

A thermodynamic analysis of quantitative structure-activity relationships for hydrophobic organic chemicals

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ABSTRACT

An experimental analysis is presented of the molecular interactions controlling the activity and solubility of chlorinated dibenzo-*p*-dioxins (PCDDs) in water. For this purpose, the enthalpy, entropy and free-energy contributions of fusion, vaporization, solvation and aqueous solution are determined. It is shown that, due to enthalpy-entropy compensation in the water, the solvation of hydrophobic organic chemicals in water is independent of molecular size, total surface area or molar volume. The observed relationship between the aqueous solubility and molar volume (or total surface area) is caused by the phenomenon that, with increasing molar volume, molecules require more energy to leave the pure (subcooled liquid) phase. This suggests that the relationship between aqueous solubility and molecular structure, and, consequently, many quantitative structure-activity relationships (QSARs) for hydrophobic organic substances, reflect molecular interactions between the solute molecules in the pure subcooled liquid phase rather than solute-water interactions.

INTRODUCTION

Quantitative structure-activity relationships (QSARs) are based on the premise that one or several molecular properties control either the chemical's concentration or the chemical's activity (e.g. toxicity) at the site of (toxic) action. For example, it has been shown repeatedly that toxic effects, such as acute and chronic lethality, of non-reactive organic substances in aquatic organisms are related to the chemical's hydrophobicity, which is usually expressed by the 1-octanol-water partition coefficient or the chemical's aqueous solubility. Various molecular properties such as total surface area (TSA) [1-7], molecular volume (TMV) [2, 6, 8], molar volume [9-13],

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molecular weight [3, 13, 14], solvatochromic parameters [15, 16] and molecular connectivity [17-21] have been proposed to express or correlate the chemical's hydrophobicity, aqueous solubility and lipid-water or 1-octanol-water partitioning tendency. However, the observed correlations are often limited to chemically related compounds or to homologous series and they do not have a general applicability. Consequently, there is a considerable debate about the choice of molecular descriptor(s) in QSARs, and the bases of the actual structure-activity relationship are often empirical rather than mechanistic considerations.

Preferably, the QSAR should be based on an understanding of the role of those molecular characteristics that cause the actual (toxic) response. In the aquatic toxicology of simple hydrophobic organic chemicals, this often pertains to the molecular phenomena controlling the chemical's activity or fugacity in the water. To explore, experimentally, the molecular phenomena controlling the activity of hydrophobic organic chemicals in water, a thermodynamic analysis of the aqueous solution process of chlorodibenzo-*p*-dioxins (PCDDs) is presented. The PCDDs represent a group of hydrophobic organic chemicals ranging in aqueous solubility over seven orders of magnitude [22], thus providing the opportunity to investigate the structure-activity relationships of hydrophobic organic chemicals.

THEORY

The essence of the thermodynamic analysis is to separate the molecular interactions controlling aqueous solubility into the interactions between (i) solute and water molecules and (ii) between solute and solute molecules, by viewing the solution of a chemical in water as the sum of two processes. First, the chemical in a (subcooled) liquid state enters the gas phase, i.e. vaporization. Second, the chemical in the gas phase is incorporated into the water matrix, i.e. solvation. This is illustrated in Fig. 1. The molar Gibbs free energy of solution ($\Delta G_{s,i}$) can thus be treated as the sum of the molar Gibbs free energy of vaporization ($\Delta G_{v,i}$) and the molar Gibbs free energy of solvation ($\Delta G_{sv,i}$), i.e.

$$\Delta G_{s,i} = \Delta G_{v,i} + \Delta G_{sv,i} \quad (1)$$

Similarly, the enthalpy ($\Delta H_{s,i}$) and entropy of solution ($\Delta S_{s,i}$) can be treated as the sum of, respectively, the enthalpies and entropies of vaporization, i.e. $\Delta H_{v,i}$ and $\Delta S_{v,i}$, and the enthalpies and entropies of solvation, i.e. $\Delta H_{sv,i}$ and $\Delta S_{sv,i}$, i.e.

