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Interaction of some barbituric acid derivatives with hydroxypropyl-β-cyclodextrin

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Summary

The interaction between 39 barbituric acid derivatives and hydroxypropyl-β-cyclodextrin (HPβCD) was studied by reversed-phase charge-transfer thin-layer chromatography. Except for one derivative, each barbiturate formed inclusion complexes with HPβCD, the complex always being more hydrophilic than the uncomplexed drug. The intensity of interaction significantly increased with increasing lipophilicity of the guest molecule proving the preponderant role of hydrophobic interactions in inclusion complex formation. The di- and trisubstituted derivatives probably formed complexes of different stoichiometry. Free-Wilson analysis proved that the intensity of interaction increases with increasing size of the substituents at least in the studied range.

Introduction

Cyclodextrins (CDs) form inclusion complexes with many drugs of various chemical structures, modifying their stability, solubility, translocation in the organism and biological effects (Szejtli, 1988). βCD, although readily available, has a relatively low solubility, and therefore in many cases its hydrophilic derivatives (methylated, hydroxypropylated or crosslinked), have been studied. The interaction betwen barbiturates and crosslinked water-soluble βCD polymer has previously been studied (Cserháti et al., 1986a) and it was found that the stability of the complex increased with increasing chain length of the alkyl substituents. The inclusion complex stability of barbiturates also depends on the dimensions of cyclodextrin cavity (Szejtli et al., 1988). The inclusion complex formation between barbiturates and HPβCD has not yet been studied. On account of its high solubility, excellent drug solubilizing capacity and practically zero hemolytic effect, HPβCD is expected to be used as a parenteral drug carrier. Using HPβCD, injectable aqueous solutions can be made from very poorly soluble drugs (Pitha et al., 1986).

Charge-transfer reversed-phase thin-layer chromatography has been extensively applied to study inclusion complex formation (Cserháti et al., 1983, 1984a,b, 1986b). The theory and the methods to calculate interactive strengths from

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the retention data in charge-transfer reversed-phase chromatography have been published (Cserháti et al., 1987).

Experimental

The structures of the barbituric acid derivatives are shown in Table 1. Polygram UV_{254} plates (Macherey-Nagel, Dürren, Germany) were impregnated with paraffin oil. The barbituric acid derivatives were dissolved in methanol at a concentration of 4 mg/ml; 5 ml of each solution was spotted onto the plates. Ethanol was chosen as the organic solvent miscible with water, since it forms only a weak inclusion complex with βCD (Buvári et al., 1983/1984; Harada and Takahashi, 1984). The ethanol concentration in the eluent was varied from 0 to 50% (v/v) in steps of 5%. HPβCD (average number of hydroxypropyl groups per CD molecule 2.7; product of Chinoin Pharmaceutical Works, Hungary) was dissolved in the ethanol-water eluent systems at a concentration in the range of 0–25 mM in steps of 5 mM. The lipophilicity of barbituric acid derivatives was determined in minimally 12 maximally 24 different eluent systems. For each experiment, five replicate determinations were carried out. After development the plates were dried at 105°C and the barbituric acid derivatives were detected under UV light.

The R_M values characterizing molecular lipophilicity in reversed-phase thin-layer chromatography (RP-TLC) were calculated from Eqn 1.

$$R_M = \log(1/R_f - 1) \tag{1}$$

To separate the effects of ethanol and HPβCD on the lipophilicity of barbiturates and to take into consideration the possible ternary interaction between ethanol, HPβCD and the guest, the following equation was fitted to the experimental data (Cserháti et al., 1988):

$$R_M = R_{M0} + b_E \cdot E + b_H \cdot H + b_{EH} \cdot E \cdot H \tag{2}$$

where R_M represents the R_M value of a compound at a given ethanol and HPβCD concentration, R_{M0} is the R_M value of a compound extrapolated to zero ethanol and zero HPβCD concentrations, b_E denotes the decrease in the R_M value caused by an 1% increase in ethanol concentration in the eluent, b_H is the decrease in the R_M value caused by a 1 mM increase in HPβCD concentration in the eluent (interaction coefficient), b_{EH} gives an indication of the impact of the ethanol-HPβCD-guest ternary interaction on the R_M value, and E and H are the concentrations of ethanol and HPβCD, respectively.

