The Binding of Alkyl Chains to β-Cyclodextrin and 'Hydroxypropyl-β-cyclodextrin'

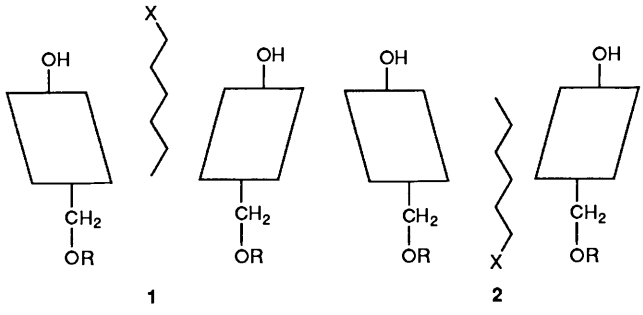
Oswald S. Tee,* Timothy A. Gadosy and Javier B. Giorgi
Department of Chemistry and Biochemistry, Concordia University, Montréal, Québec, Canada H3G 1M8

The strength of binding of aliphatic alcohols, alkanesulfonate ions and aryl alkanoates to 'hydroxypropyl-β-cyclodextrin' is very similar to that to unmodified β-cyclodextrin (β-CD). The clear inference is that both forms of β-CD bind these guests to the wider opening of the CD cavity that is surrounded by secondary hydroxy groups.

The binding of guests to cyclodextrin (CD) hosts may be detected by many techniques and often it is relatively easy to estimate the dissociation constants of the guest–host complexes.[1] However, it is not so easy to ascertain the orientation and depth of the inclusion of the guest in the CD cavity. We hereby report dissociation constants that strongly imply that the binding of the alkyl groups of simple alcohols, alkanesulfonate ions and esters occurs to the wider, 'secondary' opening of the β-CD cavity.[1]

We are studying the reactivity of 'hydroxypropyl-β-cyclodextrin' (Hp-β-CD) towards substrates that are known to react with unmodified β-cyclodextrin (β-CD). The modified CD is now available from several suppliers† and it may have many practical applications because of its high solubility in water.[2,3] In Hp-β-CD most of the primary hydroxy groups of β-CD are functionalized† with 2-hydroxypropyl groups (see **1** and **2**). We find that the cleavage of *m*-nitrophenyl and *p*-nitrophenyl alkanoates (C2–C6) by Hp-β-CD in aqueous base shows saturation kinetics,[1] and the kinetic parameters are very similar to those found previously for reaction with β-CD.[4,5] In particular, we note that (*i*) the dissociation constants (K_d) of the ester–CD complexes (Table 1) vary systematically with the acyl chain length and that the values for the *m*- and *p*-isomers are quite close to each other and (*ii*) the values of K_d are almost the same for Hp-β-CD as for β-CD, particularly for the *p*-isomers. The first observation is strong evidence that the esters of both series bind to Hp-β-CD with their acyl chains, not through their aryloxy groups. The second observation suggests that binding of the acyl chains of the esters to both CDs is to the more open, 'secondary' side of the CD cavity (**1**), since the functionalized primary hydroxy groups of Hp-β-CD would be expected to alter the binding if it took place at the narrower, 'primary' side (**2**).

We are also studying the effects of potential inhibitors of the basic cleavage of esters by Hp-β-CD, as we have done for α- and β-CD.[6,7] In this respect, we have examined the inhibition by some aliphatic alcohols and alkanesulfonate ions (RSO_3^-) of the cleavage of *m*-nitrophenyl acetate (*m*NPA) by Hp-β-CD. Analysis of the kinetics[6,8] affords 'inhibition constants' which are taken to equal K_d for the inhibitor–CD complexes.‡ As seen in Table 1, the values of K_d for 14 different alcohols are generally



