Binding of aliphatic ketones to cyclodextrins in aqueous solution

Oswald S. Tee,* Alexei A. Fedortchenko, Paul G. Loncke and Timothy A. Gadosy

Department of Chemistry and Biochemistry, Concordia University, Montréal, Québec, Canada H3G 1M8

Dissociation constants (K_d) for the complexation of 22 simple ketones with α-,β- and hydroxypropyl-β-cyclodextrin (α-CD, β-CD, and HP-β-CD) in aqueous solution have been determined. For these constants, there are various correlations involving pK_d ($= -\log K_d$) which have the form of linear free energy relationships. In particular, there are strong correlations between the pK_d values of ketones (RCOR′) and related secondary alcohols [RCH(OH)R′], including cases where R and R′ form a ring. As with other alkyl derivatives, pK_d values for alkan-2-ones and alkan-3-ones increase monotonically with chain length, with slopes about 0.4, corresponding to Gibbs energy increments of *ca.* 2.3 kJ mol^{-1} for each CH_2 group that is sequestered by the CD. The strengths of binding of linear derivatives to α-CD and β-CD correlate well, but bulky and cyclic ketones bind more weakly to α-CD, due to its smaller cavity. The pK_d values for complexation of 18 of the 22 ketones by HP-β-CD and β-CD are fairly close and linearly related with a slope of 0.96 ± 0.03. These data are a subset of a larger set for 68 aliphatic compounds for which the slope is 0.99 ± 0.02. Thus, the strength of binding of such aliphatics to HP-β-CD and β-CD is generally close, although the penetration of the CD cavity by the guests is not necessarily the same for these two CDs.

Virtually all of the current interest in cyclodextrins,[1] whether it be theoretical, practical or commercial,[2] is due to their ability to form host–guest complexes in solution and in the solid state.[1,2] Consequently, the determination of dissociation constants of such complexes[3] is a necessary, though tedious, exercise for improving our understanding of the factors involved in complexation,[4] as well as for the execution of other studies and for the purposes of prediction. Our interests in cyclodextrins (CDs) are mainly associated with the varied effects they can have on organic reactivity[5] due to their complexation of one or more of the reactants. In particular, we have been studying reactions where systematic variations in the structure of the substrates, or changes in the host, cause alterations in rate retardations and accelerations,[5–8] in an attempt to better understand some of the origins of supramolecular catalysis.[5,9]

In this paper we report dissociation constants for complexes formed in aqueous solution between various simple ketones and the three CDs most commonly used in the laboratory and industry, *viz.* α-CD, β-CD and hydroxypropyl-β-CD (HP-β-CD).[1,2] We chose to determine these constants for the purposes of extending earlier studies of the binding of aliphatics[10–12] and also as useful preparation for future studies of the effects of cyclodextrins on the chemistry of ketones. Obviously, ketones are a very important class of organic compounds and complexation of them by CDs could have many possible uses.

Results

Initial binding studies were carried out using a method based on the displacement of a fluorescent probe, 1-anilinonaphthalene-8-sulfonate ion (ANS), bound to the CD.[11] This method worked reasonably well for β-CD and HP-β-CD forming complexes with the smaller ketones, but it was found to be impractical with α-CD because in this case the binding of ANS is weak (and not easy to quantify accurately) and the change in fluorescence upon binding is relatively small. The fluorescence method was also less successful with the larger ketones which must be used at low concentration due to their poor solubilities in water. Fortunately, we found that a method based on inhibition kinetics[6c,11] generally gave very good results and so it was used in nearly all cases.

Of necessity, the cleavage of *m*-nitrophenyl acetate (MNPA) by CDs, which is the probe reaction in the inhibition method used, is carried out in basic solution. However, even though ketones undergo many reactions in strong base,[13] these do not interfere with the method because enolate formation[14] and base-catalysed condensations[15] are very much slower than cleavage of MNPA in the presence of CDs.[6c,7a,8a,8b]

The dissociation constants (K_d) for the complexation of 22 ketones by the three CDs that were determined in the present work are collected in Table 1. In Table 2 are K_d values for the binding of some alcohols to the CDs which were obtained for the purposes of comparison and which were not available from the compilations given by Matsui and co-workers[12] or from our own previous studies.[10,11]

Discussion

From the outset we presumed that unsymmetrical alkanones (RCOR′) would bind to a cyclodextrin mainly by inclusion of the larger of the two alkyl groups, as long as it was not too large to fit into the CD cavity (**1**). To test this presumption we compare the strength of binding to β-CD of methyl ketones (RCOMe) and alcohols (ROH) bearing the same alkyl groups, using the values of pK_d ($= -\log K_d$) that are plotted in Fig. 1.† For six *n*-alkyl groups (R = Me to *n*-Hex) there is a linear correlation with a slope of 0.79 ± 0.03, meaning that binding of the methyl ketones has a similar, though reduced, sensitivity to changes in R. Note that for any given R the value of pK_d for RCOMe is larger than that for ROH, indicating stronger binding of the ketone and implying that the methyl group of RCOMe makes a definite, positive contribution to its complexation. At the same time, the presence of the methyl group reduces the sensitivity of the binding to the structure of the alkyl group, R. Compared to the correlation for *n*-alkyl

† In this and later comparisons, the values of pK_d for alcohols binding to α-CD and β-CD are taken from Matsui and co-workers,[12] supplemented by ones we have determined for the purpose (Table 2). Dissociation constants for the binding of alcohols to HP-β-CD are taken from earlier work[10,11] and from Table 2.