$$\Delta H_{s,i} = \Delta H_{v,i} + \Delta H_{sv,i} \quad (2)$$

$$\Delta S_{s,i} = \Delta S_{v,i} + \Delta S_{sv,i} \quad (3)$$

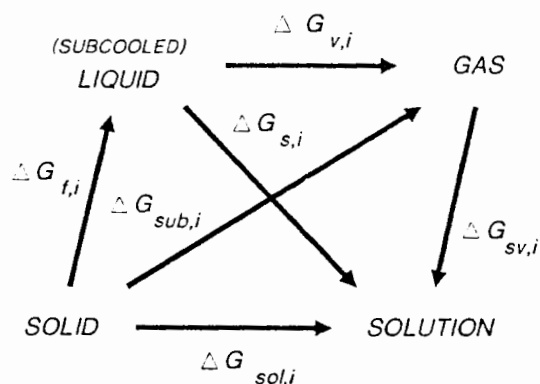


Fig. 1. Thermodynamic cycle for the solution process, showing the free energy contributions of vaporization ($\Delta G_{v,i}$), solvation ($\Delta G_{s,i}$), solution of the (subcooled) liquid solute ($\Delta G_{sub,i}$), sublimation ($\Delta G_{f,i}$) and solution of the solid solute ($\Delta G_{sol,i}$).

The molar Gibbs free energy of vaporization reflects the interactions controlling the transfer of the solute molecules from the pure (subcooled) liquid phase to the gas phase. The free energy of solvation represents the molecular interactions between the solute and water molecules. Equations (1)–(3) illustrate that it is possible to evaluate the role of solute–solute and solute–solvent interactions in the aqueous solution process if, in addition to the molar Gibbs free energy of solution, the molar Gibbs free energy of vaporization and/or solvation are known. To derive these thermodynamic properties from experimental data such as aqueous solubilities and vapour pressures, it is necessary to briefly review the thermodynamics of the solution, vaporization and solvation processes.

Solubility

The solubility of a chemical in water is generally viewed as an equilibrium partitioning process between the pure chemical phase and the chemical present as solute in solution. The total Gibbs free energy of mixing per mole of solution resulting from the transfer of solute into a solvent (Δg_{mix}), assuming non-ideal solution behaviour, is [22, 23]:

$$\Delta g_{mix} = x_w \cdot RT \cdot \ln a_w + x_{i,w} \cdot RT \cdot \ln a_{i,w} \quad (4)$$

where x_w and $x_{i,w}$ are the mole fractions (mol mol^{-1}) of respectively the water and chemical i in aqueous solution, and a_w and $a_{i,w}$ are the activities of the water and of the chemical i in aqueous solution. R is the gas constant ($8.314 \text{ J mol}^{-1} \text{ K}^{-1}$) and T is temperature (K). The activity a can also be expressed as f/f^R , where f is the chemical's fugacity and f^R is the fugacity of the pure chemical at a defined standard state, which is generally the fugacity

of the pure chemical in an actual or subcooled liquid state f^L at the system's temperature [23]. It is also defined as the product of the mole fraction solubility, x (mol mol^{-1}), and the activity coefficient γ , i.e. a or $f/f^R = x \cdot \gamma$, such that [23, 24]:

$$a_w = f_w/f_w^R = x_w \cdot \gamma_w \quad (5)$$

$$a_{i,w} = f_{i,w}/f_{i,w}^R = x_{i,w} \cdot \gamma_{i,w} \quad (6)$$

The activity coefficient, γ , is defined on a Raoult's Law basis such that when x approaches 1.0, γ approaches 1.0 and the activity a also approaches 1.0. Equation (4) can thus be rewritten as:

$$\begin{aligned} \Delta g_{\text{mix}} = & x_{i,w} \cdot RT \cdot \ln x_{i,w} + x_{i,w} \cdot RT \cdot \ln \gamma_{i,w} + x_w \cdot RT \cdot \ln x_w \\ & + x_w \cdot RT \cdot \ln \gamma_w \end{aligned} \quad (7)$$

The Gibbs free energy of mixing, Δg_{mix} , can also be expressed as the sum of the ideal Gibbs free energy of mixing, Δg^I , and the excess Gibbs free energy of mixing, Δg^E , such that $\Delta g_{\text{mix}} = (\Delta g^I + \Delta g^E)$, where [24]:

$$\Delta g^I = x_{i,w} \cdot RT \cdot \ln x_{i,w} + x_w \cdot RT \cdot \ln x_w \quad (8)$$

$$\Delta g^E = x_{i,w} \cdot RT \cdot \ln \gamma_{i,w} + x_w \cdot RT \cdot \ln \gamma_w \quad (9)$$

