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ORIGINAL ARTICLE

Solubility enhancement and QSPR correlations for polycyclic aromatic hydrocarbons complexation with α, β, and γ cyclodextrins

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Abstract Through batch equilibrium experiments, hydroxypropyl substituted α, β, and γ cyclodextrin (CDs) were shown to greatly increase the apparent solubility of eight common polycyclic aromatic hydrocarbons (PAHs) in aqueous solutions. Equations based on the volume fraction of solution composed of water and CDs have been developed to determine guest phase distribution. Based on these equations, the results of this and similar studies for CD showed that a log–log relationship exists between the fraction of CD occupied with a guest organic compound and the aqueous solubility of those guests (rsq 0.980). Analysis of potential quantitative structure property relationship (QSPR) found strong correlations between structural properties of the guests (e.g. aqueous solubility, octanol/water partitioning coefficient, molar volume, molecular surface area, and polarizability) and water/CD partitioning coefficients, phase distribution of the PAH between water and CD phases, and the fraction of CD molecules occupied with a guest PAH. Noteworthy among these, is the inverse relationship between the log of the fraction of CD molecules occupied under saturated conditions and the ratio of the molar volume of the PAH to the volume of the CD cavities (rsq for α, β, and γ: 0.887–0.892). Comparisons of the three CDs shows that while the size of the guest compound reduces its propensity to enter into the CD cavity, the effect of the guest size is lessened as the width of the CD ring increases. Development of these QSPR correlations provides a means to predict and evaluate guest/CD interactions for homologous series of compounds.

Keywords Cyclodextrin · Partitioning · PAH · Polarizability · QSPR

Introduction

Cyclodextrins are macro-ring molecules composed of glucopyranose units that have a hydrophilic polar exterior and a hydrophobic, relatively non-polar interior cavity into which compounds of similar nature and appropriate size and shape can partition [1]. There is a growing body of evidence suggesting that various derivatives of cyclodextrin (CD) can effectively remediate sites contaminated by hydrophobic organic compounds (HOCs), specifically polycyclic aromatic hydrocarbons (PAHs) [2–7]. In a field study, McCray and Brusseau [3] demonstrated that CD can significantly enhance dissolution rates of a multi-component NAPL over aquifer flushing with water. In comparison to water, Gao et al. [7] found that a 20 % wt./vol. aqueous solutions of CD were able to extract 79 times more of alkanes (nC15–nC35) and 153 times more of total PAHs (2–6 ring) from Macondo well oil contaminated quartz sand. Finally, Hoffman et al. [5] exploited the ability of a carboxyl CD derivative to complex metals to reduce the

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potential of cadmium, cobalt, and copper to inhibit biodegradation of naphthalene.

Several factors that may contribute to the stability of CD-HOC complex have been reported in the literature, (1) the structure of the host CD and guest molecule; (2) hydrophobic interactions of these two [8]; (3) hydrogen-bonding [8–10]; (4) displacement of water molecules within CD cavity by the inclusion of a guest organic compound [11, 12]; and (5) conformation changes or strain release of CD molecular [13]. CD interactions with organic chemicals are largely driven by the same hydrophobic processes often involved in phase partitioning (e.g. sorption of those chemical to soils, Henry's coefficients, and relative retention within chromatography columns).

Quantitative structure property relationships (QSPR) for HOC partitioning coefficients between water and soil or biological phases have been developed with octanol/water partitioning coefficients, K_{OW}, [14, 15], aqueous solubility [16], and high pressure liquid chromatography retention times [17]. For cyclodextrins, McCray et al. [4] showed a series of correlations for 2-hydroxypropyl-β-cyclodextrin (HPβCD). After examining eighteen common HOCs, correlations were found between the logarithm of the chemicals' K_{OW} and the log of their apparent solubility in CD solutions as well as the cyclodextrin/water partitioning coefficient. Le Bas molar volumes of organic chemicals have also been correlated with their aqueous solubility and K_{OW} values [18, 19], but this property has not been compared to cyclodextrin-guest interactions for HOCs. Total molecular surface area (TSA) is another parameter infrequently used in QSPR analysis. Valvani et al. [20] and Yalkowsky and Valvani [21] found correlations between TSA and aqueous solubility and Yalkowsky and Valvani [21] and Doucette and Andren [22] found relationships with log K_{OW}. Doucette and Andren [22] specifically examined a series of highly hydrophobic aromatic compounds, including dibenzofuran and found a linear relationship between TSA and log K_{OW}.

Weak intermolecular forces result in the formation of guest/CD complexes, such forces are expected to affect the electronic charge distribution of the guest molecule. Such deformation of the guest molecule's charge distribution in the complex is expressed in its polarizability. Polarizability is a measurement of how an applied electric field can deform the charge distribution of an atom or a molecule and is directly proportional to atomic or molecular size [23]. Formally, polarizability is the ratio of the induced dipole moment in the atom or molecule to the strength of the applied electric field. Many studies exist have shown a direct correlation between polarizability and aqueous solubility [24–28]. In addition, Ledesma and Wornat [29] related polarizability of a series of PAHs to their retention times in liquid chromatography which is largely driven by hydrophobicity.

Recently, Kimura et al. [30] evaluated the correlation with calculated values from density functional theory (DFT) of polarizability with the measured thermodynamic properties of inclusion of eight pentane derivatives into the cavities of underivatized α-CD determined by micro-calorimeter. They found strong inverse correlations between the log DFT calculated values and Gibbs energies and enthalpies of inclusion and direct correlations with the entropies of inclusion.

In this study, we aim to address some of the gaps in knowledge on the interactions of CDs with PAHs. PAHs are common environmental contaminants and they are usually present in a range of molecular sizes. While water/CD partitioning coefficients have been examined for HPβCD, there is no systematically investigation on the other two most common 2-hydroxypropyl CD derivatives (i.e. HPαCD and HPγCD) and thus the effect of CD ring size on PAH/CD interactions is poorly known. In addition, while QSPR analysis has found correlations between guest/CD systems and K_{OW} and aqueous solubility, potential relationships with other molecular parameters such as molar volume, molecular surface area, and polarizability have not been thoroughly investigated.