Table 1 Dissociation constants of host–guest complexes formed between ketones and cyclodextrins in aqueous solution[a]

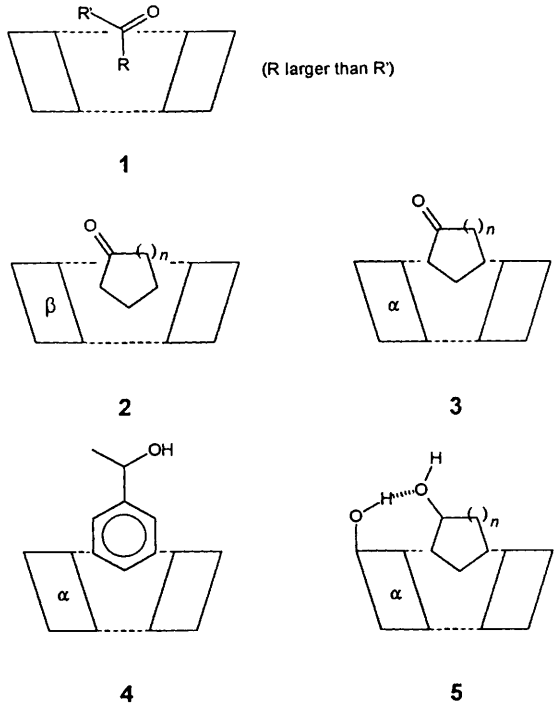
Ketone	K_d/mmol dm^{-3} α-CD	β-CD	HP-β-CD
Acetone	340 ± 6	367 ± 42[b]	415 ± 10
Butan-2-one	102 ± 4	107 ± 2[b]	128 ± 7, 111 ± 5[b]
Pentan-2-one	25.7 ± 0.9	39.0 ± 1.7[b]	56.5 ± 5.1[b]
Hexan-2-one	7.55 ± 0.09	16.4 ± 0.7[b]	18.7 ± 1.6
Heptan-2-one	2.80 ± 0.04	4.76 ± 0.21[c]	6.56 ± 0.03
Octan-2-one	0.972 ± 0.089	1.73 ± 0.03	1.97 ± 0.18
Pentan-2-one	49.9 ± 1.3	56.9 ± 2.3	72.3 ± 4.7
Hexan-2-one	16.4 ± 0.3	21.2 ± 0.4	27.3 ± 1.3
Heptan-3-one	6.00 ± 0.10	9.62 ± 0.66	11.7 ± 0.4
Octan-3-one	2.59 ± 0.14	3.76 ± 0.33	6.09 ± 0.62
Cyclobutanone	137 ± 3	106 ± 3	80.2 ± 5.4
Cyclopentanone	75.4 ± 1.0	19.6 ± 0.6	32.5 ± 3.4
Cyclohexanone	68.7 ± 3.4	2.51 ± 0.05	5.85 ± 0.62
Cycloheptanone	71.8 ± 3.3	0.635 ± 0.085	1.96 ± 0.21
Cyclooctanone	47.5 ± 1.7	0.484 ± 0.025	0.941 ± 0.132
3-Methylbutan-2-one	123 ± 3	15.0 ± 0.4	22.6 ± 2.4
3-Methylpentan-2-one	28.3 ± 0.6	6.98 ± 0.20	9.94 ± 0.40
5-Methylhexan-2-one	19.3 ± 0.4	3.14 ± 0.10	3.72 ± 0.30
3,3-Dimethylbutan-2-one[d]	105 ± 4	1.71 ± 0.16	3.98 ± 0.47
4-Methylpentan-2-one	54.3 ± 2.1	12.7 ± 0.56	15.0 ± 0.73
Heptan-4-one	9.22 ± 0.34	8.79 ± 0.12	10.9 ± 0.13
Acetophenone	78.9 ± 3.3	8.11 ± 0.55	7.04 ± 0.21

[a] In aqueous solution, at 25 °C. Except where indicated otherwise, the values of K_d were determined by inhibition kinetics, in a phosphate buffer of pH 11.6. [b] Determined by displacement of a fluorescent probe, in a phosphate buffer of pH 8.00. [c] A value of 4.94 ± 0.50 mmol dm^{-3} was obtained by the fluorescent probe method. [d] Pinacolone.

Table 2 Dissociation constants of host–guest complexes formed between alcohols and cyclodextrins in aqueous solution[a]

Alcohol	K_d/mmol dm^{-3} α-CD	β-CD	HP-β-CD
Heptan-2-ol	1.07 ± 0.04	2.33 ± 0.02	3.01 ± 0.22
Hexan-3-ol	6.00 ± 0.08	17.7 ± 0.27	20.8 ± 1.6
Heptan-3-ol	2.55 ± 0.03	5.00 ± 0.11	6.52 ± 0.40
Octan-3-ol	0.823 ± 0.015	1.22 ± 0.09	1.40 ± 0.14
1-Phenylethanol	76.0 ± 2.8	9.54 ± 0.25	6.44 ± 0.31

[a] At 25 °C. The values of K_d were determined by inhibition kinetics, in an aqueous phosphate buffer of pH 11.60.



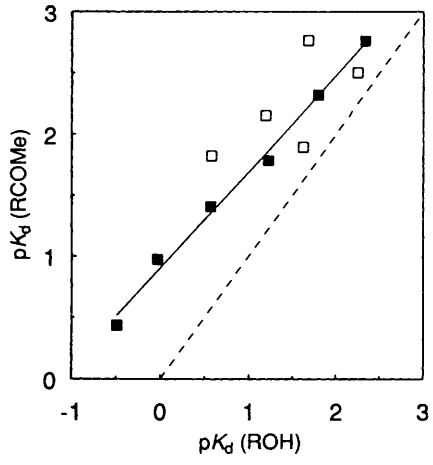


Fig. 1 Comparison of the strength of binding of methyl ketones (RCOMe) and alcohols (ROH) to β-CD. The symbols are: ■, R = *n*-alkyl; □, R = branched alkyl. The solid line is the correlation for the *n*-alkyl groups (slope = 0.79 ± 0.03; r = 0.997), compared to which the three positive outliers are for R = isopropyl, *sec*-butyl, *tert*-butyl and the negative ones are for R = isobutyl, isopentyl. Note that all of the points deviate above the dashed line that corresponds to pK_d (RCOMe) = pK_d (ROH), meaning that each methyl ketone binds more strongly than the corresponding alcohol.

ketones, the points for branched ketones show deviations (Fig. 1), the largest being for pinacolone (3,3-dimethylbutan-2-one) (R = *tert*-butyl) which binds 10 times more strongly to β-CD than *tert*-butyl alcohol does. This deviation may result because the hydroxy group of the alcohol has strong interactions with the aqueous medium that constrain *tert*-butyl alcohol to sit higher than pinacolone in the cavity of β-CD, resulting in weaker hydrophobic and van der Waals interactions of the *tert*-butyl group.