It is generally believed [2-7, 9, 10, 23, 24] that, for the very dilute solutions of hydrophobic organic chemicals in water, the term $x_w \cdot RT \cdot \ln \gamma_w$ in Eqn (9) can be ignored with respect to $x_{i,w} \cdot RT \cdot \ln \gamma_{i,w}$. When the excess free energy change is then expressed on a partial molar basis as ΔG^E , i.e. the excess free energy change per mole of solute, Eqn (9) simplifies to:

$$\Delta G^E = \Delta g^E/x_i = \Delta G_{s,i} = RT \cdot \ln \gamma_{i,w} \quad (10)$$

In the environmental and pharmaceutical literature the excess free energy change per mole of solute (ΔG^E) is often referred to as the molar Gibbs free energy of solution, $\Delta G_{s,i}$.

Equation (10) provides the thermodynamic framework of the solution process for very dilute solutions of hydrophobic organic chemicals. We will now demonstrate how the molar Gibbs free energy of solution and the activity coefficient of dioxin congeners, which are solids at normal experimental temperatures, can be derived from solubility measurements.

Solubility of solid solutes

For an aqueous solution of chemical i in equilibrium with pure chemical i in a solid state, the fugacity of chemical i in aqueous solution, i.e. $f_{i,w}$ or $x_{i,w} \cdot \gamma_{i,w} \cdot f_i^L$, equals the fugacity of chemical i in the pure solid state, i.e. $f_{i,s}$. $f_{i,s}$ can be expressed as $x_{i,s} \cdot \gamma_{i,s} \cdot f_i^s$, where f_i^s is the fugacity of the pure chemical

in the solid state [23, 24]. It thus follows that for the aqueous solution at equilibrium:

$$f_{i,w} = x_{i,w} \cdot \gamma_{i,w} \cdot f_i^L = x_{i,i} \cdot \gamma_{i,i} \cdot f_i^s = f_{i,i} \quad (11)$$

Assuming negligible solubility of water in the solid phase, it follows that $x_{i,i}$ and $\gamma_{i,i}$ are approximately unity such that Eqn (11) simplifies to:

$$\gamma_{i,w} = (f_i^s/f_i^L)/x_{i,w} \quad (12)$$

where f_i^L is the fugacity of the pure chemical in the subcooled liquid state [23, 24]. The fugacity ratio (f_i^L/f_i^s) can be related to the molar Gibbs free energy of fusion $\Delta G_{f,i}$ as [23, 24]:

$$\Delta G_{f,i} = RT \cdot \ln (f_i^L/f_i^s) \quad (13)$$

For solid solutes, $x_{i,w}$ can then be expressed as:

$$\Delta G_{sol,i} = \Delta G_{f,i} + \Delta G_{s,i} = -RT \cdot \ln x_{i,w} \quad (14)$$

where $\Delta G_{sol,i}$ is the molar Gibbs free energy of solution of the solid chemical i , which is the sum of the free energies of fusion ($\Delta G_{f,i}$) and solution of the subcooled liquid ($\Delta G_{s,i}$).

$\Delta G_{f,i}$ can be expressed as the sum of the molar enthalpy of fusion, $\Delta H_{f,i}$, and $-T \cdot \Delta S_{f,i}$, where $\Delta S_{f,i}$ is the molar entropy of fusion. $\Delta H_{f,i}$ and $\Delta S_{f,i}$ are often expressed as:

$$\Delta H_{f,i} = \Delta H_{f,i}^M + \Delta c_p \cdot (T - T_M) \quad (15)$$

$$\Delta S_{f,i} = \Delta S_{f,i}^M + \Delta c_p \cdot \ln (T/T_M) \quad (16)$$

where $\Delta H_{f,i}^M$ and $\Delta S_{f,i}^M$ are, respectively, the molar enthalpy and entropy of fusion at the melting point T_M , and Δc_p is the difference in heat capacity between the subcooled liquid and solid forms of the solute, thus assuming that Δc_p is constant over the temperature range from T to T_M .