In this study, equilibrium batch studies were conducted to determine the apparent solubility enhancement of eight PAHs in aqueous solutions of three different ring sizes of 2-hydroxypropyl CD derivatives: HPαCD, HPβCD, and HPγCD. Specifically, the objectives were to: (1) determine the cyclodextrin-induced solubility enhancement factors of eight common PAH pollutants (acenaphthene, anthracene, benzo(k)fluoranthene, chrysene, dibenzofuran, fluoranthene, fluorene, and naphthalene) through batch equilibrium studies conducted with hydroxypropyl substituted CDs of differing cavity widths in 300 g L^{-1} aqueous solutions, (2) determine if strong correlations exist between (a) water/cyclodextrin partitioning coefficients, (b) PAH phase distribution, and (c) fraction of CD cavities occupied with a guest for the tested PAHs with a commonly reported chemical properties: (a) aqueous solubility, (b) octanol–water partition coefficient, (c) molar volume, (d) total molecular surface area, and (e) polarizability.

Materials and methods

Chemicals

HPαCD, HPβCD, and HPγCD were donated by Wacker Chemie AG (USA) and used as received. HPαCD and HPγCD were pharmaceutical grade with a purity in wt./wt. units: 5.0 % water; unmodified CD <0.1 %; <0.1 % ash

(which according to Wacker is largely sodium chloride); ~0.1 % propylene glycol; and 94.8 % HP derivatized CD. Analytical grade HPβCD was used and its purity was 5.0 % water; unmodified CD <0.1 %; 2.0 % ash; <0.1 % propylene glycol; and 92.6 % HP derivatized CD. The reported average molecular weights of HPαCD, HPβCD and HPγCD were 1180, 1424, and 1580 respectively. The general molecular formula for hydroxypropyl derivatized cyclodextrin is $C_{6g}\ H_{10g-n}O_{5g}{\cdot}n(C_3H_7O)$ where g denotes the number of glucose units (i.e. 6, 7, and 8 for α, β, and γ respectively) and n denotes the average number of hydroxypropyl substitutions on the secondary ring of the CDs. Using this molecular formula, the average number of hydroxypropyl substitutions per CD molecule for the HPαCD, HPβCD and HPγCD used in this study are: 3.40, 4.99, and 5.06 respectively.

The PAHs under study are: acenaphthene (99 % purity), anthracene (99 % purity), benzo(k)fluoranthene (98 % purity), chrysene (98 % purity), dibenzofuran (99+ % purity), fluoranthene (99 % purity), fluorine (98 % purity), and naphthalene (99+ % purity). They were purchased from the Sigma Aldrich Chemical Co. High purity deionized water was generated by a US Filter water purification system (Siemens, Warrendale, PA) to 18.2 MΩ and was disinfected by ultraviolet light irradiation.

Solubility enhancement procedures

In this study, aqueous CD solutions with concentrations of 300 g L^{-1} were prepared by addition of CD powder to high purity water. The amount of each PAH needed to saturate 18 ml of targeted concentration of CD solution was projected from the relationship between octanol/water partitioning coefficients and the solubility enhancement factor of an HPβCD solution developed by McCray et al. [4]. This amount was then multiplied by four as a margin of error. The target amount of each PAH were weighed (Denver Instruments, model P-8002D, accuracy ±1 mg), added to 18 ml of the 300 g L^{-1} CD solutions in a 20 ml headspace vial (Ampolletas, S.A) and immediately sealed with a Teflon lined screw cap after filling. After enclosing in aluminum foil to prevent photo degradation, continuous mixing was providing during the experimental period with a constant agitation speed of 110 rpm through a rotary shaker (Model: LE "Big Bill", Sybron Thermolyne). In this method, the 2 ml headspace within the vials promoted mixing and resulted in minimal PAH mass loss due to limited volatility. A preliminary experiment demonstrated that after 30 days of mixing, the concentration of target PAHs in aqueous CD solution changed by <0.1 % day to day, which is considered to represent equilibrium. In this study, incubation was performed at 25.0 ± 0.4 °C for 36 days to ensure near equilibrium conditions. Each PAH/CD combination was performed in triplicate.

The relative amount of each PAH in solution was measured through fluorescence spectroscopy and the concentration determined through comparison with standards of known concentration. Specifically, fluorescence measurements were made with a Shimadzu RF-5000 equipped with a 150 W xenon lamp, monochromators (ion-blazed, halographic concave grating F/2.5), and a high performance R452-01 photomultiplier detector. A series of seven standards were created from a 2 L stock solution of the target CD and a PAH concentration 10 % of projected saturation level. If the calibration equation was poor, the stock solution concentration was reduced. Prior to analysis, a subsample taken from the test batch sample was diluted with PAH free solution of the target CD solution whose concentration was 300 g L^{-1}CD.

Theory/calculation

Blyshak et al. [31] and Singer et al. [32] among others reported that the association of chemicals and CD molecules can be modeled using a simple reaction equilibrium model Eq. (1) with the stoichiometry (higher host:guest ratio) of 1:1.

$$\text{Guest} + \text{CD} \overset{K_s}{\leftrightarrow} \text{Guest} - \text{CD} \tag{1}$$

where Guest denotes the activity of the target compound in the water phase outside of the CD cavity, CD denotes the activity of unoccupied cyclodextrin molecules, Guest-CD is the activity of the target compound within the CD cavity and the K_s is defined as the binding or stability constant. These are defined in Eq. (2):

$$K_s = \frac{[\text{G} - \text{CD}]}{[\text{G}][\text{CD}]} \tag{2}$$

Most pharmaceutical CD studies are performed with underivatized CD, whose solubility in water is less than derivatives such as HPβCD, and they are performed with relatively insoluble compounds at molar concentrations much lower than that of CD. In such systems, Eq. (2) can be readily simplified where the quest activity in solution [G] is assumed to be equal to the aqueous solubility, S_w. Furthermore, in these studies relatively few CD molecules are occupied with a guest and thus the unoccupied CD activity is essentially equal to the total CD concentration. Under these conditions, Eq. (2) can be rearranged to:

$$S_A = S_W(1 + K_{cw}C_{CD}) \tag{3}$$

where S_A is the apparent solubility of the guest in solution, C_{CD} is total CD concentration in solution, and the reaction model binding constant, K_s, has been substituted with a