Although Fig. 1 supports the notion that unsymmetrical alkanones bind to CDs mainly by inclusion of the larger alkyl group, it is not correct to infer that the larger group is the sole determinant. For example, the K_d values for pentan-2-one

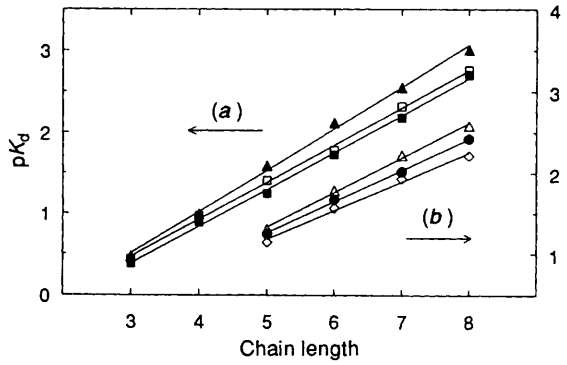


Fig. 2 Chain length dependence of the strengh of binding of ketones to cyclodextrins. (*a*) Alkan-2-ones (left-hand scale): α-CD, ▲; β-CD, □; HP-β-CD, ■. (*b*) Alkan-3-ones (right-hand scale): α-CD, △; β-CD, ●; Hp-β-CD, ◇. The two sets are offset for clarity. The correlations are given in Table 3.

(MeCOPr), hexan-3-one (EtCOPr), and heptan-4-one (PrCOPr) decrease appreciably along the series, for complexation by all three CDs (Table 1). Likewise, pentan-3-one (EtCOEt) and heptan-3-one (EtCOBu) bind more strongly than butan-2-one (MeCOEt) and heptan-2-one (MeCOBu), respectively. Both of these observations indicate that for unsymmetrical ketones the smaller of the two alkyl groups flanking the ketone carbonyl also makes a contribution to the binding (**1**), as concluded in the previous paragraph for alkan-2-ones.

It is also instructive to look at the strengths of binding of the five isomeric C_6 ketones studied. For the complexation of these derivatives by β-CD and by HP-β-CD the order is: $MeCOBu^t > MeCOBu^s > MeCOBu^i > MeCOBu > EtCOPr$, *i.e.* the bulkier, more branched ketones are bound more strongly. This order must be determined largely by the snugness of fit and van der Waals interactions since hydrophobicity, as judged from ketone solubility, has a reverse order. By contrast, the order for complexation by α-CD is almost the opposite: $MeCOBu > EtCOPr > MeCOBu^s > MeCOBu^i > MeCOBu^t$ because the branched ketones are too bulky to fit properly into the narrower cavity of α-CD.[1] Similar considerations apply to the binding of cyclic ketones, as discussed later.

In previous studies we and others have noted that the strength of binding of simple *n*-alkyl derivatives‡ to CDs increases more or less monotonically with chain length, up to about C_8.[5,7,8a,8b,10,11,12,16] This behaviour is revealed by linear correlations of pK_d with chain length, and, for reasons given previously,[5,7a] such correlations may be considered as linear free energy relationships (LFERs). Similar correlations are found with the present results for ketones, as shown in Fig. 2, which displays the chain length dependence of pK_d for the binding of alkan-2-ones (MeCO-*n*-alkyl) and alkan-3-ones (EtCO-*n*-alkyl) to the three CDs; the actual correlations are summarised in Table 3, along with others for comparison. Broadly speaking, the slopes of the LFERs of alkan-2-ones and alkan-3-ones are close to those for other alkyl derivatives (Table 3), indicating a comparable sensitivity to structural change. The slopes are also consistent with the usual view that the hydrophilic end groups of the CD-bound guests are more or less in the bulk medium so that binding is largely determined by inclusion of the alkyl portion of the guests in the CD cavity. However, there may be some minor variations for head groups with dissimilar solvation requirements or different hydrogen-bonding abilities,[7a] as discussed above for *tert*-butyl alcohol and pinacolone and later for other alcohols and ketones.

The slopes of the correlations in Fig. 2 are in the range 0.36–0.51, corresponding to free energy increments of 2.1–2.9 kJ mol^{-1} for each methylene group that is sequestered from the aqueous medium by inclusion in the CD cavity. These values are approaching those (3.0–3.6 kJ mol^{-1}) for the free energies of transfer of methylene groups from water to various organic media, including micelles,[17] from which it might be construed that hydrophobic effects[17,18] are the primary factor governing the binding of simple aliphatics to CDs. However, van der Waals forces, which depend upon size and surface area and increase linearly with chain length, contribute significantly as well.[4,7c,12,16]

‡ Alcohols, alkanes, amines, alkanoate ions, alkanesulfonate ions and aryl alkanoate esters.[7,8a,10–12,16]

Table 3 Structural dependence of the binding of aliphatic guests to cyclodextrins. Correlations between pK_d and chain length or ring size (*n*)[a]