If Eqns (15) and (16) are substituted into Eqn (13), and since $\Delta S_{f,i}^M = \Delta H_{f,i}^M/T_M$, it follows that the molar Gibbs free energy of fusion can be expressed as:

$$\begin{aligned} \Delta G_{f,i}/RT = \ln (f_i^L/f_i^s) = & [\Delta H_{f,i}^M(1/T - 1/T_M)] \\ & - [(\Delta c_p/R) \cdot (T_M/T - 1)] + [(\Delta c_p/R) \cdot \ln (T_M/T)] \end{aligned} \quad (17)$$

If the experimental temperature, T , and the chemical's melting point, T_M , are not far apart, the two right-hand terms in Eqn (17) (containing Δc_p) are small compared with the left-hand term and even have the tendency to compensate each other [24], thus giving:

$$\Delta G_{f,i}/RT = \ln (f_i^L/f_i^s) = (\Delta H_{f,i}^M/R) \cdot (1/T - 1/T_M) \quad (18)$$

which, in essence, assumes that $\Delta c_p = 0$; i.e. the enthalpy of fusion is independent of temperature.

It has been argued that if T and T_M are far apart, such as for many high K_{OW} chemicals, the two right-hand terms in Eqn (17) may not be ignored with respect to the third term [25, 26]. The enthalpy of fusion is thus dependent on temperature. In that case, a reliable value for Δc_p is necessary to calculate the solute's activity accurately. Since Δc_p values are not readily available and difficult to measure it has been suggested that $\Delta S_{f,i}^M$ or $\Delta H_{f,i}^M/T_M$ is a satisfactory estimate for Δc_p [24-28], thus giving:

$$\Delta G_{f,i} = \ln(f_i^L/f_i^s) = (\Delta H_{f,i}^M/RT) \cdot \ln(T/T_M) \quad (19)$$

It thus appears that there are two possible expressions for $\Delta G_{f,i}$ and thus two equations relating $x_{i,w}$ to $\gamma_{i,w}$, depending on the estimated value for Δc_p , i.e.

$$\ln x_{i,w} = -[\Delta H_{f,i}^M \cdot (1 - (T/T_M))/RT - \ln \gamma_{i,w}] \quad (20)$$

when Δc_p is assumed to be zero and

$$\ln x_{i,w} = -[\Delta H_{f,i}^M \cdot \ln(T_M/T)/RT - \ln \gamma_{i,w}] \quad (21)$$

when Δc_p is assumed to be $\Delta S_{f,i}^M$.

For the PCDDs, $\Delta H_{f,i}^M$ and $\Delta S_{f,i}^M$ at 25°C have been derived from experimental data by Rordorf [29] and T_M has also been measured. It thus follows that $\Delta G_{s,i}$ and $\gamma_{i,w}$ of the PCDDs can be derived from Eqns (20) or (21). Which equation should be used is presently the subject of some controversy [26, 30]. However, as we will discuss later, the experimental data indicate which equation applies.

Temperature dependence of the solubility

The molar enthalpy ($\Delta H_{s,i}$ or $\Delta H_{sol,i}$) and entropy ($\Delta S_{s,i}$ or $\Delta S_{sol,i}$) of aqueous solution can be determined by measuring the temperature dependence of the aqueous solubility. This is demonstrated by substituting the Gibbs function into Eqn (14):

$$\ln x_{i,w} = [-(\Delta H_{sol,i}/R) \cdot 1/T] + (\Delta S_{sol,i}/R) \quad (22)$$

$\Delta H_{sol,i}$ can thus be derived from the slope, and $\Delta S_{sol,i}$ from one intercept, of the $\ln x_{i,w}$ versus $1/T$ plot. $\Delta H_{s,i}$ and $\Delta S_{s,i}$ by subtracting, respectively, $\Delta H_{f,i}$ and $\Delta S_{f,i}$.

Vaporization

The molar Gibbs free energy of vaporization ($\Delta G_{v,i}$) can be determined from the vapour pressure, p_i , of the pure chemical, i.e. for the solid dioxin

congeners:

$$\Delta G_{v,i} = -RT \cdot \ln p_i - \Delta G_{f,i} \quad (23)$$

As demonstrated earlier, $\Delta G_{f,i}$ can be represented by Eqn (18) or (19), depending on the estimate of Δc_p . If the vapour pressure is measured at various temperatures, it is possible to derive the enthalpies and entropies of the vaporization process. For the solid dioxin congeners, substitution of the Gibbs function into Eqn (23) gives:

$$\ln p_i = [-(\Delta H_{vap,i}/R) \cdot 1/T] + (\Delta S_{vap,i}/R) \quad (24)$$

which demonstrates that the enthalpy of vaporization, $\Delta H_{vap,i}$, can be derived from the slope, and the entropy of vaporization, $\Delta S_{vap,i}$, from the intercept, of the $\ln p_i$ versus $1/T$ plot. The enthalpy and entropy of vaporization of the subcooled liquid, i.e. respectively $\Delta H_{v,i}$ and $\Delta S_{v,i}$, then follow by subtracting, respectively, $\Delta H_{f,i}$ and $\Delta S_{f,i}$.