partitioning model coefficient, K_{cw}.Wang and Brusseau [2] made these assumptions and used this model to evaluate the water/CD partitioning coefficient of their experimental results for saturated levels of a series of HOCs in HPβCD solutions over a range of concentrations (0 and 70 $g_{CD}\ L^{-1}$). Wang and Brusseau [2] recognized that the partitioning coefficient for highly soluble compounds would be poorly determined by Eq. (3) and produced Eq. (4) which still substitutes S_w for [G], but does not assume [G−CD] ≪ [CD] yielding:

$$S_A = S_W\left(1 + \frac{K_{cw}}{1 + K_{cw}S_W}C_{CD}\right) \tag{4}$$

Because Wang and Brusseau [2] and later McCray et al. [4] did not know either the purity or degree of substitution of the HPβCD they employed in their experiments, they used Eq. (3) to determine K_{cw}. Further, they used S_A and S_w in units of mg of HOC per L and C_{CD} in units of g or kg per L. Using their approach, the units of K_{CW} for Eqs. (3) and (4) are different.

Because the occupied CD fraction is not negligible in our experiments, we use molar units for S_A, S_w, and C_{CD} and Eq. (4) for determination of K_{cw}. Therefore, our units for K_{cw} are $L^2\ mol_{HOC}^{-1}\ mol_{CD}^{-1}$. Because [G] may not be equal to S_w, we attempt to account for this in subsequent equations by reducing the size of the water fraction of solution by the amount displaced by the addition of CD.

Because the stoichiometry (host:guest ratio) is assumed to be 1:1, the moles of CD occupied is equal to the moles of PAH present as guests and the fraction of CD molecules occupied can be determined.

$$f_{GCD} = \frac{S_A - nS_w}{C_{CD}} = \frac{(E-n)}{E}\frac{S_A}{C_{CD}} \tag{5}$$

where f_{GCD} is the fraction of CD cavities occupied by a PAH and n is the volumetric fraction of water in solution. In this study, the water fraction was the same in all three CDs (79.1 % for the 300 g L^{-1} CD solution). The phase distribution of the PAH can be taken from Eq. (5) where the fraction of the total PAH present solution that is contained within cyclodextrin subphase, F_{GCD}, is given by:

$$F_{GCD} = \frac{S_A - nS_w}{S_A} = \frac{(E-n)}{E} \tag{6}$$

and the fraction of the total solution PAH present within the water subphase, F_{GW}, is given by:

$$F_{GW} = 1 - \frac{S_A - nS_w}{S_A} = \frac{n}{E} \tag{7}$$

Determination of relative chemical parameters

Table 1 lists the values for the chemical parameters used in QSPR analysis of the selected PAHs in this paper with sources provided for derived literature values. Of note, Shaw [33] reviewed published aqueous solubilities and recommended values for six of the eight PAHs in this study. Values for dibenzofuran are from Shiu et al. [34] and benzo(k)fluoranthene from De Maagd et al. [35]. Because K_{OW} is being used for QSAR relationships in this paper, values recommended by Hansch et al. [36] for that application are employed. Because they did not list a K_{OW} for benzo(k)fluoranthene, the value from De Maagd et al. [35] was selected.

Molar volume is the volume occupied by one mole of a substance at a given temperature and pressure. Molar volumes for normal boiling conditions are widely calculated using the methods developed by Le Bas [37]. Le Bas [37] assigned set volumes for certain elements and ring structures. Others, such as Schotte [38] who more precisely defined the potential volume components and included the impact of structural arrangement in the computed volumes, have expanded on this approach. The values computed for Le Bas molar volumes agree with those published in MacKay et al. [39].

Three computational chemistry techniques were used to determine polarizabilities of the test molecules. In our study, the calculated polarizabilities refer to the average isotropic polarizabilities. We used a semi-empirical quantum chemistry method (SEQC) (model: PM6), a ab initio quantum chemistry method (AIQC) (model: HF 6-31G(d)), and a density functional theory method (model: B3LYP 6-31G(d)). Spartan'10 (Wavefunction, Inc.) was used to perform the computational chemistry calculations. For more information on the underlying equations employed by this software to calculate these results see Stewart [40] for the PM6 method, Roothaan [41] and Atkins and Friedman [42] for the AIQC method, and Lee et al. [43] and Becke [44] for the DFT method. The computed polarizability values for the examined PAHs appear in Table 1.

Results and discussion

Apparent concentrations of PAHs in aqueous phases

The experimental results for apparent PAH solubilities are summarized in Table 2. Specifically, the averages of three replicates are listed with the coefficient of variation (COV). The average of the COVs is 1.6 % and the two largest values were 4.4 and 4.7 %, both for the least soluble tested PAH (benzo(k)fluoranthene) with the two lowest solubility enhancing CDs (HPαCD and HPβCD). With this low level of variability, error bars are not visible on graphs. As expected for all three tested CDs, the concentration of each target PAH in the 300 g L^{-1} CD solutions is significantly greater than their aqueous solubilities (Table 1). This

Table 1 Chemical properties of guest PAHs

Parameter	Molecular weight[a] (g mol^{-1})	Aqueous solubility (μmol L^{-1})	Log octanol water partitioning coefficient (Dim-less)	Total molecular surface area ($Å^2$)	Molar volume		Polarizability		
					Le Bas (cm^3 mol^{-1})	Schotte (cm^3 mol^{-1})	AIQC (A.U.)	DFT (A.U.)	SEQC (A.U.)
Naphthalene	128.17	242[b]	3.3[e]	155.8[f]	147.6	148.29	92.847	98.907	84.413
Acenaphthene	154.21	29.8[b]	3.92[e]	180.8[f]	173.1	169.09	111.503	118.800	98.657
Fluorene	166.22	13.4[b]	4.18[e]	194[f]	187.9	179.66	120.987	130.413	110.687
Dibenzofuran	168.2	25.1[c]	4.12[e]	176.3 [g]	173.1	178.83	113.805	123.772	110.593
Anthracene	178.23	0.269[b]	4.45[e]	202.2[f]	196.7	200.13	142.391	154.535	134.49
Fluoranthene	202.26	0.875[b]	5.16[e]	218[f]	217.3	220.93	155.146	168.539	147.16
Chrysene	228.28	0.00657[b]	5.73[e]	241[f]	250.8	251.97	180.625	199.812	171.195
Benzo(k)fluoranthene	252.31	0.00432[d]	6.11[d]	266[f]	268.9	272.77	208.254	232.486	199.472