Guests	CD	*n*	Slope ± sd	*r*	Note
Alkan-2-ones	α-CD	3–8	0.512 ± 0.015	0.998	*b*
	β-CD	3–8	0.459 ± 0.010	0.999	*b*
	HP-β-CD	3–8	0.456 ± 0.011	0.999	*b*
Alkan-3-ones	α-CD	5–8	0.429 ± 0.019	0.998	*b*
	β-CD	5–8	0.388 ± 0.011	0.999	*b*
	HP-β-CD	5–8	0.359 ± 0.022	0.996	*b*
Cycloalkanones	α-CD	4–8	0.094 ± 0.027	0.899	*b*
	β-CD	4–8	0.617 ± 0.083	0.974	*b*
	HP-β-CD	4–8	0.508 ± 0.039	0.991	*b*
Alkan-1-ols	α-CD	1–8	0.538 ± 0.024	0.994	*c*
	β-CD	1–8	0.547 ± 0.016	0.997	*c*
	HP-β-CD	2–7	0.626 ± 0.030	0.995	*c*
Alkan-2-ols	α-CD	3–8	0.496 ± 0.052	0.979	*c*, *d*
	β-CD	3–8	0.502 ± 0.022	0.996	*c*
	HP-β-CD	3–7	0.474 ± 0.031	0.994	*c*
Alkan-3-ols	α-CD	5–8	0.381 ± 0.033	0.993	*c*
	β-CD	5–8	0.524 ± 0.034	0.996	*c*
	HP-β-CD	5–8	0.381 ± 0.033	0.993	*c*
Cycloalkanols	α-CD	4–8	0.156 ± 0.028	0.954	*c*
	β-CD	4–8	0.539 ± 0.087	0.963	*c*
RSO_3^-	α-CD	5–8	0.274 ± 0.029	0.989	*e*
	β-CD	4–8	0.479 ± 0.041	0.989	*e*
	HP-β-CD	4–8	0.488 ± 0.015	0.999	*e*
RNH_2	β-CD	3–7	0.524 ± 0.016	0.999	*e*
	HP-β-CD	3–8	0.490 ± 0.008	0.999	*e*

[a] In aqueous solution, at 25 °C. The slope, standard deviation (sd) and correlation coefficient (*r*) are taken from the linear least squares analysis of pK_d against *n*. Similar correlations have been presented in earlier work.[7a,11] [b] Based on K_d values given in Table 1, determined in the present work. [c] Based on literature values taken from Matsui and co-workers[12] (for α-CD and β-CD) and from Tee *et al.*[11] (for HP-β-CD), with additional values from Table 2, determined in the present work. [d] The plot is decidedly curved downward. [e] Taken from Tee *et al.*[11]

By virtue of the correlations of pK_d with chain length, noted above in Table 3, one can find various LFERs between pK_d values for the linear ketones, and with those of other linear derivatives, some of which are summarised in Table 4. While these relationships may appear to be trivial, they are very useful for making comparisons between the preferences of different CD hosts and between the binding of aliphatic ketones and other types of guests. In particular, one may examine if non-linear derivatives deviate appreciably from the correlations defined by the linear compounds. On this basis, we will compare the binding of ketones to HP-β-CD and β-CD (Fig. 3), to β-CD and α-CD (Fig. 4), as well as that of ketones and secondary alcohols to β-CD (Fig. 5) and α-CD (Fig. 6).

In Fig. 3 the plot of pK_d(HP-β-CD) against pK_d(β-CD) is shown for all of the ketones studied. Compared to the line defined by the six alkan-2-ones (slope = 0.99 ± 0.03; intercept = −0.08 ± 0.05; r = 0.999), the most significant deviations are those for the three largest cycloalkanones (C_6,C_7,C_8) and pinacolone ($MeCOBu^t$), all of which bind about twice as strongly to β-CD as to HP-β-CD. Conceivably, these derivatives penetrate far enough into the CD cavity that their binding is affected by the 2-hydroxypropyl groups of HP-β-

Table 4 Correlations between the strength of the binding (pK_d) of ketones and aliphatic guests to cyclodextrins[a]

Ketones–CD	Other guest–CD	Slope ± sd	r	N
Alkan-2-ones–α-CD	Alkan-2-ones–β-CD	1.11 ± 0.05	0.997	6
Alkan-3-ones–α-CD	Alkan-3-ones–β-CD	1.10 ± 0.05	0.998	4
Alkanones–α-CD	Alkanones–β-CD	1.09 ± 0.05	0.992	11[b]
Alkan-2-ones–HP-β-CD	Alkan-2-ones–β-CD	0.99 ± 0.03	0.999	6
Alkan-3-ones–HP-β-CD	Alkan-3-ones–β-CD	0.92 ± 0.06	0.996	4
Alkanones–HP-β-CD	Alkanones–β-CD	0.98 ± 0.02	0.998	11[b]
All ketones–HP-β-CD	All ketones–β-CD	0.88 ± 0.03	0.986	22[c]
Alkan-2-ones–α-CD	Alkan-2-ols–α-CD	1.00 ± 0.08	0.988	6
Alkanones–α-CD	Alkanols–α-CD	1.00 ± 0.07	0.983	10[d]
Cycloalkanones–α-CD	Cycloalkanols–α-CD	0.58 ± 0.23	0.827[e]	5
Ketones–α-CD	2° Alcohols–α-CD	0.96 ± 0.07	0.953	19[f]
Alkan-2-ones–β-CD	Alkan-2-ols–β-CD	0.91 ± 0.03	0.997	6
Cycloalkanones–β-CD	Cycloalkanols–β-CD	1.13 ± 0.07	0.994	5
Ketones–β-CD	2° Alcohols–β-CD	0.99 ± 0.05	0.981	19[f]
Ketones–HP-β-CD	2° Alcohols–HP-β-CD	0.85 ± 0.07	0.969	12[g]