Eqn 2 was applied separately for each compound. To test the validity of the hypothesis that the slope values of Eqn 2 (b_E, b_H and b_{EH}) characterize the lipophilicity (Valkó, 1984; Valkó et al., 1984) linear correlation was calculated between the R_{M0} and b_E values (coefficient of the ethanol concentration):

$$R_{M0} = a_1 + b_1 \cdot b_E \tag{3a}$$

between the R_{M0} and b_H values:

$$R_{M0} = a_2 + b_2 \cdot b_H \tag{3b}$$

and between the R_{M0} and b_{EH} values:

$$R_{M0} = a_3 + b_3 \cdot b_{EH} \tag{3c}$$

The calculations were carried out three times: (i) For each compound; (ii) only for compounds with two substituents; and (iii) only for compounds with more than two substituents

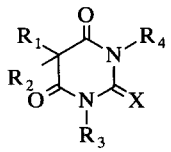
Calculations ii and iii were motivated by the assumption that the stoichiometry of inclusion complexes may be different for disubstituted (assumed molar ratio 1 : 1) and for tri- or tetrasubstituted barbituric acid derivatives (more than one cyclodextrin molecule interacts with one barbiturate molecule).

The fact that the contribution of the b_{EH} value (ethanol-HPβCD complex formation) varied significantly among the barbituric acid derivatives suggests the possible formation of ternary complexes (ethanol-cyclodextrin-barbiturate) and of complexes of higher, but unknown stoichiometry.

Free-Wilson analysis was applied to determine the substituents exerting the greatest influence on the complex stability. To compare the interaction coefficients (b_H values) with the complex stability constants determined (Uekama et al., 1978) or calculated (Lopata et al., 1985) elsewhere, linear

TABLE 1

Chemical structure of barbituric acid derivatives



General structure

Compound no.	R_1	R_2	R_3	R_4	X
1	methyl	1-methylpentyl	H	H	O
2	ethyl	ethyl	H	H	O
3	ethyl	1-methylbutyl	H	H	O
4	ethyl	3-methylbutyl	H	H	O
5	ethyl	1-methylpropyl	H	H	O
6	ethyl	*n*-pentyl	H	H	O
7	butyl	1-methylpropyl	H	H	O
8	butyl	1-methylbutyl	H	H	O
9	ethyl	*n*-octyl	H	H	O
10	ethyl	3-dimethyloctyl	H	H	O
11	allyl	isopropyl	H	H	O
12	allyl	isobutyl	H	H	O
13	allyl	1-methylbutyl	H	H	O
14	allyl	1-cyclohexenyl	methyl	H	O
15	allyl	2-cyclopentyl	H	H	O
16	ethyl	1-cyclohexenyl	H	H	O
17	ethyl	ethyl	H	H	S
18	ethyl	1-methylbutyl	H	H	S
19	allyl	1-methylbutyl	H	H	S
20	ethyl	1,3-dimethylbutyl	H	H	S
21	ethyl	phenyl	H	H	O
22	ethyl	ethyl	phenyl	H	O
23	ethyl	ethyl	benzoyl	H	O
24	ethyl	ethyl	benzoyl	benzoyl	O
25	ethyl	ethyl	*p*-Cl-benzoyl	H	O
26	ethyl	ethyl	*p*-NO_2-benzoyl	H	O
27	ethyl	phenyl	*p*-NO_2-benzoyl	*p*-NO_2-benzoyl	O
28	ethyl	phenyl	phenyl	H	O
29	ethyl	phenyl	benzoyl	methyl	O
30	ethyl	phenyl	*p*-NH_2-benzoyl	methyl	O
31	ethyl	phenyl	*o*-NO_2-benzoyl	methyl	O
32	ethyl	phenyl	*p*-NO_2-benzoyl	methyl	O
33	ethyl	phenyl	*m*-NO_2-benzoyl	methyl	O
34	ethyl	ethyl	*p*-NO_2-benzoyl	methyl	O
35	ethyl	ethyl	benzoyl	methyl	O
36	methyl	phenyl	benzoyl	H	O
37	methyl	phenyl	benzoyl	methyl	O
38	ethyl	phenyl	benzoyl	H	O
39	ethyl	propyl	H	H	O

correlations were calculated between the b_H and corresponding complex stability constants taken from the works of Uekama et al. (1978) and Lopata et al. (1985).