RESULTS

The enthalpies ($\Delta H_{sol,i}$) and entropies of solution ($\Delta S_{sol,i}$) of the PCDD congeners were derived from reported aqueous solubilities [22, 31, 32] at various temperatures. They were determined from, respectively, the slope and the intercept of the $\ln x_{i,w}$ vs $1/T$ plot according to Eqn (22) and are listed in Table 1. Correlation coefficients (r) of linear regression were ≥ 0.985 except for 1,2,3,4-T₄CDD ($r = 0.977$) and 1,2,3,4,6,7,8-H₇CDD ($r = 0.971$). For 1,2,3,4-T₄CDD the $\ln x_{i,w}$ vs $1/T$ relationship shows a tendency to curve in a similar fashion as has been observed for PCBs [25, 26], suggesting a temperature dependence of the enthalpy of solution. However, due to the experimental error in the solubility measurements, this rather small deviation from linearity cannot be considered significant at the 95% probability level ($p < 0.05$). Considering the experimental error, $\Delta H_{sol,i}$ and $\Delta S_{sol,i}$ thus appear to be independent of temperature. Consequently, (i) $\Delta H_{f,i}$ and $\Delta S_{f,i}$ are approximately constant with temperature, (ii) the assumption that Δc_p is zero is justified and Eqn (20) can be used to determine γ_w and $\Delta G_{s,i}$ of the PCDDs, (iii) $\Delta H_{f,i}$ and $\Delta S_{f,i}$ are approximately equal to, respectively, $\Delta H_{f,i}^M$ and $\Delta S_{f,i}^M$ [Eqns (15) and (16)], and (iv) $\Delta H_{sol,i} = (\Delta H_{f,i}^M + \Delta H_{s,i})$ and $\Delta S_{sol,i} = (\Delta S_{f,i}^M + \Delta S_{s,i})$.

Since $\Delta H_{f,i}^M$ and $\Delta S_{f,i}^M$ of various PCDD congeners have been measured by Rordorf [29] (Table 1), the enthalpies and entropies of solution of the subcooled liquid, i.e. $\Delta H_{s,i}$ and $\Delta S_{s,i}$, could be determined as $(\Delta H_{sol,i} - \Delta H_{f,i}^M)$ and $(\Delta S_{sol,i} - \Delta S_{f,i}^M)$ and are listed in Table 1.

Thanks to the excellent measurements of the enthalpies and entropies of sublimation, i.e. respectively $\Delta H_{sub,i}$ and $\Delta S_{sub,i}$, for various PCDD congeners by Rordorf [29], the enthalpies and entropies of vaporization, i.e.

TABLE I

Molar volumes (V , $\text{cm}^3 \text{mol}^{-1}$) and enthalpies ($\Delta H_{s,i}$), entropies ($\Delta S_{s,i}$) and free energies ($\Delta G_{s,i}$) of the (subcooled) liquid-to-aqueous solution process (kJ mol^{-1}) of some PCDDs at 25°C . Original data from refs 22, 31 and 32

PCDD ^a	V	$\Delta H_{s,i}$	$-T \cdot S_{s,i}$	$\Delta G_{s,i}$
DD	192.0	27.96	6.68	34.64
1-MCDD	212.9	19.40	18.40	37.80
2-MCDD	212.9	35.05	5.08	40.13
2,3-DCDD	233.8	24.58	18.01	42.59
2,7-DCDD	233.8	19.48	24.59	44.07
2,8-DCDD	233.8	21.38	22.71	44.09
1,2,4-T ₃ CDD	254.7	12.93	31.04	43.97
1,2,3,4-T ₄ CDD	275.6	1.89	46.32	48.21
1,2,3,7-T ₄ CDD	275.6	3.20	44.14	47.34
1,2,3,4,7-P ₅ CDD	296.5	5.10	42.72	47.82
1,2,3,4,7,8-H ₆ CDD	317.4	-2.60	51.92	49.32
1,2,3,4,6,7,8-H ₇ CDD	338.3	-11.70	61.80	50.10

^aDD, Dibenzo-*p*-Dioxin; MCDD, MonoChloroDibenzo-*p*-Dioxin; DCDD, DiChloroDibenzo-*p*-Dioxin; T₃CDD, TriChloroDibenzo-*p*-Dioxin; T₄CDD, TetraChloroDibenzo-*p*-Dioxin; P₅CDD, PentaChloroDibenzo-*p*-Dioxin; H₆CDD, HexaChloroDibenzo-*p*-Dioxin; H₇CDD, HeptaChloroDibenzo-*p*-Dioxin.