[a] In aqueous solution at 25 °C. The slope, standard deviation (sd) and correlation coefficient (r) are from linear regression of pK_d for the ketones in column one against those for the other guests in column two; N is the number of points. Several of the relationships can be viewed in Figs. 3–6. [b] Comprising the alkan-2- and -3-ones, plus heptan-4-one. [c] For all of the ketones in Table 1. Without the points for the three largest cycloalkanones (C_6,C_7,C_8) and pinacolone there is a better correlation (slope = 0.96 ± 0.03; r = 0.990; 18 points). [d] Ketones comprising the alkan-2- and -3-ones. [e] Probably distorted because of specific interactions involving the hydroxy groups of the alcohols—see text. [f] For all the ketones in Table 1 except 3-methylpentan-2-one, 5-methylhexan-2-one, and heptan-4-one. [g] Ketones comprising the alkan-2- and -3-ones, cyclopentanone, cyclohexanone and acetophenone.

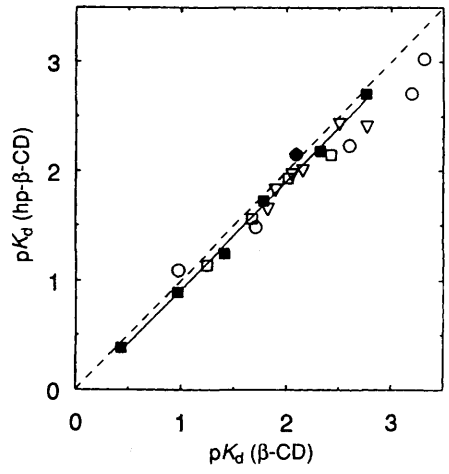


Fig. 3 Comparison of the strength of binding of ketones to HP-β-CD and to β-CD. The symbols are: ■, alkan-2-ones; □, alkan-3-ones; ○, cycloalkanones; ●, acetophenone; ▽, others. The diagonal dashed line corresponds to pK_d (HP-β-CD) = pK_d (β-CD) and the solid line to the correlation for the alkan-2-ones.

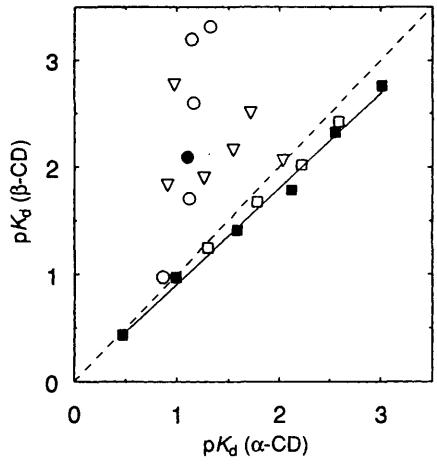


Fig. 4 Comparison of the strength of binding of ketones to β-CD and α-CD. The symbols are as in Fig. 3. The diagonal dashed line corresponds to pK_d (β-CD) = pK_d (α-CD); points above this line correspond to ketones which bind more strongly to β-CD than to α-CD. The solid line indicates the correlation for alkan-2-ones.

CD[1b] which may form an intrusive floor to the cavity.[8a] Without those four compounds, there is a good correlation (slope = 0.96 ± 0.03; r = 0.990; 18 points) with relatively little dispersion, suggesting that there are no major differences in the manner in which the ketones bind to the two CDs, although in general the binding to HP-β-CD appears to be slightly weaker. The data plotted in Fig. 3 are a subset of a much larger set for 68 aliphatic compounds§ for which the slope of the correlation for complexation by HP-β-CD and β-CD is 0.99 ± 0.02 (r = 0.980). Thus, the strength of binding of simple aliphatics to HP-β-CD and β-CD is, on average, virtually the same, although the depth of penetration of the CD cavity by these guests need not be the same for the two CDs. This last statement is based on the observation that for several reactions mediated by β-CD and HP-β-CD we have found that the transition state stabilisation afforded by HP-β-CD is less than that by β-CD,[8a,8c,8d,8e] and also that there are distinct differences for some aromatics.[11]

§ The set consists of 10 alkanoate esters,[10,11] 23 alcohols[11,12] (with those in Table 2), 5 alkanesulfonate ions,[10,11] 8 alkylamines,[11] and the 22 ketones in Table 1.

These observations imply that the 2-hydroxypropyl groups on the primary side of HP-β-CD[1b,2a,2c] can influence the inclusion of species in the cavity, even though it is not always evident from the values of dissociation constants, K_d.

Next, we compare complexation of the ketones by β-CD and α-CD (Fig. 4). For these two CDs, the pK_d values of the linear alkanones correlate well but those of the branched ketones, the larger cycloalkanones (C_5 to C_8), and acetophenone show marked deviations *above* the correlation line because these derivatives bind much more strongly to β-CD than to α-CD. The most reasonable conclusion is that the branched and cyclic ketones ($> C_4$), are too bulky to penetrate far enough into the narrower cavity of α-CD[1] to give such a good fit as they do with β-CD. Moreover, the same conclusion may be drawn for structurally-related alcohols,[5b,12a,b] including 1-phenylethanol (Table 2), and for alkyl-substituted phenols and their acetates.[12b] Consistent with the foregoing, we note that the pK_d values for the binding of cycloalkanones to α-CD are small and they do not vary much with ring size, whereas for complexation by β-CD and HP-β-CD the pK_d values are larger and they increase appreciably with ring size, with slopes of about 0.5 (Table 3). Therefore, we suggest that the cavity of β-CD[1] can

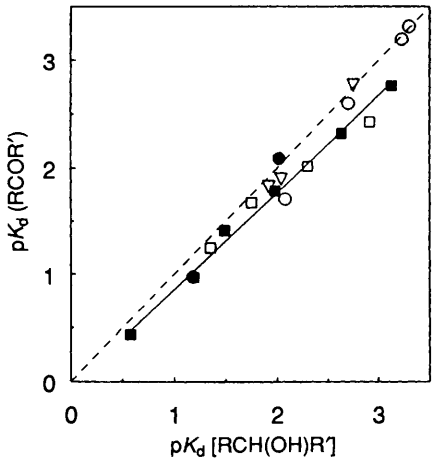


Fig. 5 Correlation between the strength of binding of ketones and related secondary alcohols to β-CD. The symbols are as in Fig. 3. The diagonal dashed line corresponds to pK_d (RCOR') = pK_d [RCH(OH)R'] and the solid one to the correlation for alkan-2-ones and alkan-2-ols (Table 4). The correlation for all the data is: slope = 0.99 ± 0.05; intercept = −0.14 ± 0.15; r = 0.981 (19 points).