Results and Discussion

The apparent lipophilicity (in this case expressed by the R_M value) of each barbituric acid derivative decreases with increasing organic phase concentration (Fig. 1). That is the barbiturates do not show any anomalous behaviour in the ethanol contration range applied which would restrict the applicability of Eqn 2. Our calculation fully supports the proposals of Valkó (1984) and Valkó et al. (1984) that the slope value (b_E) is also suitable for characterizing molecular lipophilicity (see Eqn 3a). The significance level of the fitness of linear correlation betwen R_{M0} and b_E was over 99.9%: $R_{M0} = -1.1 + 6.85b_E$; $n = 39$; $r = 0.9643$.

As HPβCD is more hydrophilic than any barbiturate, the HPβCD-barbiturate complex must be more hydrophilic than the uncomplexed barbiturate. Our data support this hypothesis: HPβCD reduces the lipophilicity of barbiturates (Fig. 2). The results of the calculations (the parameters of Eqn 2) are listed in Table 2.

Except for compound 10, the fit of Eqn 2. to the experimeental data was in each case over the significance level of 99.9% ($F_{calc} > F_{99.9\%}$), proving the exactness of the equation. Each independent variable (ethanol, HPβCD concentration and their interaction) influenced significantly the R_M of barbiturates. In the case of compound 35, the lipophilicity depended only on the ethanol concentration in the eluent, i.e., this compound did not form an inclusion complex with HPβCD. Except for compound 10, the changes of the three independent variables accounted for 90–99% of the change in barbiturate lipophilicity (see r^2 values). The individual values of the b_E, b_H and b_{EH} coefficients indicate that the influence of the three independent variables on the lipophilicity of different barbituric acid derivatives is rather different in magnitude, but considering their average value, it can be concluded that the effect of ethanol concentration is the strongest and that of ternary complex formation is the weakest. Our systems always contained much more ethanol and HPβCD than barbiturate, therefore, the intensity of the ethanol-HPβCD) interaction was independent of the type of barbiturate, being present only at very low concentration.

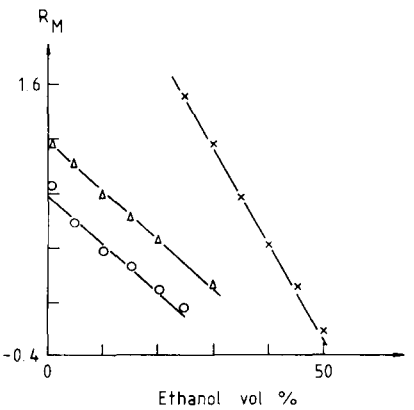


Fig. 1. Dependence of R_M value of some barbituric acid derivatives on the ethanol concentration in the eluent. (×) Compound 10; (△) compound 14; (○) compound 11.

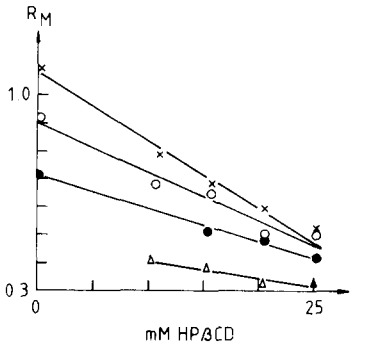


Fig. 2. Dependence of R_M value of compound 18 on the HPβCD concentration in the eluent. (×) 15% ethanol; (○) 20% ethanol; (●) 25% ethanol; (△) 30% ethanol.

Nevertheless, our data contradict this supposition, since the b_{EH} values sometimes showed large deviations from each other. The formation of a ternary complex (HPβCD-barbiturate-ethanol, or 2HPβCD-barbiturate) is assumed. The parameters of Eqn 3b (i.e., the dependence of the host-guest association of the HPβCD (host) concentration) are compiled in Table 3. Considering all compounds together, at first sight it would

appear that their complex forming ability is independent of their lipophilicity (column 1). However, taking into consideration the number of substituents (columns 2 and 3) significant linear correlations were found in both cases.

