Stability constants of α-cyclodextrin complexes of *para*-substituted aromatic ketones in aqueous solution

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Stability constants for α-cyclodextrin complexes of 21 *para*-substituted acetophenones and related aryl ketones have been determined spectrophotometrically or potentiometrically. It has been found that the presence of ketone-containing substituents generally results in destabilisation of complex formation. It is postulated that steric hindrance at the narrow end of the cyclodextrin cavity causes the benzene ring to be displaced from its optimal position or orientation.

Cyclodextrins[1] are hollow, truncated-cone shaped molecules made up of six or more glucose units linked together covalently by oxygen atoms and held in shape *via* hydrogen bonding between the secondary hydroxy groups on adjacent units at the wider rim of the cavity. They are chemically stable and in aqueous solution form host–guest inclusion complexes with molecules and ions that can fit at least partially into the cavity. They are used extensively as models to study non-covalent interactions important in biological processes such as molecular recognition and enzyme catalysis.

The shape of α-cyclodextrin, which is made up of six glucose units, is such that a benzene ring fits snugly in the cavity but cannot easily enter or leave *via* the narrow end.[2] Hence it seems likely that directional forces pushing a substituted or 1,4-disubstituted benzene derivative into the cavity result in stronger binding, whereas forces pushing the derivative out of the wider end of the cavity result in weaker binding.[3] The situation is far more complicated for loosely fitting host–guest complexes, such as those involving β-cyclodextrin (with seven glucose units) and benzene derivatives, where additional cross-interaction forces determine the optimum set of positions of the guest in the cavity.[3]

The anisotropic nature of the interaction of α-cyclodextrin and substituted or 1,4-disubstituted benzene derivatives is reflected in the recently published correlation equation, eqn. (1),[3] based on literature stability constants of about fifty

$$\log K_{11} = 1.28 \pm 0.11 + (1.38 \pm 0.16)\sigma_x - (2.35 \pm 0.33)\sigma_x\sigma_y + (0.120 \pm 0.013)(1 - \text{carb}^-)R_{mx} - (0.27 \pm 0.12)\text{Ysub}^- \quad (1)$$

inclusion complexes. K_{11} is the stability constant of the 1:1 complex; σ_x and R_{mx} are, respectively, the Hammett σ_p substituent constant and the molar refractivity of the more electron-withdrawing substituent that we propose is located in the narrower, primary O(6)H, end of the α-cyclodextrin cavity that represents the positive end of the cyclodextrin dipole; and σ_y is the Hammett constant for the substituent that protrudes from the wider secondary O(2)H and O(3)H rim of the cavity. Ysub^- is an identity variable for complexes involving negatively charged y-substituents and carb^- is an identity variable specifically for when this substituent is a carboxylate. The correlation analysis leading to eqn. (1) covered values of log K_{11} from about 0.5 to 3.5 and yielded a standard deviation of 0.34 and a correlation coefficient 0.92.[3] There was only one outlier, the value of log K_{11} for 1,4-diacetylbenzene was 1.01 whereas eqn. (1) predicted a value of 2.72.[3b] We were unable to offer an explanation for the outlier at that time.

Subsequently we reported the stability constants of the α-cyclodextrin complexes of over twenty *para*-substituted methyl phenyl sulfides, sulfoxides and sulfones.[4,5] These results were used to challenge eqn. (1), which seemed to fail spectacularly, at first sight, for complexes of those derivatives where the sulfur containing group was more electron-withdrawing than the substituent *para* to it. These were the derivatives where we proposed that the sulfur containing substituent was located in the narrower end of the cyclodextrin cavity. Experimentally determined K_{11} values were often much less than those predicted according to eqn. (1) and a plot of the log of the experimentally determined K_{11} against log K_{11} calculated according to eqn. (1) was roughly perpendicular to the predicted line.[4] A careful consideration of the shape of the sulfur substituents and the α-cyclodextrin cavity showed that the derivatives could not enter the cavity with the sulfur at the narrow end and retain a snug fit of the benzene ring with the interior of the cavity. Once we modified our hypothesis so that the substituent *para* to the sulfur group was designated as the x-substituent then we found excellent agreement between experimentally determined stability constants and those predicted by eqn. (1).[4] This suggests that the substituent *para* to the sulfur group is actually located in the narrow end of the cyclodextrin cavity, although, based on consideration of the detailed charge distribution calculated for the cyclodextrin cavity,[2,6] we are unwilling to discount the possibility that in some cases, perhaps, the benzene ring is simply displaced from the optimal position attained with a less bulky substituent.