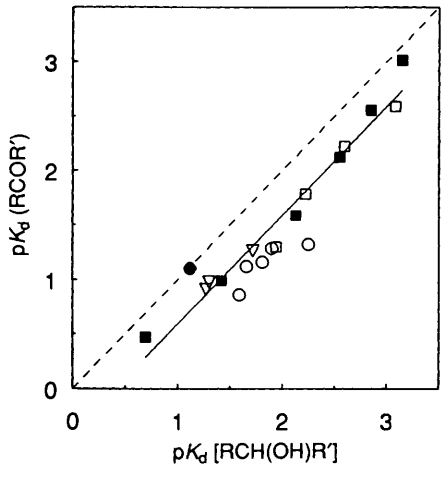


Fig. 6 Correlation between the strength of binding of ketones and related secondary alcohols to α-CD. The symbols are as in Fig. 3. The diagonal dashed line corresponds to pK_d (RCOR') = pK_d [RCH(OH)R'] and the solid one to the correlation for alkan-2-ones and alkan-2-ols. Note that almost all of the alcohols bind appreciably more strongly than their ketone analogues, particularly in the case of the cycloalkanols.

readily accommodate cycloalkanones (and cycloalkanols)[12] with up to eight carbons (**2**) but the smaller cavity of α-CD cannot, so that the cyclic derivatives are more or less constrained to 'perch' on top (**3**), giving rise to similar K_d values for guests with rings of different sizes (Table 1).

It is also of interest to compare the binding of ketones (RCOR') by CDs to that of the corresponding secondary alcohols [RCH(OH)R']. Generally speaking, binding of the ketones to β-CD is slightly weaker than that of the alcohols, but the two sets of values are strongly correlated (Table 4), as shown in Fig. 5, and the overall slope is essentially unity (0.99 ± 0.04; r = 0.981, 19 points), even though the correlation includes branched and cyclic derivatives, as well as linear ones. A similar correlation exists for binding HP-β-CD (Table 4), albeit with fewer data points. These observations strongly suggest that the geometries and modes of inclusion of ketones and related secondary alcohols by CDs are very similar, at least for binding to β-CD and HP-β-CD.

The situation for ketones and secondary alcohols binding to α-CD seems to be more complicated (Fig. 6). Overall there is a fair correlation (r = 0.953; 19 points) with near unit slope (0.96 ± 0.07) but the correlation for the alkan-2-ones and alkan-2-ols is relatively poor because the chain length dependence of pK_d for the alcohols[12] is decidedly curved while that for the ketones is linear (Table 3). Almost all of the alcohols bind more strongly than their ketone analogues (Fig. 6), suggesting that there may be hydrogen-bonding between the hydroxy groups of the alcohols and those on the rim of the α-CD which strengthens complexation. By contrast, 1-phenylethanol [PhCH(OH)Me] and acetophenone (PhCOMe) bind with equal strength, implying that the phenyl ring alone governs the binding of these compounds and that the geometry is such that favourable hydrogen-bonding interactions are not possible for 1-phenylethanol **4**. On the other hand, all of the cycloalkanols bind appreciably more strongly than the cycloalkanones, suggesting that such interactions may be important for the former (**5**).

Conclusions

This paper presents a large body of data for the complexation of ketones by three cyclodextrins. Several relationships have been found which are helpful in probing the factors that may be involved in the binding, as well as being useful for predictive purposes. Certain distinct conclusions also emerge from the data. (i) The binding of unsymmetrical ketones to the CDs is largely, but not solely, determined by inclusion of the larger of the two alkyl groups. (ii) With linear derivatives, the strength of binding increases monotonically with the ketone chain length, with a slope corresponding to *ca.* 2.5 kJ mol^{-1} for each methylene group that is included in the CD cavity. (iii) The binding of ketones to β-CD and HP-β-CD appears to be quite similar, although the depth of penetration of the cavities may differ. (iv) Compared to β-CD, the smaller cavity of α-CD does not permit strong binding of branched or cyclic ($>C_4$) ketones which are constrained to perch on the rim of α-CD. (v) Ketones and analogous secondary alcohols show quite comparable dependences of complexation on structure. With α-CD, the alcohols bind more strongly, suggesting that hydrogen-bonding between the alcoholic OH and the CD hydroxy groups may contribute to the binding.

Overall, the results presented in this paper provide a firm foundation for future studies of the influence of cyclodextrins on the chemistry of ketones in aqueous solution.

Experimental

As in previous studies,[8a,10,11] 'hydroxypropyl-β-cyclodextrin' was purchased from Wacker-Chemie (Munich, Germany) while α-CD, β-CD and all of the ketones and alcohols were purchased from Aldrich. The reader should be aware that the 'hydroxypropyl-β-cyclodextrin' used is not a discrete compound but a mixture of hydroxypropylated derivatives with an average degree of substitution that corresponds to about 6 of the 7 primary hydroxy groups of β-CD being alkylated.[1b,2a,2c] While this situation is not ideal for quantitative measurements, it causes no major problems as long as the material has a consistent composition and gives reproducible results. Moreover, since it is a material of some commercial importance its chemistry needs to be explored.