This finding suggests that the properties of

TABLE 2

Parameters of linear correlations between the lipophilicity (R_M) of barbiturates and the ethanol (E) and HPβCD (HO) concentration in the eluent ($R_M = R_{M0} + b_E \cdot E + b_H \cdot H + b_{EH} \cdot E \cdot H$)

Parameter	Compound no.					
	1	2	3	4	5	6
n	16	15	17	17	16	17
R_{M0}	1.76	0.30	1.33	1.29	0.91	1.20
$-b_E$ ($\times 10^{-2}$)	3.39 ± 0.39	3.22 ± 0.23	3.22 ± 0.21	3.37 ± 0.16	3.34 ± 0.19	3.14 ± 0.19
$-b_H$ ($\times 10^{-2}$)	4.87 ± 0.25	1.74 ± 0.29	4.01 ± 0.38	4.28 ± 0.29	4.00 ± 0.29	3.72 ± 0.35
b_{EH} ($\times 10^{-3}$)	1.25 ± 0.31	1.09 ± 0.27	1.11 ± 0.19	1.25 ± 0.15	1.55 ± 0.25	1.10 ± 0.18
$F_{calc.}$	89.3	93.3	204.9	360.9	128.4	201.1
r^2	0.9571	0.9622	0.9793	0.9882	0.9698	0.9798
b_E (%)	21.6	60.5	24.8	24.2	47.9	25.4
b_H (%)	51.9	22.3	48.5	48.1	35.5	47.0
b_{EH} (%)	26.5	17.3	26.6	27.7	16.7	27.6
	7	8	9	10	11	12
n	16	16	24	24	15	15
R_{M0}	2.05	2.14	2.87	1.62	0.74	1.02
$-b_E$ ($\times 10^{-2}$)	4.02 ± 0.38	4.30 ± 0.32	5.81 ± 0.49	3.72 ± 1.34	3.30 ± 0.22	3.49 ± 0.30
$-b_H$ ($\times 10^{-2}$)	4.97 ± 0.63	5.39 ± 0.53	7.36 ± 1.06	6.38 ± 2.87	3.39 ± 0.28	3.89 ± 0.37
b_{EH} ($\times 10^{-3}$)	1.47 ± 0.30	1.61 ± 0.25	1.81 ± 0.33	1.90 ± 0.89	1.36 ± 0.26	1.47 ± 0.35
$F_{calc.}$	83.6	136.8	53.8	2.6	111.7	72.3
r^2	0.9543	0.9716	0.8997	0.2836	0.9693	0.9518
b_E (%)	23.4	23.1	31.7	24.0	48.8	47.2
b_H (%)	48.3	48.4	40.5	41.4	34.2	35.9
b_{EH} (%)	28.3	28.5	27.9	34.5	17.0	16.8
	13	14	15	16	17	18
n	17	20	20	20	15	23
R_{M0}	1.34	1.13	1.00	1.03	0.65	2.06
$-b_E$ ($\times 10^{-2}$)	2.98 ± 0.23	3.38 ± 0.22	3.73 ± 0.39	3.53 ± 0.31	2.71 ± 0.28	4.58 ± 0.31
$-b_H$ ($\times 10^{-2}$)	2.70 ± 0.43	4.53 ± 0.32	5.39 ± 0.60	5.34 ± 0.48	3.13 ± 0.35	6.13 ± 0.51
b_{EH} ($\times 10^{-3}$)	0.52 ± 0.22	1.30 ± 0.19	2.03 ± 0.36	1.37 ± 0.29	1.03 ± 0.33	1.63 ± 0.19
$F_{calc.}$	146.5	162.4	47.4	94.3	52.9	133.8
r^2	0.9713	0.9682	0.8890	0.9464	0.9352	0.9548
b_E (%)	33.8	39.6	36.4	38.7	47.5	26.1
b_H (%)	48.0	37.7	36.8	40.9	37.4	42.1
b_{EH} (%)	18.2	22.7	26.8	20.4	15.2	31.8
	19	20	21	22	23	24
n	23	16	17	15	22	20
R_{M0}	2.13	1.66	0.89	1.27	2.21	4.39
$-b_E$ ($\times 10^{-2}$)	4.39 ± 0.38	3.98 ± 0.30	3.45 ± 0.32	3.77 ± 0.20	5.14 ± 0.25	8.14 ± 0.53
$-b_H$ ($\times 10^{-2}$)	6.82 ± 0.62	5.30 ± 0.49	4.87 ± 0.42	3.92 ± 0.44	3.17 ± 0.43	4.72 ± 1.25
b_{EH} ($\times 10^{-3}$)	1.80 ± 0.63	1.45 ± 0.23	1.09 ± 0.28	1.44 ± 0.31	0.90 ± 0.14	1.05 ± 0.30
$F_{calc.}$	93.1	175.3	110.9	131.7	346.2	260.1
r^2	0.9363	0.9777	0.9624	0.9729	0.9830	0.9799
b_E (%)	23.4	22.5	42.2	59.2	43.3	44.0
b_H (%)	43.9	50.2	39.8	28.1	31.2	30.1
b_{EH} (%)	32.7	27.2	18.0	12.7	25.4	25.9