[a] Mackay et al. [39]

[b] Shaw [33]

[c] Shiu et al. [34]

[d] De Maagd et al. [35]

[e] Hansch et al. [36]

[f] Dabestani and Ivanov (1999)

[g] Doucette and Andren [22]

finding can be explained by partitioning of PAHs into the hydrophobic CD cavity. The CD cavity provides a lower energy environment for hydrophobic (i.e. low-polarity) chemicals than water. To gain a clearer understanding of the CD solubility enhancement phenomena, solubility enhancement factors, E (dimensionless), were calculated based on the ratios of the apparent concentration in the presence, S_A (mol L^{-1}), and absence of CD, S_W (mol L^{-1}). The calculated values of E are listed in Table 2. As Blanford et al. [45] reported, these values can be employed to project the potential improvement of aquifer flushing with CD solutions over standard water flushing.

Little comparable data exists in the literature for these types of CDs with PAHs. McCray et al. [4] reported the solubility enhancement factors for several HOCs including naphthalene and anthracene in 10 % wt./vol. HPβCD solution at 21.5 °C. Wang and Brusseau [2] reported values for a several HOCs including naphthalene, anthracene, trichloroethylene, chlorobenzene and DDT for six concentrations of HPβCD between 0 and 7 % wt./vol. at 23 ± 1 °C.

Table 2 Apparent aqueous solubility of tested PAHs in 30 % CD solutions

PAHs	Aqueous solubility* (S_W) (mg L^{-1})	HPαCD		HPβCD		HPγCD	
		Apparent conc. (S_A) (mg L^{-1})	SEF (S_A/S_W)	Apparent conc. (mg L^{-1})	SEF (S_A/S_W)	Apparent conc. (mg L^{-1})	SEF (S_A/S_W)
Naphthalene	31*	1867 ± 47	60.24 ± 1.52	2166.4 ± 15.4	69.87 ± 0.50	2706 ± 38	87.28 ± 1.23
Acenaphthene	3.8*	1076 ± 15	282.3 ± 3.8	1119.6 ± 18.5	294.6 ± 4.9	1184 ± 3	311.7 ± 0.7
Fluorene	1.9*	423.6 ± 11.3	223.1 ± 6.0	443.1 ± 4.0	233.6 ± 2.1	497.7 ± 6.2	261.6 ± 3.2
Dibenzofuran	4.69^	624.5 ± 10.8	133.1 ± 2.3	657.5 ± 15.2	140.2 ± 3.2	812.2 ± 13.6	173.2 ± 2.9
Anthracene	0.062*	38.70 ± 0.13	623.8 ± 2.1	40.83 ± 0.26	658.3 ± 4.2	43.01 ± 0.17	692.8 ± 2.9
Fluoranthene	0.24*	128.8 ± 1.7	536.8 ± 7.0	147.5 ± 1.2	614.4 ± 4.9	147.8 ± 0.7	616.1 ± 2.7
Chrysene	0.0019*	6.174 ± 0.206	3244 ± 108	7.05 ± 0.05	3713 ± 28	7.837 ± 0.120	4121 ± 63
Benzo(k)fluoranthene	0.00109[+]	12.53 ± 0.560	11480 ± 514	13.18 ± 0.62	12180 ± 573	13.53 ± 0.23	12407 ± 210

± Connotes 1 standard deviation of three samples

* IUPAC recommended values (Shaw [33])

^ Shiu et al. [34]

[+] De Maagd et al. [35]

In order to make the most direct comparison, the results of these publications are rescaled using the same methods of determining K_{CW} as this paper. The values for K_{CW} in L^2 mol_{CD}^{-1} mol_{PAH}^{-1} for naphthalene for HPβCD by Wang and Brusseau [3], McCray et al. [4] and this study are 748, 959, and 386 and for anthracene are 3,456, 3,336, and 3,373, respectively (Table 3). The differences between the three studies for naphthalene are substantial, but anthracene values fall within a narrow range.

Differences between measured values of stability and partitioning coefficients arise from variation in methods. Connors [46] evaluated literature values for stability constants for underivatized α, β, and γ-cyclodextrin at 25 ± 5 °C. In his search, he found sixteen published stability constants for 4-nitrophenol with α-CD and seventeen of 4-nitrophenolate for β-CD. After dropping the highest values, he found that the remaining values were log-normally distributed with COVs of 0.043 and 0.032. In the case of naphthalene and anthracene, we only have three values, but COVs of the log K_{CW} values are 0.073 and 0.002. The final difference could arise from the salt content of the CDs. The HPβCD used in this study likely had a higher salt content (Wacker direct communication that the ash is predominantly sodium chloride) and the CD concentration used was much greater than the other studies. Salt is known to affect aqueous solubility [47]. Because a greater fraction of naphthalene is present in the aqueous phase than anthracene, differences in salt content of employed HPβCD would result in more significant differences in calculated K_{CW} values for this more soluble HOC.

Additional comparisons with the literature can be evaluated through comparisons of the fraction of HPβCD cavities associated with a guest, assuming a 1:1 association, with the aqueous solubility of the guest. A review of the literature did not reveal a similar comparison although the volume of published works on CDs is immense. Comparison of the results from the literature [2, 4, 48] and this paper show a significant log–log relationship between these two variables (Fig. 1a). On this graph, the three groups who examined multiple guests found high levels of correlation between the two variables (i.e. Wang and Brusseau [2] (0.993), McCray et al. [4] (0.891), and this paper (0.974). Despite the fact that the degree to which cyclodextrin enhances the apparent solubility of hydrophobic organic chemicals is inversely related to their aqueous solubility, the fraction of CD molecules associated with these guests under saturated conditions increases logarithmically with the logarithm of the potential guest's aqueous solubility.

Molar volume and polarizability computational results

Table 1 shows the calculated molar volumes of the PAHs used in this study determined by both the Le Bas and Schotte methods. The values computed for Le Bas molar volumes agree with those published in MacKay et al. [39] and the difference between the two are within ±4.4 %.