All reactions and spectroscopic measurements were carried out at 25.0 ± 0.1 °C in a stopped-flow spectrophotometer purchased from Applied Photophysics, Leatherhead, UK. This apparatus may be used to monitor absorbance or fluorescence, as desired.

Some of the K_d values for CD·ketone complexes were estimated using the competition between the ketone and a fluorescent probe, 1-anilino-8-naphthalenesulfonate (ANS), as recently described in detail.[11] A 0.4 M phosphate buffer (pH 8.00) containing 20.0 mmol dm^{-3} β-CD and 0.20 mmol dm^{-3} ANS (or 10.0 mmol dm^{-3} HP-β-CD and 0.05 mmol dm^{-3} ANS)

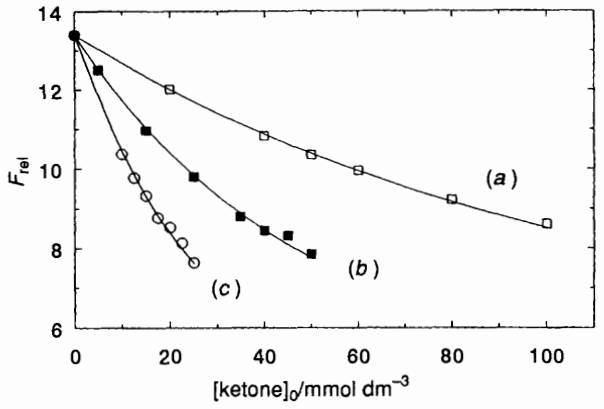


Fig. 7 Sample data for the effects of ketones on the fluorescence of ANS in the presence of β-CD (10.0 mmol dm^{-3}): (*a*) butan-2-one, □; (*b*) pentan-2-one, ■; (*c*) hexan-2-one, ○. The curves are splines through points calculated with the relevant dissociation constants in Table 1.

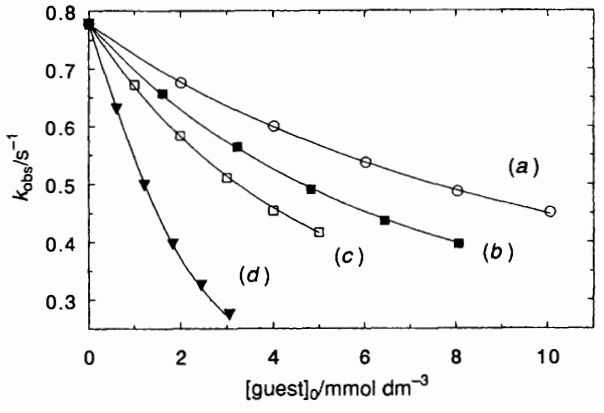


Fig. 8 Sample data for the inhibition of the cleavage of *m*-nitrophenyl acetate by β-CD (2.0 mmol dm^{-3}) due to the following guests: (*a*) heptan-4-one, ○; (*b*) heptan-3-ol, ■; (*c*) 5-methylhexan-2-one, □; (*d*) cyclooctanone, ▼. The curves are splines through points calculated with the relevant dissociation constants in Table 1 or 2.

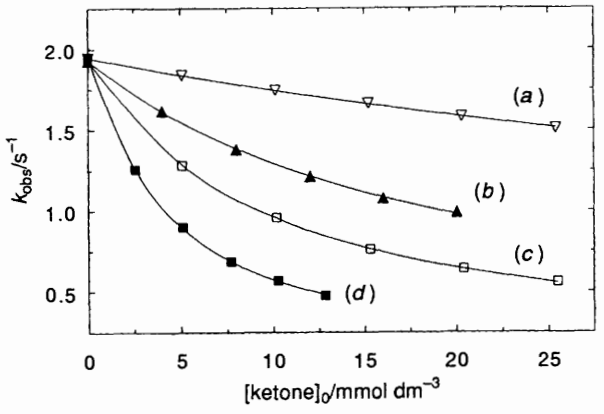


Fig. 9 Sample data for the inhibition of the cleavage of *m*-nitrophenyl acetate in the presence of α-CD (2.0 mmol dm^{-3}) by the following ketones: (*a*) cyclopentanone, ▽; (*b*) hexan-3-one, ▲; (*c*) hexan-2-one, □; (*d*) heptan-2-one, ■. The curves are splines through points calculated with the relevant dissociation constants in Table 1.

was mixed 1 : 1 with a solution of the ketone in water (*vide infra*) so that the final concentrations were half of these. The observation cell was irradiated at 383 nm, and the emission was monitored at either 474 nm (β-CD) or 468 nm (HP-β-CD). The observed fluorescence due to CD-bound ANS decreases with added ketone, and the data were analysed [11] to determine the K_d values. Three sets of data and calculated curves are shown in Fig. 7.

Table 5 Typical upper concentrations used in the determination of the dissociation constants of ketone–CD complexes in aqueous solution

	[Ketone]$_0$/mmol dm^{-3}		
Ketone	α-CD	β-CD	HP-β-CD
Acetone	250	200	505
Octan-2-one	0.65	0.40	1.4
Pentan-3-one	50	50	50
Octan-3-one	3.1	0.47	1.1
Heptan-4-one	20	10	7.4
Cyclobutanone	160	160	160
Cyclooctanone	3.3	3.1	2.7
3-MethylButan-2-one	20	25	12
3,3-Dimethylbutan-2-one	26	25	19
Acetophenone	10	10	7.6

Most of the K_d values were obtained using a method based upon the inhibition of the CD-mediated cleavage of *m*-nitrophenyl acetate.[6c,11] In these experiments a 0.4 M phosphate buffer (pH 11.60) containing 4.0 mmol dm^{-3} of the CD was mixed 1:1 in the stopped-flow spectrophotometer with an aqueous solution containing 100 μmol dm^{-3} *m*-nitrophenyl acetate and the guest (ketone or alcohol) (*vide infra*). The first-order release of the *m*-nitrophenolate ion at 390 nm was monitored to find pseudo-first-order rate constants (k_{obs}) from which an estimate of K_d was calculated. This process was repeated at several [guest]$_0$, and the K_d values were then averaged, as in previous work.[6c,11] Several examples of the data, along with calculated curves, are plotted in Figs. 8 and 9.