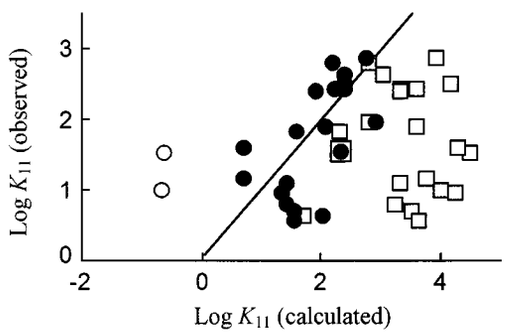

Fig. 1 Plot of the observed values of the log of the 1:1 stability constant *versus* values calculated according to eqn. (1). The squares indicate log K_{11} (calculated) values using eqn. (1) with the more electron-withdrawing substituent designated as the x-substituent. The filled and open circles indicate log K_{11} (calculated) values using eqn. (1) with the substituent *para* to the ketone group designated as the x-substituent, see text. The open circles represent the phenolate anions, 4′-oxidoacetophenone and 4′-oxidopropiophenone. The line is that of log K_{11} (observed) equal to log K_{11} (calculated).

Table 1 Stability constants (±standard deviation) for 1:1 and, where detectable, 1:2 complexes of acetophenones and related benzene derivatives with α-cyclodextrin

Compound	Buffer	K_{11}/dm^3 mol^{-1}	K_{12}/dm^3 mol^{-1}
Acetophenone	Phosphate	⩽12 [a]	— [b]
4′-Bromoacetophenone	Phosphate	448 ± 63	26 ± 17
4′-Methylacetophenone	Phosphate	5.0 ± 1.6	—
4′-Oxidoacetophenone anion	Carbonate	10.0 ± 1.3 [c]	—
4′-Hydroxyacetophenone	Nitrate	14.9 ± 0.4 [d]	—
4′-Methoxyacetophenone	Phosphate	3.6 ± 2.4	—
4-Acetylbenzoic acid	Nitrate	621 ± 19 [e]	—
4-Acetylbenzoate anion	Nitrate	4.3 ± 1.6 [e]	—
Methyl 4-acetylbenzoate	Phosphate	96 ± 7	—
4′-Nitroacetophenone	Phosphate	35 ± 4	—
4′-Fluoroacetophenone	Phosphate	6.4 ± 5.4	—
4-Nitrobenzoyl cyanide	Phosphate	67 ± 7	—
4′-Bromo 2,2,2-trifluoroacetophenone	Water	276 ± 39	—
4′-Chloro 2,2,2-trifluoroacetophenone	Water	256 ± 20	—
4′-Methoxy 2,2,2-trifluoroacetophenone	Water	9 ± 6	—
4′-Bromopropiophenone	Carbonate	278 ± 40	26 ± 17
4′-Chloropropiophenone	Water	72 ± 4	—
4′-Oxidopropiophenone anion	Carbonate	34 ± 2 [c]	—
4′-Hydroxypropiophenone	Nitrate	41 ± 2 [d]	25 ± 3 [d]
4′-Bromobutyrophenone	Water	760 ± 110	47 ± 23
4′-Bromo-4-chlorobutyrophenone	Phosphate	314 ± 11	—

[a] This compares with a value of 12.6 dm^3 mol^{-1} calculated from the dissociation constant obtained by competitive kinetics in phosphate buffer pH 11.6, ref. 7, where the cyclodextrin is partially ionised [the pK_a of the secondary OH(2) is 12.2, ref. 1]. [b] Indicates that the stability constant was not detectable under the conditions employed. [c] By competitive spectrophotometric method. [d] By combined potentiometric titration and competitive spectrophotometric method. [e] By potentiometric titration.

The value of log K_{11} for the α-cyclodextrin complex of methyl 4-methylsulfanylphenyl ketone, $CH_3C(O)C_6H_4SCH_3$, 1.56,[5] is much lower than the value, 3.38, predicted by eqn. (1). This may be related to the low observed value of the previously mentioned outlier, 1,4-diacetylbenzene, $CH_3C(O)C_6H_4C(O)CH_3$. The $CH_3C(O)$ group in the narrow end of the cyclodextrin cavity may prevent the snug fit of the benzene ring in a similar manner to CH_3S. This idea is supported by the values of the stability constants of the substituted acetophenone and related aromatic ketone complexes reported in this paper.

