenzoic acids, PH

and the charge on the carboxylate. Secondly, we explained the exceptional lack of dependence of the stability constant of substituted benzoates on the nature (in particular, the molar refractivity) of the substituent in the 4-position by postulating that the ion–dipole repulsion was great enough to abolish close packing at the narrow end of the cavity.[17] Thus the greater dependence of the stability of the perbenzoate complexes, which are less subject to this repulsive interaction, on the nature of the 4-substituent are unexceptional in this respect, when compared with complexes involving uncharged derivatives.

Two other significant differences in the patterns of stability constants are apparent when the peracids and their conjugate bases are compared with the parent species. First, the perbenzoate complexes are more stable than those of the perbenzoic acids. Secondly, the effect of the nature of the substituents on the stability constants is the same for the perbenzoic acids and the perbenzoates, as shown by the linear free energy relationship between the respective log stability constants in Fig. 1. Now, taking Fig. 1 as a whole, the reasonable conclusion that can be drawn is that the linear relationships between the logarithm of the stability constants with the benzoates, perbenzoates and perbenzoic acids indicate that similar factors are contributing to the stability of these three classes of complexes and so they must all, on the one hand, have the same orientation in the cyclodextrin complex with the carboxylate, percarboxylate and percarboxylic acid groups, respectively protruding from the wider end of the cyclodextrin cavity. On the other hand, the benzoic acid complexes change orientation depending on the relative affinities of the carboxylic acid group and the substituent group for the narrow end of the cyclodextrin cavity. This manifests as a break in the linear free energy relationship. Unfortunately it is not possible to define the precise position of the break from the present results, hence the dashed lines in Fig. 5. The different pattern of binding for the perbenzoic acids and benzoic acids cannot be explained in terms of the slightly higher molar refractivity of the percarboxylic acid substituent, nor in terms of σ-values, which would not be expected to differ considerably between the parent acids and peracids. The factor preventing the inclusion of the percarboxylic acid substituent in the narrow end of the cavity is the length of the substituent, resulting in unfavourable steric repulsions that preclude the optimal interactions between the substituted benzene ring and the cyclodextrin cavity. It follows that the reduced stability of the perbenzoic acid complexes compared with those of the perbenzoates is due to the greater electron-withdrawing ability of the percarboxylic acid group compared with the percarboxylate causing a reduced host–guest dipole–dipole interaction in the former case.

β-Cyclodextrin Complexes.—The importance of dipole–dipole interactions in complexes of this type has recently been acknowledged.[25] A full interpretation of the factors influencing the stability is not possible because many of the stability constants were too low to be determined (Table 1). What is clear however, is that the overall pattern of stability constants is different, in some respects, to that seen with α-cyclodextrin. This is expected if the size of the substituent is an important factor, since the diameter of the β-cyclodextrin cavity is considerably larger than that of α-cyclodextrin. The most remarkable observation is that the β-cyclodextrin complexes of the perbenzoic acids exhibit the same pattern of stabilities as the β-cyclodextrin complexes of the benzoic acids, which is similar to the pattern shown by the α-cyclodextrin complexes of the benzoic acids. Thus, when the percarboxylic acid substituent is included in the narrow end of the β-cyclodextrin cavity it does not encounter the same steric repulsion that it does with α-cyclodextrin. This is consistent with the NMR solution studies of 1,4-disubstituted benzene complexes of β-cyclodextrin that shows the guest molecules completely penetrating the cavity of the cyclodextrin so that both substituents are largely in contact with the aqueous environment.[16] The low value of the stability constant of the β-cyclodextrin complex of 3-chloroperbenzoate does not seem to fit into any pattern. We have no explanation of this, other than to note that the cross-interactions of the factors affecting the stability of β-cyclodextrin complexes are far more convoluted than is the case for α-cyclodextrin.[17]

Acknowledgements

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