Table 3 Water/CD partitioning coefficients, fraction of PAH in aqueous phase, fraction of CD occupied with a PAH under saturated conditions

PAHs	Water/CD partitioning coefficient (K_{cw}: L^2 mol_{CD}^{-1} mol_{PAH}^{-1})			Fraction of PAH in aqueous phase for 300 g L^{-1} CD solutions			Fraction of CD occupied with a PAH under saturated conditions		
	HPαCD	HPβCD	HPγCD	HPαCD	HPβCD	HPγCD	HPαCD (%)	HPβCD (%)	HPγCD (%)
Naphthalene	261.3	386.0 748[◇], 959[‡]	542.2	1.29E−2	1.11E−2 2.64E−2[◇], 1.48E−2[‡]	9.06E−3	5.97	8.57 15.43[◇], 18.91[‡]	11.62
Acenaphthene	1,205.9	1,563	1,803	2.75E−3	2.64E−3	2.54E−3	2.89	3.71	4.26
Fluorene	931.3	1,209	1,472	3.49E−3	3.33E−3	3.02E−3	1.05	1.36	1.66
Dibenzofuran	556.4	728.2	983	5.85E−3	5.56E−3	4.57E−3	1.53	1.99	2.67
Anthracene	2,586	3,373 3,456[◇], 3,336[‡]	3,848	1.25E−3	1.18E−3 4.98E−3[◇], 3.50E−3[‡]	1.14E−3	0.090	0.117 0.120[◇], 0.116[‡]	0.134
Fluoranthene	2,229	3,156	3,431	1.45E−3	1.27E−3	1.28E−3	0.264	3.73	0.406
Chrysene	13,460	19,030	22,890	2.40E−4	2.10E−4	1.92E−4	0.0112	0.0158	0.0191
Benzo(k)fluoranthene	47,640	61,950	68,940	6.78E−5	6.45E−5	6.38E−5	0.0206	0.0268	0.0298

Wang and Brusseau [2] used HPβCD concentration between 0 and 7 % wt./vol. at 23 ± 1 °C. They reported molecular weight of 1500 and their purity projected at 98 % (wt./wt.) based on discussion with supplier. McCray et al. [4] used 10 % wt./vol. HPβCD solution at 21.5 °C with a reported purity is 98.7 % with the average molecular weight average molecular weight of 1,460 projected from discussions with supplier

[◇] Calculated from results of Wang and Brusseau [2] and from [‡] McCray et al. [4]

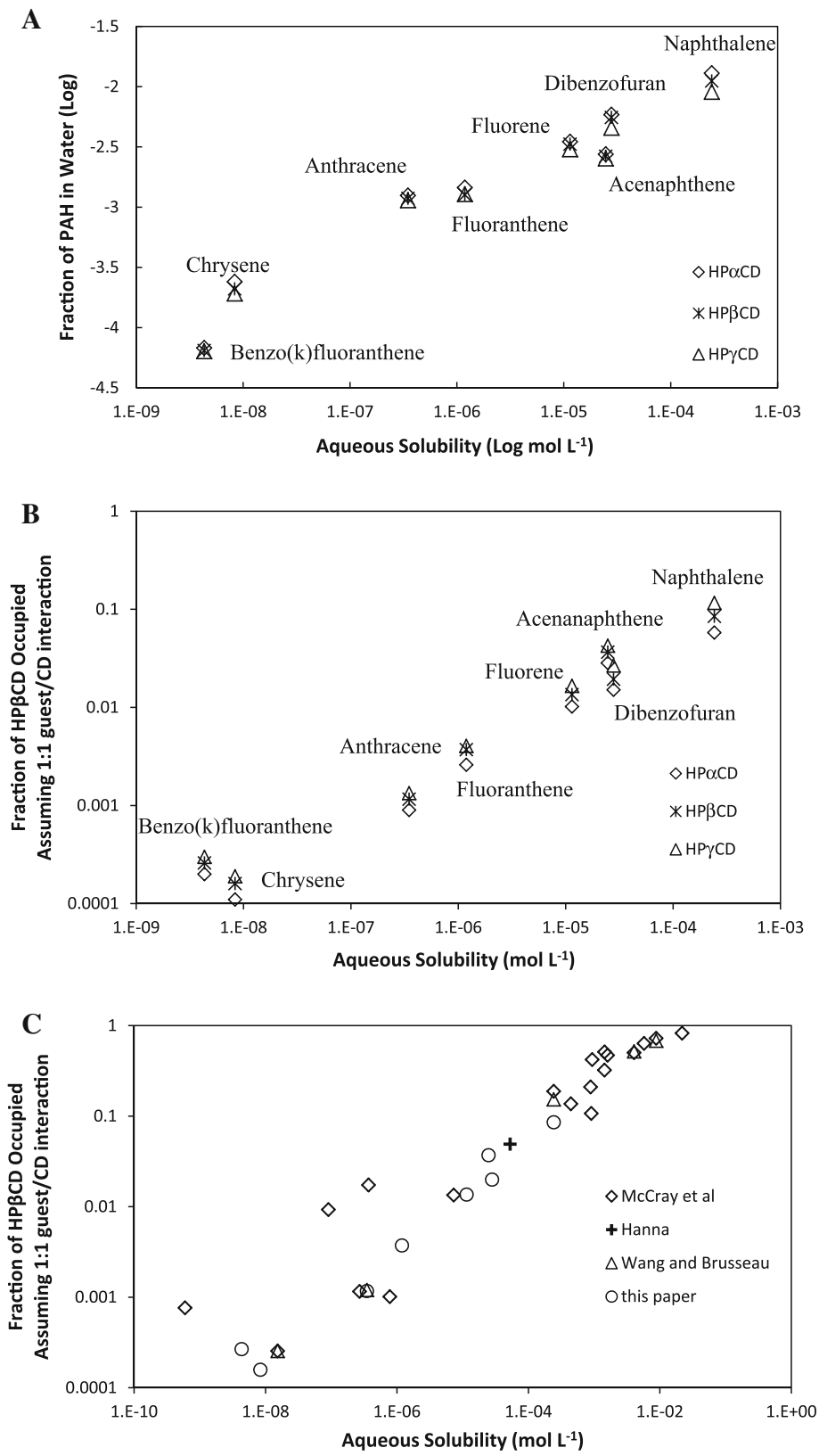

Fig. 1 Guest chemical aqueous solubility correlation with PAH fraction in the water phase **a** (HPαCD (◇); HPβCD (×); HPγCD (△)). **b** Correltation with fraction of HPβCD associated with a guest PAH under saturated conditions (HPαCD (◇); HPβCD (×); HPγCD (△)). **c** Correlation with fraction of HPβCD associated with a guest under saturated conditions (this paper (○); McCray et al. [4] (◇); Wang and Brusseau [2] (△); Hanna et al. [48] (+))