The chemical properties of cyclodextrin complexes of ketones are potentially important and the binding of aliphatic ketones to cyclodextrins has recently been described.[7]

Experimental

The ketones were purchased from Aldrich. Other materials and the methods are as described previously.[4,8] The majority of stability constant determinations were carried out spectrophotometrically in acetate, phosphate or carbonate buffers, pH 4.0, 7.6 or 10.0, respectively, and ionic strength 0.1 mol dm^{-3}. For compounds that absorbed far down in the ultraviolet, determinations were carried out in distilled water to minimise background subtraction errors. For the 4′-acetylbenzoic acid and its anion a potentiometric titration was carried out in 0.05 mol dm^{-3} $NaNO_3$. For the phenolate anions 4′-oxidopropiophenone and 4′-oxidoacetophenone, binding constants were determined using competitive spectrophotometry, with *p*-nitrophenol as the indicator species. The determinations were carried out in a solution containing 5.3×10^{-5} mol dm^{-3} *p*-nitrophenol and 1×10^{-3} mol dm^{-3} α-cyclodextrin and pH 10.4 carbonate buffer, ionic strength 0.1 mol dm^{-3}. Twelve different concentrations of phenolate anion were used in the range 4×10^{-3} mol dm^{-3} to 3×10^{-2} mol dm^{-3}. The analysis used a binding constant of 2400 dm^3 mol^{-1} for the *p*-nitrophenolate anion.[9] Binding constants for the anions were then used in the analysis of data from potentiometric titrations to yield stability values for the conjugate acids.

Results and discussion

Stability constants of 1:1 and, where significantly greater than zero, 1:2 complexes are given in Table 1. The 1:2 stability constants are generally low compared with those of the substituted methyl phenyl sulfides, although significant 1:2 stability constants were not obtained for the sulfoxides and sulfones.[4] Plots of the log of the observed 1:1 stability constant against that calculated according to eqn. (1) are shown in Fig. 1. The squares represent log K_{11} values calculated as we originally proposed, on the basis of the more electron-withdrawing substituent being the x-substituent, *i.e.* the substituent located in the narrow end of the cyclodextrin cavity (this is the substituent containing the ketone group in all cases except 4′-nitroacetophenone). The majority of the observed stability constants are considerably less than the calculated values: the line in Fig. 1 represents log K_{11} (observed) equal to log K_{11} (calculated). This can be interpreted in terms of the ketone group sterically preventing the benzene ring reaching its optimum position in the cyclodextrin cavity. This is similar to the previously reported situation with aryl alkyl sulfides, sulfoxides and sulfones. It is notable that the STERIMOL B5 parameter[10] that describes the maximum width of substituents is 3.17 Å for methyl sulfoxide and 3.13 Å for acetyl. If, however, the assumption is made that the ketone-containing group protrudes from the wider end of the cyclodextrin cavity then the calculated stability constants represented by the circles in Fig. 1 are calculated. [It should be noted that where the guest has both a negative σ_x and a positive σ_y, so that it is orientated such that it experiences an unfavourable dipole–dipole interaction with the cyclodextrin then the sign of the $\sigma_x\sigma_y$ interaction term in eqn. (1) is reversed.] With the exception of the two phenolate anions, open circles in Fig. 1, which are predicted to have very low stability constants, the calculated stability constants now show a much better agreement overall with the observed values. As we have discussed previously for the sulfur-containing benzene derivatives,[4] although the present results are indicative of steric hindrance to binding by the carbonyl-containing group at the narrow end of the cyclodextrin cavity, they do not represent proof that the carbonyl-containing group protrudes from the wide end of the cavity, although it is tempting to presume so in the majority of cases.

In the original formulation of eqn. (1) it was assumed that negatively charged substituents protrude from the wide end of the cyclodextrin cavity because of solvation. This may not

always be so in reality since we have obtained a finite stability constant for the α-cyclodextrin complex of 4-sulfonatobenzoate.[11] Thus it is possible that each of the two phenolate anions are located with the oxido group at the narrow end of the cyclodextrin cavity. In this position there would be a favourable anion–cyclodextrin ion–dipole interaction which is not accounted for as a term in eqn. (1), thus leading to the underestimation of the binding constant. Alternatively, it is possible that anionic 1,4-disubstituted benzene derivatives that have a sterically bulky group in the *para*-position do not form full inclusion complexes but that only the anionic part associates with the narrow end of the cyclodextrin with the benzene ring in the aqueous environment. This is similar to the position of the sulfonato group in the crystal structure of the α-cyclodextrin–sodium benzene sulfonate complex.[12]

In conclusion, correlations such as eqn. (1) provide reasonable predictions of the stability constants of full inclusion complexes between substituted and 1,4-disubstituted benzene derivatives and α-cyclodextrin, provided the gross orientation is chosen correctly by consideration of substituent size and shape. Conversely, incorrect choice of gross orientation for a family of derivatives can be detected by systematic deviations of observed and predicted stability constants.

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