Enthalpies ($\Delta H_{v,i}$), entropies ($\Delta S_{v,i}$) and free energies ($\Delta G_{v,i}$) of vaporization [i.e. (subcooled) liquid-to-gas] (kJ mol^{-1}) of some PCDDs at 25°C

PCDD ^a	$\Delta H_{v,i}^{(b)}$	$-T \cdot \Delta S_{v,i}^{(c)}$	$\Delta G_{v,i}^{(d)}$
DD	69.65	-68.03	1.62
1-MCDD	77.15	-70.86	6.29
2-MCDD	78.66	-71.85	6.81
2,3-DCDD	79.53	-68.56	10.97
2,7-DCDD	78.71	-66.77	11.94
2,8-DCDD	85.71	-70.59	15.12
1,2,4-T ₃ CDD	84.89	-70.97	13.92
1,2,3,4-T ₄ CDD	87.33	-68.58	18.75
1,2,3,7-T ₄ CDD	92.81	-70.63	22.18
1,2,3,4,7-P ₅ CDD	95.02	-70.33	24.69
1,2,3,4,7,8-H ₆ CDD	92.68	-67.05	25.63
1,2,3,4,6,7,8-H ₇ CDD	95.89	-67.94	27.95

^bCalculated from $(\Delta H_{\text{sub},i} - \Delta H_{f,i})$; $\Delta H_{\text{sub},i}$ and $\Delta H_{f,i}$ from ref. 29. ^cCalculated from $[-T \cdot \Delta S_{\text{sub},i} - (-T \cdot \Delta S_{f,i})]$; $\Delta S_{\text{sub},i}$ and $\Delta S_{f,i}$ from ref. 29. ^dFrom $\Delta H_{v,i} - T \cdot \Delta S_{v,i}$.

Enthalpies ($\Delta H_{sv,i}$), entropies ($\Delta S_{sv,i}$) and free energies ($\Delta G_{sv,i}$) of solvation (i.e. vapour-to-aqueous solution) (kJ mol^{-1}) of some PCDDs at 25°C

PCDD ^a	$\Delta H_{sv,i}^{(e)}$	$-T \cdot \Delta S_{sv,i}^{(f)}$	$\Delta G_{sv,i}^{(g)}$
DD	-41.69	74.71	33.02
1-MCDD	-57.75	89.27	31.52
2-MCDD	-43.61	76.93	33.32
2,3-DCDD	-54.95	86.57	31.62
2,7-DCDD	-59.23	91.35	32.12
2,8-DCDD	-64.33	93.30	28.97
1,2,4-T ₃ CDD	-71.96	102.0	30.05
1,2,3,4-T ₄ CDD	-85.44	114.9	29.46
1,2,3,7-T ₄ CDD	-89.61	114.8	25.15
1,2,3,4,7-P ₅ CDD	-89.92	113.1	23.13
1,2,3,4,7,8-H ₆ CDD	-95.28	119.0	23.69
1,2,3,4,6,7,8-H ₇ CDD	-107.6	129.7	22.15

^aFrom ($\Delta H_{sv,i} - \Delta H_{v,i}$). ^fFrom [$-T \cdot \Delta S_{sv,i} - (-T \cdot \Delta S_{v,i})$]. ^gFrom ($\Delta G_{sv,i} - \Delta G_{v,i}$).