TABLE 2 (continued)

Parameter	Compound no.					
	25	26	27	28	29	30
n	21	19	21	21	23	22
R_{M0}	4.82	2.66	4.64	3.85	3.75	3.00
$-b_E$ ($\times 10^{-2}$)	9.38 ± 0.54	5.15 ± 0.16	8.77 ± 0.66	7.07 ± 0.53	6.90 ± 0.29	6.20 ± 0.20
$-b_H$ ($\times 10^{-2}$)	5.69 ± 1.24	3.02 ± 0.33	11.38 ± 1.60	4.33 ± 1.17	2.43 ± 0.68	2.44 ± 0.44
b_{EH} ($\times 10^{-3}$)	1.06 ± 0.31	0.81 ± 0.10	2.55 ± 0.38	0.91 ± 0.29	0.54 ± 0.18	0.62 ± 0.12
$F_{calc.}$	224.1	604.8	78.5	165.7	528.7	750.3
r^2	0.9753	0.9918	0.9327	0.9669	0.9882	0.9921
b_E (%)	43.6	47.7	25.0	41.4	55.9	49.7
b_H (%)	33.3	29.8	40.9	32.9	24.2	25.8
b_{EH} (%)	23.0	22.5	34.0	25.7	19.9	24.5
	31	32	33	34	35	36
n	14	12	27	23	23	20
R_{M0}	4.22	4.11	2.16	2.97	2.35	2.68
$-b_B$ ($\times 10^{-2}$)	8.06 ± 0.34	6.81 ± 0.54	4.50 ± 0.17	5.60 ± 0.18	4.78 ± 0.29	5.50 ± 0.19
$-b_H$ ($\times 10^{-2}$)	4.79 ± 1.86	3.29 ± 1.91	3.04 ± 0.31	2.49 ± 0.46	0.06 ± 0.71	2.63 ± 0.41
b_{EH} ($\times 10^{-3}$)	1.03 ± 0.44	0.71 ± 0.44	0.78 ± 0.09	0.52 ± 0.12	0.03 ± 0.19	0.56 ± 0.13
$F_{calc.}$	253.3	102.0	608.9	566.9	208.1	481.0
r^2	0.9870	0.9745	0.9876	0.9890	0.9705	0.9890
b_E (%)	33.3	30.7	45.1	49.5	95.4	54.0
b_H (%)	34.8	36.1	30.0	28.3	1.4	28.7
b_{EH} (%)	31.9	33.1	24.8	22.2	3.2	17.3
	37	38	39			
n	20	20	15			
R_{M0}	3.25	3.14	0.47			
$-b_E$ ($\times 10^{-2}$)	6.13 ± 0.16	6.31 ± 0.27	3.71 ± 0.20			
$-b_H$ ($\times 10^{-2}$)	3.40 ± 0.33	4.41 ± 0.58	1.93 ± 0.25			
b_{EH} ($\times 10^{-3}$)	0.88 ± 0.10	1.09 ± 0.18	1.05 ± 0.23			
$F_{calc.}$	888.2	275.3	174.6			
r^2	0.9940	0.9810	0.9794			
b_E (%)	48.4	43.2	62.7			
b_H (%)	29.9	33.5	22.2			
b_{EH} (%)	21.7	23.4	15.0			

HPβCD-barbiturate complexes strongly depend on the number of substituents on the ring. Although this method is not suitable for the determination of complex stoichiometry, it is assumed that it is different for disubstituted and for tri- or tetrasubstituted barbituric acid derivatives.