Regarding polarizability, there are some differences between the three sets of computed values, but these differences are fairly consistent. As can been seen in Table 1, the SEQC method produced the lowest computed values and DFT the highest. The average normalized difference between the three models and the average of the

three computational methods is 0.055 with a COV of 0.577 and a maximum of 0.100.

QSPR results for correlation of K_{cw} with selected chemical parameters

For the subject PAHs and CDs, significant levels of correlations are found between the log of K_{cw} and linear values of the PAH molecular weight, molar volumes, total molecular surface area, and polarizability along with the log aqueous solubility and octanol/water partitioning coefficients. Table 4 shows QSPR correlation using linear regression (rsq, slope, and intercepts). In this analysis, log K_{CW} is held as the independent variable. Among the nine sets being compared, K_{OW} and molecular weights are the least correlated and TSA and the results of the two non-empirical polarizability models (AIQC and DFT) were the most correlated.

From the computed values of the slopes, it is apparent that only aqueous solubility is inversely correlated with K_{CW}. This observation can be readily understood because hydrophobic forces are largely responsible for potential guests being associated with CD cavities. Additional inspection of the slopes shows relatively little difference between the three CDs (maximum COV is 0.0095). Conversely, the intercepts were strongly related to CD cavity volume. Saenger et al. [49] reported the cavity volumes of αCD, βCD, and γCD respectively as 174, 262, and 472 $Å^3$ $molecule^{-1}$ and rescaled into units of L^3 mol^{-1} are 0.1048, 0.1578, and 0.2842. Linear regression between CD cavity size and the intercepts of the nine parameters with log K_{CW} had high levels of correlation (rsq ranged between 0.972 and 0.978). Beyond statistical correlations, it is interesting to evaluate the relationship between CD cavity sizes and these intercepts. With the exception of aqueous solubility which has an inverse relationship, the intercept values decrease with cavity size. This implies for each parameter that accessibility for guests increases with the volume of the CD cavity because each of the properties increases with PAH size.

In the QSPRs for K_{CW}, acenaphthene was commonly the least correlated. When considering all 27 data sets, the computed value from the slope and intercept over predicted the parameter values for this PAH by 4–20 %. One of the strengths of QSPR analysis is that it permits quantitative analysis of chosen parameter values. The originally employed value for the aqueous solubility of acenaphthene was 3.8 mg L^{-1} which resulted in an average correlation (rsq) of 0.940. Optimization improved the average rsq to 0.962 with the S_w of this PAH to 8.2. In comparison, the average of ten aqueous solubilities of acenaphthene at 25 °C published since 1972 [39] is 4.1 mg L^{-1} with a maximum value of 7.37.

QSPR relationship between PAH phase distribution and selected chemical parameters

Equations (6) and (7) permit an analysis of the fractions of each PAH within the water and CD phases. These fractions are function of the concentration of CD, but are independent of the degree of guest saturation. Table 4 also provides the results of QSPR analysis of the degree of correlation of the nine chemical parameters with the log of the fraction of PAH in the aqueous phase for 300 g L^{-1} CD solutions. Due to the relation of Eq. (4) with (6) and (7) the results of linear regression are similar. Specifically, the rsq values are only 0.001–0.006 greater for the fraction of PAH in the water phase. Since the fraction of the potential guest PAH present within the water phase, F_{GW}, and K_{cw} have the opposite mathematical relationship to the enhancement factor, the slopes of QSPR analysis are opposite in sign, but similar in absolute value (i.e. F_{GW} slopes are relatively greater by only 2.00–2.016 %). While there is a trend in the slopes and intercepts of QSPR analysis of F_{GW} among the three CDs, it is difficult to assign those differences to the size of the CD cavities. That is because the differences in CD molecular weights inhibit using the same CD molar concentrations and aqueous fractions of solution.

The real value of F_{GW} is the insight it provides into the causes of phase distribution. The contribution of hydrophobic interactions to the formation of CD-HOC complexes can readily be seen in the direct relationship between PAH aqueous solubility and the fraction of the PAHs present outside of the CD cavities (Fig. 1a). Figure 1a shows that for all three CDs the fraction of PAH mass present in the water phase unassociated with the CD cavities increases in a log–log relationship with the guest aqueous solubility (rsqs 0.949–0.954).

QSPR correlation between chemical parameter and the logarithm of the fraction of cd molecules occupied

Because S_A is a linear function of the concentration of CD, the fraction of CD molecules occupied by a guest compound is independent of CD concentration. As a result, even though the CD solutions used in this study and others mentioned herein were from experiments with different concentrations, comparisons can be aptly made between the fraction of CD associated with a guest and the other chemical parameters. Figure 1b shows the fraction of the three CD from this study that are associated with a guest PAH and the aqueous solubility of those guests. As can be seen in this figure, there is a log–log relationship between aqueous solubility and the ratio of guest to CD molecules under saturated conditions (rsqs 0.972–0.977 Table 4).