Enthalpies (ΔH_{fi}), entropies (ΔS_{fi}) and free energies (ΔG_{fi}) of fusion (i.e. the solid-to-subcooled liquid) (kJ mol^{-1}) of some PCDDs at 25°C. Original data from ref. 29

	ΔH_{fi}	$-T \cdot \Delta S_{fi}$	ΔG_{fi}
DD	22.6	-17	5.6
1-MCDD	21.4	-17	4.7
2-MCDD	18.5	-15	3.3
2,3-DCDD	26.7	-18	8.5
2,7-DCDD	26.8	-16	10.4
2,8-DCDD	23.3	-16	6.9
1,2,4-T ₃ CDD	33.9	-25	8.9
1,2,3,4-T ₄ CDD	31.2	-20	10.9
1,2,3,7-T ₄ CDD	36.6	-24	12.2
1,2,3,4,7-P ₅ CDD	42.4	-27	15.6
1,2,3,4,7,8-H ₆ CDD	48.1	-26	21.9
1,2,3,4,6,7,8-H ₇ CDD	53.9	-30	24.1

$\Delta H_{v,i}$ and $\Delta S_{v,i}$ could be determined as ($\Delta H_{sub,i} - \Delta H_{fi}^M$) and ($\Delta S_{sub,i} - \Delta S_{fi}^M$) and are listed in Table 1. The enthalpies and entropies of solvation, i.e. $\Delta H_{sv,i}$ and $\Delta S_{sv,i}$, were determined from the enthalpies and entropies of sublimation and solution as, respectively, ($\Delta H_{sol,i} - \Delta H_{sub,i}^M$) and ($\Delta S_{sol,i} - \Delta S_{sub,i}^M$). They are also listed in Table 1. Table 1 further lists the molar Gibbs free energies of solution, vaporization and solvation at 298 K. In Fig. 2(a-d), the enthalpies, entropies and free energies of solution, vaporization and solvation are plotted versus the molar volume, V , calculated by the LeBas method [33].

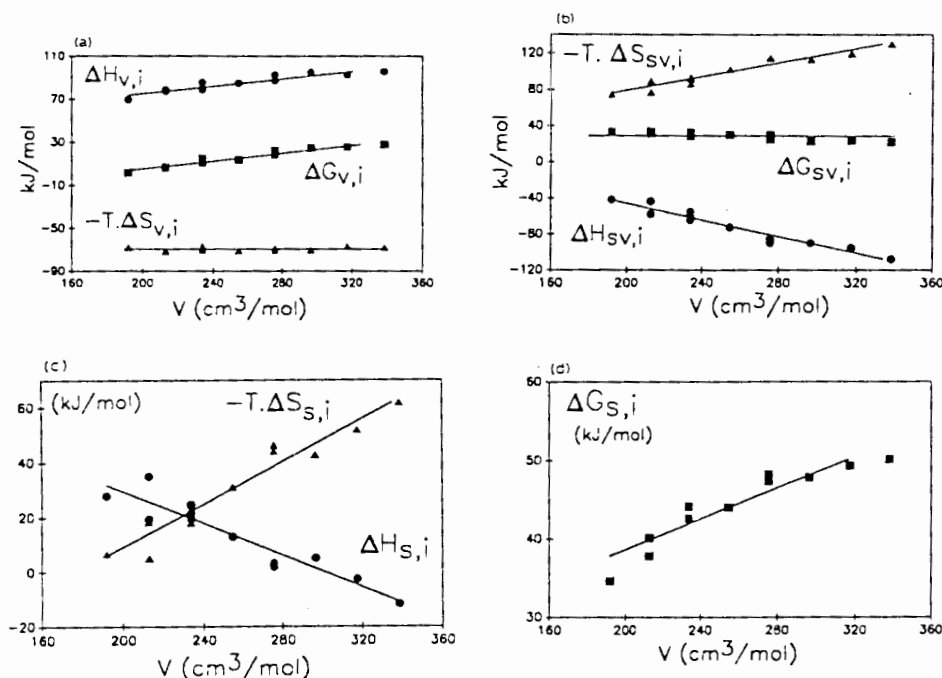


Fig. 2. (a) Molar enthalpies, i.e. $\Delta H_{v,i}$ (●), entropies, i.e. $-T \cdot \Delta S_{v,i}$ (▲), and free energies, i.e. $\Delta G_{v,i}$ (■), of vaporization of PCDDs (kJ mol⁻¹) versus molar volume, V (cm³ mol⁻¹). (b) Molar enthalpies, i.e. $\Delta H_{sv,i}$ (●), entropies, i.e. $-T \cdot \Delta S_{sv,i}$ (▲), and free energies, i.e. $\Delta G_{sv,i}$ (■), of solvation of PCDDs (kJ mol⁻¹) versus molar volume, V . (c) Molar enthalpies of solution, i.e. $\Delta H_{s,i}$ (●), and entropies, i.e. $-T \cdot \Delta S_{s,i}$ (▲), of the (subcooled) liquid solute of PCDDs (kJ mol⁻¹) versus molar volume, V . (d) Molar free energies of solution of the (subcooled) liquid solute, i.e. $\Delta G_{s,i}$ of PCDDs (kJ mol⁻¹), versus molar volume, V .