The extent of barbiturate-ethanol-HPβCD ternary complex formation depends on the lipophilicity of barbiturates only in the case of barbiturates bearing two substituents on their ring (Table 4). With three or four substituents, either there is simply no room for an ethanol molecule, or such higher substituted barbiturates interact with more than one HPβCD molecule. The behaviour of this complicated system cannot be described by simple linear regression. The results of Free-Wilson analysis are compiled in Table 5. Only 10 substituents from the 32 occurring in the studied derivatives account for the 83.36% of the total variance. That is, the presence or absence of most substituents plays only a minor role in determining the complex stability. The shorter alkyl substituents (methyl, ethyl, propyl) decrease the stability of complexes while larger alkyl groups (*n*-octyl) increase the complex stability. This means that the barbituric acid derivatives containing larger alkyl chains fit the cyclodextrin cavity better than do the other derivatives. The

TABLE 3

Parameters of linear correlations between the lipophilicity (R_{M0}) of barbiturates and the inclusion forming capacity (b_H) of hydroxypropyl-βCD with barbiturates (Eqn 3b) ($R_{M0} = a_2 + b_2 \cdot b_H$)

Parameter	i	ii	iii
n	39	21	18
a_2	1.44	−0.24	2.26
b_2 (×10²)	1.75	3.51	2.28
r	0.2648	0.8155	0.4725
Significance level (%)	> 90	99.9	95

i, for each compound; ii, for compounds with two substituents; iii, for compounds with more than two substituents.

TABLE 4

Parameters of linear correlations between the lipophilicity (R_{M0}) of barbiturates and the b_{EH} value (Eqn 3c): effect of HPβCD-ethanol interaction or ternary complex formation ($R_{M0} = a_3 + b_3 \cdot b_{EH}$)

Parameter	i	ii	iii
n	39	21	18
a_3	2.53	0.15	2.74
b_3 (×10²)	−3.06	8.76	4.35
r	0.1256	0.4830	0.2067
Significance level (%)	> 90	95	> 90

i, for each compound; ii, for compounds with two substituents; iii, for compounds with more than two substituents.

TABLE 5

Effect of various substituents on inclusion complex formation (results of Free-Wilson analysis)

Substituent		Activity contribution
Type	Position	
Methyl	R_4	−17.53± 4.13
Ethyl	R_2	−19.78± 9.22
Propyl	R_2	−25.98± 9.22
S	X	14.90± 5.56
p-NO_2-benzyl	R_3	16.89±10.31
o-NO_2-benzoyl	R_3	20.19± 9.75
Benzoyl	R_4	21.68± 9.80
n-Octyl	R_2	28.30± 9.22
p-Cl-benzyl	R_3	31.40± 9.80
p-NO_2-benzoyl	R_4	68.51± 9.22

$F_{calc.} = 14.00$; $r^2 = 0.8336$; $a = 45.28$.

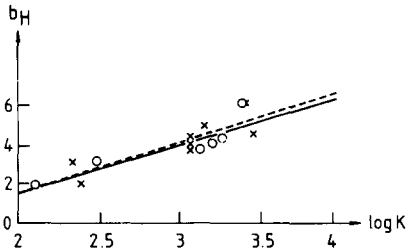


Fig. 3. Linear correlations between the interaction coefficients (b_H values) and the corresponding complex stability constants (for βCD) taken from Uekama et al. (1978) (○———○) and Lopata et al. (1985) (×———×).

bulkier substituents also fit the cyclodextrin cavity more completely. The substitution of oxygen by sulphur considerably enhanced the complex stability.

Our complex stability data (interaction coefficient) showed good agreement with the published values (Uekama et al., 1978; Lopata et al., 1985) (Table 6), the coefficients of the linear regressions being 0.8896 ($n = 8$) and 0.8462 ($n = 8$), respectively (see Fig. 3). This indicates that our method is suitable to characterize complex stability. It does not necessitate complicated instrumentation and is easy to carry out.

Acknowledgment

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TABLE 6

Comparison of the interaction coefficients (b_H values) with the complex stability constant determined (log $K_{det.}$; Uekama et al., 1978) or calculated (log $K_{calc.}$; Lopata et al., 1985)

Compound	b_H	log $K_{det.}$	log $K_{calc.}$
39	1.930	2.114	2.380
17	3.129	2.477	2.347
6	3.715	3.114	3.063
3	4.011	3.196	3.063
4	4.283	3.243	3.063
14	4.283	3.185	3.455
21	4.867	3.270	3.146
18	6.127	3.380	3.373

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