Table 4 Correlation of chemical parameter with CD/PAH distribution parameters

Chemical parameters	Molecular wt.	Aqu. sol.	K_{ow}	Surface area	Le Bas	Schotte	AIQC	DFT	SEQC
Degree of correlation between chemical parameter and logarithm of the water/CD partitioning coefficient									
Correlation coefficient (RSQ)									
HPαCD	0.915	0.947	0.903	0.955	0.945	0.932	0.956	0.956	0.933
HPβCD	0.918	0.950	0.909	0.957	0.949	0.938	0.960	0.960	0.938
HPγCD	0.916	0.950	0.904	0.950	0.947	0.937	0.958	0.959	0.937
Slope of linear regression									
HPαCD	52.58	−2.26	1.23	47.76	54.31	55.98	51.51	59.58	50.87
HPβCD	52.96	−2.28	1.24	48.08	54.76	56.49	51.93	60.07	51.29
HPγCD	54.82	−2.36	1.29	49.63	56.64	58.49	53.71	62.18	53.11
Intercept of linear regression									
HPαCD	8.72	1.76	0.49	44.39	20.12	15.33	−31.74	−46.04	-38.19
HPβCD	0.55	2.11	0.29	37.03	11.47	6.25	−39.93	−55.51	-46.30
HPγCD	−10.34	2.58	0.04	27.65	0.36	−5.44	−50.46	−67.89	-56.92
Degree of correlation between chemical parameter and logarithm of the fraction of PAH in the water phase									
Correlation coefficient (RSQ)									
HPαCD	0.918	0.949	0.905	0.957	0.946	0.934	0.957	0.957	0.935
HPβCD	0.921	0.953	0.912	0.960	0.952	0.941	0.962	0.962	0.940
HPγCD	0.922	0.954	0.910	0.954	0.951	0.941	0.961	0.962	0.941
Slope of linear regression									
HPαCD	−52.32	2.25	−1.23	−47.50	−54.02	−55.68	−51.23	−59.25	−50.60
HPβCD	−52.53	2.26	−1.23	−47.67	−54.28	−56.00	−51.47	−59.52	−50.84
HPγCD	−54.17	2.33	−1.27	−49.01	−55.92	−57.74	−53.00	−61.35	−52.42
Intercept of linear regression									
HPαCD	36.49	0.56	1.14	69.67	48.87	44.94	−4.46	−14.47	−11.28
HPβCD	34.01	0.67	1.08	67.49	46.16	42.03	−6.98	−17.38	−13.80
HPγCD	27.36	0.95	0.93	61.87	39.44	34.94	−13.30	−24.84	−20.23
Degree of correlation between chemical parameter and logarithm of the fraction of CD molecules occupied									
Correlation coefficient (RSQ)									
HPαCD	0.846	0.972	0.854	0.853	0.877	0.887	0.882	0.880	0.883
HPβCD	0.849	0.974	0.854	0.856	0.878	0.887	0.883	0.881	0.884
HPγCD	0.854	0.977	0.861	0.866	0.884	0.892	0.890	0.887	0.889
Slope of linear regression									
HPαCD	−37.11	1.68	−0.88	−33.13	−38.39	−40.07	−36.30	−41.94	−36.31
HPβCD	−37.19	1.69	−0.88	−33.22	−38.46	−40.12	−36.37	−42.03	−36.38
HPγCD	−36.58	1.66	−0.87	−32.75	−37.84	−39.44	−35.80	−41.34	−35.77
Intercept of linear regression									
HPαCD	92.81	−1.65	2.44	122.20	106.82	103.44	50.76	49.50	42.13
HPβCD	97.35	−1.86	2.55	126.22	111.58	108.46	55.25	54.67	46.62
HPγCD	101.65	−2.06	2.65	129.87	115.97	113.12	59.37	59.50	50.84

Closer inspection of Fig. 1b and the values within Table 3 show that the ratio of guest to CD increases with the size of the CD cavity. While hydrophobic forces inhibit aqueous solubility and drive potential guest compounds into the CD cavities, the relative ease with which guest compounds associate with the cavities potentially decreases due to relative size of the compound to the CD cavity and the number of water molecules within the CD cavity that must be displaced upon partially entering the cavity.

To provide context for the literature values, Fig. 1c shows the saturated guest/CD ratio results for HPβCD for this study along with those of Wang and Brusseau [2], McCray et al. [4], and Hanna et al. [48]. Because Fig. 1c is plotted with log axes three of the least correlated guest

compounds can be seen. Specifically, these HOC are all long chain alkanes from McCray et al. [4], decane, undecane, and octadecane. Including those three points results in an rsq of 0.918, but when they are excluded the remaining thirty-two points have an rsq of 0.980. While there are only three members of this subgroup, internally their correlation between log f_{GCD} and log S_w is significant (0.9996). Thus, this implies homologous guest/CD interactions for these long chain alkanes.

Molecular size effects on guest/cd interactions

Figure 2 more closely examines effects of the relative sizes of the CD cavity and the size of the potential guest compounds on their interactions. In this figure, the molar volumes of the target PAHs, determined by the Schotte method, are normalized by the CD cavity volume derived from Saenger et al. [49] and compared to the log of the relative fraction of CDs occupied with a guest. As can be seen, the guest to CD cavity volume ratios correlate fairly well with the occupation ratios (rsqs 0.887–0.892). Further, the plot specifically shows for all three CDs, the fraction of CD cavities associated with that PAH is inversely related to the size of the guest. From the relative slopes of the three CDs in Fig. 2, the implied affect of the guest's size resulting in a lower propensity to associate with the CD cavity appears to be lessened as the width of the CD ring increases.

Polarizability and correlation with guest/CD interactions

As discussed previously, the computed values of polarizability were found to be inversely correlated with the log of the aqueous solubility of guest PAHs. Because aqueous solubilities are by definition (i.e. guest/CD distribution equations) related to equilibrium distribution of the PAHs between the water and CD phases, significant correlations with these parameters and the calculated polarizabilities are expected. Figure 3 shows the strong inverse correlations between the results of the three polarizability models and the log of the calculated fraction of PAHs in the water phase for HPβCD. The semi-empirical method was the least correlated (rsq 0.940) while the non-empirical methods showed the same slightly higher level of correlation (0.962).

Within the results (Fig. 3), the values for acenaphthene, fluoranthene, and dibenzofuran are the most poorly correlated. As stated previously, the results for acenaphthene and fluoranthene were found to least relate to the chemical properties and this was most likely due to the chosen value of aqueous solubility. The fact that the structure of dibenzofuran is the least homologous to the other PAHs examined in this study may partially explain its relatively poor agreement. Based on the trends in Fig. 3, the computed polarizability would project a lower fraction of dibenzofuran being present outside of the CDs. This poor correlation could be an artifact of the oxygen moiety within this PAH reducing its polarizability relative to the similarly shaped molecule fluorene. Future studies may use molecular modeling to more qualitatively evaluate the effect of polar moieties on the preferred orientations and the energies of guest/CD cavities associations.