β-CD, R = H; Hp-β-CD, R = $CH_2CH(OH)CH_3$
X = OH, SO_3^-, or $COOC_6H_4NO_2$

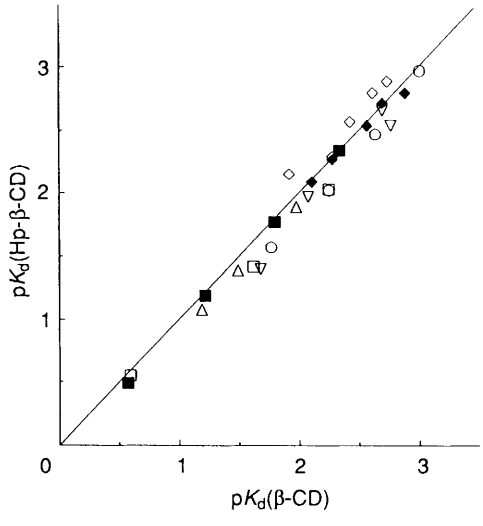


Fig. 1 Correlation between the binding of aliphatics to Hp-β-CD and to β-CD. The data are from Table 1, with $pK_d = -\log K_d$. The data straddle the line pK_d (Hp-β-CD) = pK_d (β-CD); the correlation line given in the text is barely different. ◆, *p*NP esters; ◇, *m*NP esters; ■, *n*-alkanols; □, isoalkanols; △, alkan-2-ols; ▽, other ROH; ○, RSO_3^-

similar for the two CDs, being essentially equal for the linear alcohols. For the bulkier alcohols the binding to Hp-β-CD appears to be slightly weaker, as is the case for RSO_3^- also.[11] Conceivably, these guests sit deeply enough in the cavity of Hp-β-CD just to feel the presence of the hydroxypropyl groups on the primary side.

Overall, the two sets of K_d values in Table 1 are remarkably alike, as seen in Fig. 1 which plots the pK_d values for the two CDs against each other. The actual least-squares correlation line has slope = 1.03 ± 0.04, intercept = −0.13 ± 0.13 and

† We used the Hp-β-CD supplied by Aldrich which has an average molecular weight of 1500, corresponding to the functionalization of about six of the seven primary hydroxy groups of β-CD. This material is not homogeneous and so the absolute values of measured parameters may vary from sample to sample. However, we feel that trends in parameters are meaningful, especially in the present case where the values of K_d for Hp-β-CD and β-CD are virtually identical (*vide infra*).
‡ Inhibition constants found for the cleavage of *m*NPA by α- and β-CD generally agree well with values of K_d obtained in other ways.[6,8]

Table 1 Dissociation constants for guest–host complexes formed between aliphatic guests and β-cyclodextrin and 'hydroxypropyl-β-cyclodextrin'[a]

Guest	K_d/mmol dm^{-3} β-CD	Hp-β-CD
(*a*) *m*-Nitrophenyl esters		
Acetate	12	7.0
Propanoate	5.2	5.1
Butanoate	3.7	2.7
Pentanoate	2.4	1.6
Hexanoate	1.8	1.3
(*b*) *p*-Nitrophenyl esters		
Acetate	7.8	8.2
Propanoate	5.2	5.4
Butanoate	2.7	2.9
Pentanoate	2.0	1.9
Hexanoate	1.3	1.6
(*c*) Alcohols		
Propan-1-ol	270	320
Butan-1-ol	60	64
Pentan-1-ol	16	17
Hexan-1-ol	4.6	4.6
Butan-2-ol	65	84
Pentan-2-ol	32	41
Hexan-2-ol	10.5	13
Isopropyl alcohol	260	280
Isobutyl alcohol	24	38
Isopentyl alcohol	5.6	9.3
tert-Butyl alcohol	21	40
Neopentyl alcohol	1.7	2.9
Cyclopentanol	8.3	10.7
Cyclohexanol	2.0	2.2
(*d*) Alkanesulfonate ions[b]		
C5	17	27
C6	5.6	9.5
C7	2.3	3.4
C8	0.97	1.07