In general, we tried to use guest (ketone or alcohol) concentrations up to 2–5 times the expected K_d value, based on the binding of the similar alkyl-bearing compounds to the CD,[10–12] but this was often not possible. With acetone, which binds only weakly, its concentration was kept $\leqslant$0.5 mol dm^{-3} to avoid any significant 'solvent effect'. The larger ketones have quite limited solubilities in water, but the problem is less acute for branched and cyclic ketones which are more soluble than their linear counterparts. Table 5 shows typical upper limits for the ketone concentrations used with the three different CDs; typical concentration ranges and the number of data points used can also be judged from the data in Figs. 7–9.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for an operating grant (to O. S. T.), a post graduate scholarship (to T. A. G.), and for an equipment grant towards the purchase of the stopped-flow spectrophotometer.

References

1 (*a*) M. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer-Verlag, New York, 1978; (*b*) J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.
2 (*a*) J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988; (*b*) J. F. Stoddart and R. Zarzycki, *Recl. Trav. Chim. Pays-Bas* 1988, **107**, 515; (*c*) J. Szejtli, *Carbohydr. Polym.*, 1990, **12**, 375; (*d*) G. Wenz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 803.
3 K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley-Interscience, New York, 1987.
4 (*a*) H.-J. Schneider, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1417; (*b*) H.-J. Schneider, *Chem. Soc. Rev.*, 1994, **23**, 227.
5 (*a*) O. S. Tee, *Carbohydr. Res.*, 1989, **192**, 181; (*b*) O. S. Tee, *Adv. Phys. Org. Chem.*, 1994, **29**, 1.
6 (*a*) O. S. Tee and B. K. Takasaki, *Can. J. Chem.*, 1985, **63**, 3540; (*b*) O. S. Tee and M. Bozzi, *J. Am. Chem. Soc.*, 1990, **112**, 7815; (*c*) O. S. Tee, M. Bozzi, J. J. Hoeven and T. A. Gadosy, *J. Am. Chem. Soc.*, 1993, **115**, 8990; (*d*) O. S. Tee, M. Bozzi, N. Clement and T. A. Gadosy, *J. Org. Chem.*, 1995, **60**, 3509.
7 (*a*) O. S. Tee, C. Mazza and X.-X. Du, *J. Org. Chem.*, 1990, **55**, 3603; (*b*) O. S. Tee and X.-X. Du, *J. Am. Chem. Soc.*, 1992, **114**, 620;

(*c*) O. S. Tee, C. Mazza, R. Lozano-Hemmer and J. B. Giorgi, *J. Org. Chem.*, 1994, **59**, 7602.
8 (*a*) T. A. Gadosy and O. S. Tee, *J. Chem. Soc., Perkin Trans. 2*, 1994, 715; 1994, 2069; (*b*) O. S. Tee and T. A. Gadosy, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2191; (*c*) O. S. Tee and T. A. Gadosy, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2307; (*d*) T. A. Gadosy and O. S. Tee, *J. Chem. Soc., Perkin Trans. 2*, 1995, 71; (*e*) O. S. Tee and M. J. Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1237.
9 (*a*) J.-M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89; (*b*) H.-J. Schneider and H. Dürr, *Frontiers in Supramolecular Organic Chemistry and Photochemistry* VCH, Weinheim, 1990; (*c*) F. Vögtle, *Supramolecular Chemistry*, Wiley, Chichester, 1991.
10 O. S. Tee, T. A. Gadosy and J. B. Giorgi, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1705.
11 T. A. Gadosy, J. B. Giorgi and O. S. Tee, *Can. J. Chem.* 1996, in the press.
12 (*a*) Y. Matsui and K. Mochida, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2808; (*b*) Y. Matsui, T. Nishioka and T. Fujita, *Top. Curr. Chem.*, 1985, **128**, 61; (*c*) Cf. H. Fujiwara, H. Arakawa, S. Murata, and Y. Sasaki, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3891.
13 J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, Wiley, New York, 4th edn. 1992.
14 J. R. Keeffe and A. J. Kresge, *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, New York, 1990, ch. 7.
15 H. Maskill, *The Physical Basis of Organic Chemistry*, Oxford University Press, Oxford, 1985, p. 341; I. Eskendirov, B. Kabongo, L. Glasser and V. D. Sokolovskii, *J. Chem. Soc., Faraday Trans.*, 1995, **91**, 991.
16 (*a*) I. Satake, T. Ikenoue, T. Takashita, K. Hayakawa and T. Meda, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2746; (*b*) I. Satake, S. Yoshida, K. Hayakawa, T. Meda and Y. Kusumoto, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3991; (*c*) J. W. Park and H. J. Song, *J. Phys. Chem.*, 1989, **93**, 6454; (*d*) I. Sanemasa, T. Osajima, and T. Deguchi, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2814.
17 (*a*) C. Tanford, *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*, Wiley, New York, 2nd edn. 1980; (*b*) M. H. Abraham, *J. Am. Chem. Soc.*, 1982, **104**, 2085.
18 W. Blokzijl and J. B. F. N. Engberts, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1545.

Paper 5/04129E
Received 26*th June* 1995
Accepted 31*st January* 1996