Quantitative Structure–Stability Relationships Among Inclusion Complexes of Cyclodextrins I: Barbituric Acid Derivatives

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Abstract □ Quantitative structure–stability relationships (QSSRs) are formulated for the inclusion complexation of 17 barbituric acid derivatives with α- and β-cyclodextrin. The variation in the complex stability constants K_α and K_β is found to be partly accounted for by the molar refractivity or the hydrophobicity of the substituent R_1 at position 5 of the barbiturate ring. In addition, K_α also depends upon whether or not R_1 is branching or cyclic, and K_β also depends upon whether the guest molecule is a barbiturate or a thiobarbiturate. The results suggest that in α-cyclodextrin–barbiturate complexes the cyclodextrin cavity includes only R_1, while in β-cyclodextrin complexes both R_1 and (part of) the barbiturate ring are included. This complexation model is compared with those proposed by other authors.

Inclusion complexes of cyclodextrins are of rapidly increasing importance in medicinal and pharmaceutical chemistry, since the chemical stability, aqueous solubility, and bioavailability of a number of drugs can be improved by complexation.[1] In addition, cyclodextrins are known models for various enzymes[1] and, as such, may be useful in exploring the mechanism of enzymatic reactions. It is therefore desirable to gain more insight into the mechanism of complexation and to predict the stability of given complexes. Toward this end, a useful means may be the linear free-energy relationship (LFER) approach.[2] This was shown by Nishioka and Fujita[3] who used cyclodextrin as a hydrolytic enzyme model when investigating the stability of cyclodextrin–phenyl acetate complexes as a function of the structures of substituted phenyl acetates. The applicability of such approaches to various types of guest molecules deserves examination.

In this paper some quantitative structure–stability relationships (QSSRs) concerning the inclusion complexation of a series of barbituric acid derivatives with α- and β-cyclodextrin are reported. Several authors[4-6] have studied this complexation process and observed that the improved aqueous solubility and dissolution rate of barbiturates result in an enhancement of their absorption and bioavailability.

Experimental Section

Using high-performance liquid chromatography, Uekama et al.[7] have determined stability constants, K_α and K_β, for 1:1 inclusion complexes of α- and β-cyclodextrin, respectively, formed in aqueous solution (mobile phase) at pH 5 with 17 barbituric acid derivatives. At this pH barbiturates are essentially un-ionized. Structures and stability constants for the 17 barbiturates are shown in Table I.

The substituent R_1 showing sufficient variability was characterized by LFER parameters. Its hydrophobicity was described by the group contribution, c_1, obtained from Free–Wilson analysis[8] carried out to resolve the logarithm of the chloroform–water partition coefficient, log P_c, of barbiturates. Details on this calculation are not reported here, only the convincing statistics of the Free–Wilson equation are given: number of data points considered in the regression (n) = 17; multiple correlation coefficient (r) = 0.999; overall F statistic for the equation with 11 and 5 degrees of freedom ($F_{11,5}$) = 172; significance level for $F_{11,5}$ (p) < 0.1%; standard error of the estimate (s) = 0.067. Electronic effects and steric bulk of R_1 were represented by σ_1^*, the Taft substituent constant, and by MR_1', the molar refractivity scaled by 0.1, respectively.[9] Values of P_c, c_1, σ_1^*, and MR_1' are given in Table I.

To characterize the shape of substituent R_1, an indicator variable I_1 was introduced, taking a value of one for branching or cyclic R_1 groups and zero otherwise. Substituents R_2, R_3, and X, showing poor variability, were accounted for by indicator variables I_2, I_3, and I_X, respectively. These variables take a value of zero or one if R_2 = ethyl or methyl, R_3 = hydrogen or methyl, and X = oxygen or sulphur, respectively. Then, in accordance with the LFER model,[2] log K_α and log K_β were correlated with c_1, σ_1^*, MR_1', I_1, I_2, I_3, and I_X, using multiple regression analysis.[10]

Results and Discussion

The following equations were obtained:

$$\log K_\alpha = -0.510(\pm 0.424)I_1 + 3.038$$
$$(n = 17,\ r = 0.552,\ F_{1,15} = 6.56,\ p < 5\%,\ s = 0.404) \quad (1)$$

$$\log K_\alpha = 0.292(\pm 0.294)c_1 - 0.454(\pm 0.388)I_1 + 3.015$$
$$(n = 17,\ r = 0.689,\ F_{2,14} = 6.32,\ p < 5\%,\ s = 0.363) \quad (2)$$

$$\log K_\alpha = 0.411(\pm 0.321)MR_1' - 0.656(\pm 0.374)I_1 + 2.137$$
$$(n = 17,\ r = 0.740,\ F_{2,14} = 8.48,\ p < 0.5\%,\ s = 0.337) \quad (3)$$