[a] In aqueous solution, at 25 °C. Values of K_d for β-CD are taken from the literature, as follows: esters;[5] alcohols;[9] alkanesulfonate ions.[10] Those for Hp-β-CD were obtained by established kinetic methods.[1,5,6,8] For the two series of esters, K_d values were obtained from analysis of the saturation kinetics[5,6] found for ester cleavage by Hp-β-CD in basic solution (phosphate buffer, pH 11.6). Values of K_d for the binding of alcohols and alkanesulfonate ions to Hp-β-CD were estimated from the inhibition[6,8] of the cleavage of *m*-nitrophenyl acetate by Hp-β-CD (also at pH 11.6) brought about by varying levels of ROH and RSO_3^-. In many cases the K_d values for two CDs are probably to within experimental error of each other. [b] Introduced as the Na^+ salts. Our values for Hp-β-CD and RSO_3^- agree tolerably well with those obtained by conductimetry:[11] C5, 67; C6, 8.9; C7, 1.8; C8, 0.91 mmol dm^{-3}.

$r = 0.983$ (for 28 points, spanning 2.5 decades). In our view, the almost inescapable conclusion is that binding of the alkyl portions of the guests to the two CDs is virtually identical* and to the 'secondary' side of the β-CD cavity (**1**).

Acknowledgements

This work was supported by a grant and scholarships from the Natural Sciences and Engineering and Research Council of Canada. We thank Professor V. C. Reinsborough for helpful communications.

* We note that the binding of the aromatic 4-(2-pyridylazo)-*N*,*N*-dimethylaniline is equally strong to Hp-β-CD and β-CD (K_d = 2.9 and 3.3 mmol dm^{-3}).[12]

References

1 M. Bender and M. Komiyama, *Cyclodextrin Chemistry*, Springer Verlag, New York, 1978; W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 344; J. Szejtli, *Cyclodextrins and their Inclusion Complexes*, Akademiai Kiado, Budapest, 1982.
2 J. Szejtli, *Cyclodextrin Technology*, Kluwer, Dordrecht, 1988.
3 Abstracts of the 6th International Cyclodextrin Symposium, Chicago, USA, 1992.
4 G. M. Bonora, R. Fornasier, P. Scrimin and U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 1985, 367.
5 O. S. Tee, C. Mazza and X.-X. Du, *J. Org. Chem.*, 1990, **55**, 3603.
6 O. S. Tee and J. J. Hoeven, *J. Am. Chem. Soc.*, 1989, **111**, 8318; O. S. Tee, M. Bozzi, J. J. Hoeven and T. A. Gadosy, *J. Am. Chem. Soc.*, 1993, in press.
7 O. S. Tee and M. Bozzi, *J. Am. Chem. Soc.*, 1990, **112**, 7815; O. S. Tee, M. Bozzi, N. Clement and T. A. Gadosy, submitted to *J. Am. Chem. Soc.*
8 R. L. VanEtten, J. F. Sebastian, G. A. Clowes and M. L. Bender, *J. Am. Chem. Soc.*, 1967, **89**, 3242; R. L. VanEtten, G. A. Clowes, J. F. Sebastian and M. L. Bender, *J. Am. Chem. Soc.*, 1967, **89**, 3253.
9 Y. Matsui and K. Mochida, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2808; Y. Matsui, T. Nishioka and T. Fujita, *Top. Curr. Chem.*, 1985, **128**, 61.
10 I. Satake, S. Yoshida, K. Hayakawa, T. Maeda and Y. Kusumoto, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3991.
11 C. D. Lavandier, M. P. Pelletier and V. C. Reinsborough, *Aust. J. Chem.*, 1991, **44**, 457.
12 P. M. Demont and V. C. Reinsborough, *Aust. J. Chem.*, 1991, **44**, 759.

Paper 3/03975G
Received 8*th July* 1993
Accepted 6*th August* 1993