While QSPR analysis of polarizability with the non-CD related parameters is not a primary focus of this study, we have found similar high levels of correlations with the other parameters (Table 5). These levels of correlation imply that all of these chemical parameters will likely have similar levels of alignment with water/CD partitioning coefficients and the other CD parameters.

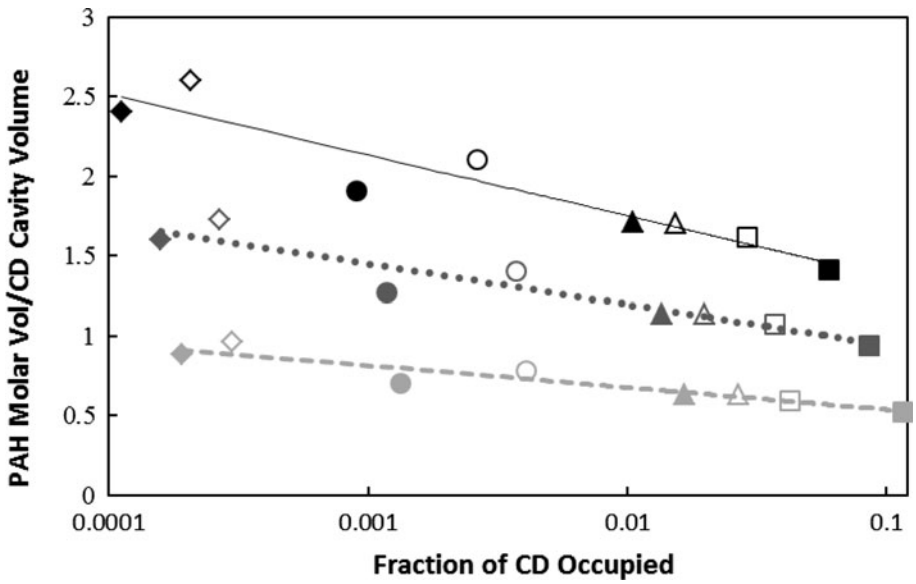

Fig. 2 Comparison of the logarithm of the fraction of CD cavities associated with a PAH guest under saturated conditions to the ratio of guest PAH molar volume (using the method of Schotte [38]) to the CD cavity volume determined by Saenger et al. [49]: HPαCD (*black with solid regression line*); HPβCD (*dark gray dotted regression line*); HPγCD (*light gray dashed regression line*); Naphthalene (■); Acenaphthene (□); Fluorene (▲); Dibenzofuran (△); Anthracene (●); Fluoranthene (○); Chrysene (◆); Benzo(k)fluoranthene (◇)

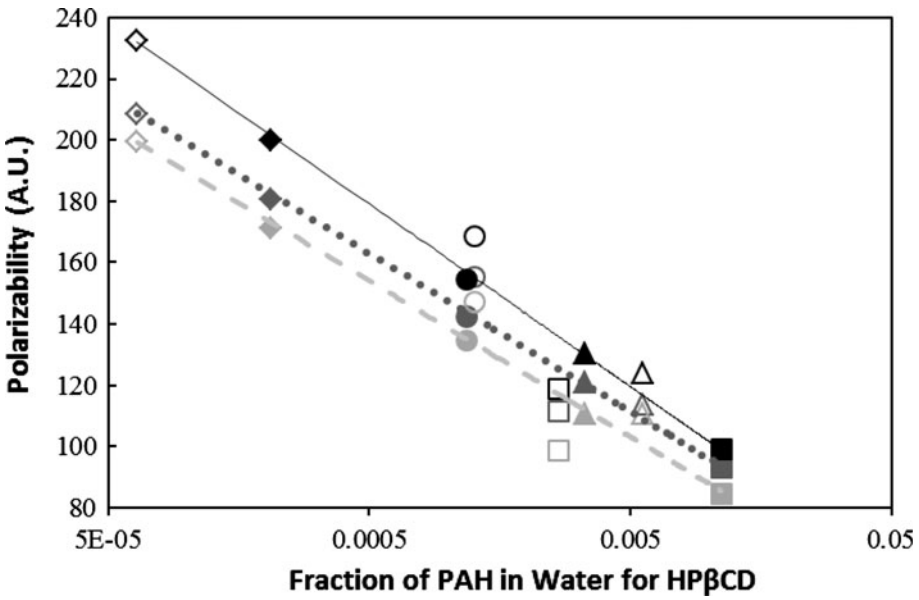

Fig. 3 Comparison of the PAH fraction in the water phase and the calculated polarizability of target PAHs: SEQC (*black symbols with solid regression line*); AIQC (*dark gray dotted regression line*); DFT (*light gray dashed regression line*); Naphthalene (■); Acenaphthene (□); Fluorene (▲); Dibenzofuran (△); Anthracene (●); Fluoranthene (○); Chrysene (◆); Benzo(k)fluoranthene (◇)

Table 5 Degree of correlation between chemical parameter and polarizability model results

Parameter	Molecular weight	Aqu. sol.	Octanol/water part. coef.	Total molecular surface area	Molar volume	
Chemical parameter format	Linear	Log	Log	Linear	Le Bas Linear	Schotte Linear
AIQC	0.977	0.949	0.973	0.985	0.991	0.961
DFT	0.978	0.948	0.972	0.984	0.992	0.957
SEQC	0.982	0.940	0.973	0.975	0.992	0.936

Conclusions

The addition of hydroxypropyl substitution of α, β, and γ CDs greatly increases the apparent solubility of eight common PAHs in water. For these compounds, the propensity of a PAH to associate with these CD derivatives increased with width of the CD ring. Quantitative analysis found strong correlations between structural properties of the guests and water/CD partitioning coefficients, phase distribution of the PAH between water and CD phases, and the fraction of CD molecules occupied with a guest PAH. Noteworthy among these, is the log–log relationship between aqueous solubility and the fraction of CD molecules associated with a guest organic compound.

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