$$\log K_\alpha = -0.675(\pm 0.338)I_1 + 3.038$$
$$(n = 16,\ r = 0.753,\ F_{1,14} = 18.4,\ p < 0.1\%,\ s = 0.305) \quad (4)$$

$$\log K_\alpha = 0.348(\pm 0.155)c_1 - 0.627(\pm 0.211)I_1 + 3.010$$
$$(n = 16,\ r = 0.920,\ F_{2,13} = 35.8,\ p < 0.1\%,\ s = 0.188) \quad (5)$$

$$\log K_\alpha = 0.413(\pm 0.175)MR_1' - 0.823(\pm 0.213)I_1 + 2.131$$
$$(n = 16,\ r = 0.925,\ F_{2,13} = 38.6,\ p < 0.1\%,\ s = 0.183) \quad (6)$$

$$\log K_\beta = 0.469(\pm 0.243)c_1 + 3.128$$
$$(n = 17,\ r = 0.728,\ F_{1,15} = 16.9,\ p < 0.1\%,\ s = 0.306) \quad (7)$$

$$\log K_\beta = 0.647(\pm 0.186)MR_1' + 1.615$$
$$(n = 17,\ r = 0.886,\ F_{1,15} = 54.8,\ p < 0.1\%,\ s = 0.207) \quad (8)$$

$$\log K_\beta = 0.736(\pm 0.139)MR_1' + 0.310(\pm 0.162)I_X + 1.279$$
$$(n = 17,\ r = 0.950,\ F_{2,14} = 64.9,\ p < 0.1\%,\ s = 0.144) \quad (9)$$

where the numbers in parentheses give 95% confidence intervals for the regression coefficients.

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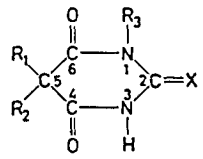
Table I—Structure, Physicochemical Parameters, and Stability Constants for Barbiturates



Barbiturate	R_1	R_2	R_3	X	Physicochemical Parameters				Log Stability Constants, M^{-1}			
									log K_α		log K_β	
					P_c^a	c_1^b	σ_1^{*c}	$MR_1'^c$	Exp.[a]	Calc.[d]	Exp.[a]	Calc.[e]
1	$(CH_2)_2CH_3$	CH_2CH_3	H	O	2.00	−0.773	−0.12	1.496	2.724	2.750	2.114	2.380
2	$(CH_2)_3CH_3$	CH_2CH_3	H	O	9.67	−0.147	−0.13	1.959	2.633	2.941	2.681	2.721
3	$(CH_2)_4CH_3$	CH_2CH_3	H	O	38.6	0.389	−0.16	2.424	2.940	3.133	3.114	3.063
4	$(CH_2)_5CH_3$	CH_2CH_3	H	O	78.5	0.784	−0.17	2.890	3.384	3.326	3.456	3.406
5	$(CH_2)_6CH_3$	CH_2CH_3	H	O	334	1.408	−0.17	3.355	3.618	3.518	3.715	3.749
6	$CH(CH_3)(CH_2)_2CH_3$	CH_2CH_3	H	O	28.0	0.334	−0.23[f]	2.424[g]	2.613	2.311	3.196	3.063
7	$(CH_2)_2CH(CH_3)_2$	CH_2CH_3	H	O	28.3	0.336	−0.16[g]	2.424[g]	2.146	2.311	3.243	3.063
8	Phenyl	CH_2CH_3	H	O	4.40	−0.422	0.60	2.536	2.230	2.357	3.270	3.146
9	Phenyl	CH_2CH_3	CH_3	O	191	−0.422	0.60	2.536	2.398	2.357	3.220	3.146
10	Cyclohex-3-enyl	CH_3	CH_3	O	153	−0.518	−0.12	2.956	2.342	2.531	3.185	3.455
11	CH_2CH_3	CH_2CH_3	H	S	11.1	−1.132	−0.10	1.030	2.699	2.557	2.477	2.347
12	$(CH_2)_2CH_3$	CH_2CH_3	H	S	27.9	−0.773	−0.12	1.496	2.875	2.750	2.732	2.690
13	$(CH_2)_3CH_3$	CH_2CH_3	H	S	103	−0.147	−0.13	1.959	2.778	2.941	2.839	3.031
14	$(CH_2)_4CH_3$	CH_2CH_3	H	S	306	0.389	−0.16	2.424	3.267	3.133	3.324	3.373
15	$(CH_2)_5CH_3$	CH_2CH_3	H	S	926	0.784	−0.17	2.890	3.458	3.326	3.684	3.716
16	$CH(CH_3)(CH_2)_2CH_3$	CH_2CH_3	H	S	326	0.334	−0.23[f]	2.424[g]	2.447	2.311	3.380	3.373
17	Phenyl	CH_2CH_3	H	S	63.9	−0.422	0.60	2.536	3.519	—	3.549	3.456

[a] Taken from Uekama et al. (ref. 7). [b] Obtained from Free–Wilson analysis carried out on log P_c (see *Experimental Section*). [c] Taken from Hansch and Leo (ref. 9) unless otherwise noted. [d] Calculated from eq. 6. [e] Calculated from eq. 9. [f] Assumed 0.07 lower than σ^* for *n*-pentyl, on the basis of a nearly constant difference between σ^* values for isopropyl (1-methylethyl), and *n*-propyl as well as *sec*-butyl (1-methylpropyl) and *n*-butyl groups. [g] Assumed equal to the respective value for *n*-pentyl.

It can be seen that eqs. 1–3 are quite unreliable. Examination of the residuals revealed that this is due to an outlier, compound 17. The reason for the poor fit of this compound is unclear, however. Nevertheless, its omission led to eqs. 4–6 which offer the same conclusions as do eqs. 1–3.

Equations 4–6 and 7–9 relating to α- and β-cyclodextrin–barbiturate complexes, respectively, are highly significant, showing a close correlation between complex stability and guest structure. Equations 6 and 9 are considered the best. For these equations, experimental and calculated stability constants are compared in Table I.

All intercorrelations among the variables included in eqs. 1–9 are insignificant, except between c_1 and MR_1' (r = 0.753). However, this significant correlation did not interfere either with the calculations or the conclusions. Its only manifestation was that similar equations were obtained with c_1 and MR_1' (see eqs. 2 and 3, 5 and 6, and 7 and 8). These equations were then interpreted as a reflection of the importance of the hydrophobic and/or steric nature of substituent R_1. (Given the series of R_1 groups considered in this study, no more may be said.)

The equations show that R_1 has a decisive role in the complexation both with α- and β-cyclodextrin. The positive coefficients for the c_1 and MR_1' terms indicate that an increase in the hydrophobicity and/or the bulk of R_1 results in a more stable complex in both cases. This suggests that in the course of the complexation, R_1 penetrates the cyclodextrin cavity and binds there through hydrophobic and/or dispersional forces. Evidently, if this assumption holds, the existence of optimum c_1 and MR_1' values could be expected both for α- and β-cyclodextrin complexes, with which an R_1 substituent could best fit the cavity. This could be modeled by quadratic relationships between log K_α or log K_β and c_1 or MR_1'. However, no such relationships were found, probably because the c_1 and MR_1' values of the R_1 groups occurring in the barbiturates studied are much less than the optimum values and fall into a range where the assumed parabolas can be approximated by straight lines.

The negative coefficients for the I_1 term in eqs. 1–6 show that branching or cyclic R_1 groups reduce the stability of the complex with α-cyclodextrin, regardless of the hydrophobicity and the bulk of R_1. This may also reflect the above complexation mechanism of R_1 penetrating the cyclodextrin cavity. The difference between the roles of R_1 in the complexation with α- and β-cyclodextrin can probably be accounted for by the difference between the respective cavity diameters, that of the former being ~0.2 nm lower than that of the latter.

The positive coefficient for the I_X term in eq. 9 indicates that thiobarbiturates form more stable complexes with β-cyclodextrin than the less hydrophobic barbiturates. This suggests a hydrophobic interaction between the barbiturate ring and the hydrophobic β-cyclodextrin cavity. In summary, the above findings on the factors responsible for the inclusion complexation of barbiturates with α- and β-cyclodextrin, i.e., that hydrophobic and steric effects predominate, are in agreement with the observations of other authors.[7,11–13]

As to the mechanism of complexation, contradictory proposals have been published in the literature. Based upon nuclear magnetic resonance investigations of β-cyclodextrin–barbiturate complexes, Thakkar et al.[14,15] concluded that the cyclodextrin cavity includes the R_1 substituent, whereas Otagiri et al.[12] inferred that the barbiturate ring and the R_2 substituent are located in the cavity. (It should be mentioned that Koizumi et al.[16] proposed a complexation model for crystalline α- and β-cyclodextrin–barbiturate complexes. We do not regard it to be relevant here, however, since this paper deals with complexation in solution. As a matter of fact, it can be assumed that the different circumstances in the solution and the crystal phase lead to different complexation mechanisms. A support to this assumption is that Uekama et al.[7] found 1:1 stoichiometry for α-cyclodextrin–barbiturate complexes in solution, while a solubility analysis of Koizumi et al.[16] showed 2:1 stoichiometry for the same complexes in crystal phase.)

Here, a third alternative is suggested: in α-cyclodextrin complexes the cavity includes only R_1, while in β-cyclodextrin

complexes both R_1 and (part of) the barbiturate ring are included. This hypothesis does not preclude other interactions between the barbiturate and cyclodextrin molecules.

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