THERMODYNAMIC ANALYSIS

From Table 1, it is now possible to (i) explore the extent to which each molecular process in the cycle (subcooled) liquid \rightarrow gas \rightarrow solution contributes to the free energy of solution (and thus to the solubility and activity coefficient in the water), and (ii) how these molecular interactions are related to the structural characteristics of the solute. Throughout the data analysis, confidence intervals will be presented between round brackets and have a 95% probability. Standard deviations are reported in square brackets. The correlation coefficient is r and sample size is n .

Vaporization

Figure 2(a) demonstrates that the enthalpy of vaporization is positive ($\Delta H_{v,i} > 0$), indicating that energy is required to break the intermolecular bonds in the subcooled liquid phase, and that $\Delta H_{v,i}$ linearly increases with

increasing molar volume, V .

$$\Delta H_{v,i} = 0.17 (\pm 0.05) \cdot V + 40.87 (\pm 6.97) \quad (25)$$

$$(n = 12, r = 0.93)$$

Apparently, when the molecules become larger in volume or size, there are "more" bonds between molecules in the subcooled liquid phase (i.e. solute-solute interactions) and more energy is required to break intermolecular interactions during vaporization.

The entropy of vaporization is positive ($\Delta S_{v,i} > 0$), representing a gain of entropy when the molecules enter the gas phase. $\Delta S_{v,i}$ is approximately similar for the PCDDs, i.e. $-T \cdot \Delta S_{v,i} = -69.35 [\pm 1.64] \text{ KJ mol}^{-1}$, and thus independent of V .

The free energy of vaporization is the balance between the unfavourable enthalpy and the favourable entropy contributions. It is positive, demonstrating that free energy is required for vaporization. Figure 2(a) shows that the free energy of vaporization of PCDDs increases, and the subcooled liquid vapour pressure (p_i) decreases, with increasing V :

$$\Delta G_{v,i} = -RT \cdot \ln p_i = 0.18 (\pm 0.03) \cdot V - 31.36 (\pm 4.66) \quad (26)$$

$$(n = 12, r = 0.97)$$

The increase of the free energy of vaporization with V is largely due to the increase of the enthalpy of vaporization with increasing molar volume. This demonstrates that the relationship between the free energy of vaporization and solute size (e.g. V) is predominantly due to breaking solute-solute interactions, which requires more energy when solute size of V increases.

Solvation

Figure 2(b) demonstrates that the transfer of the gaseous solute in the water phase (i.e. solvation) is accompanied by a negative $\Delta H_{sv,i}$ and $\Delta S_{sv,i}$, which both decrease with increasing molar volume at approximately the same rate:

$$\Delta H_{sv,i} = -0.46 (\pm 0.08) \cdot V + 47.03 (\pm 11.93) \quad (27)$$

$$(n = 12, r = 0.97)$$

$$-(T \cdot \Delta S_{sv,i}) = 0.39 (\pm 0.07) \cdot V + 3.25 (\pm 11.06) \quad (28)$$

$$(n = 12, r = 0.96)$$

It appears that the enthalpy and entropy contributions tend to compensate each other, resulting in a free energy of solvation which is similar, i.e. $28.68 (\pm 3.90) \text{ kJ mol}^{-1}$, for all PCDDs and independent of the molar volume of the solute. This implies that, with increasing congener volume, no extra energy is

required or gained to transfer a solute from the gas phase to the aqueous solution.

Aqueous solution

Figure 2(c) shows that both the enthalpy and entropy of solution of the PCDD congeners decrease with increasing V :

$$\Delta H_{s,i} = -0.29 (\pm 0.07) \cdot V + 87.90 (\pm 10.87) \quad (29)$$

$$(n = 12, r = 0.94)$$

$$-(T \cdot \Delta S_{s,i}) = 0.39 (\pm 0.07) \cdot V - 68.99 (\pm 10.95) \quad (30)$$

$$(n = 12, r = 0.97)$$

The free energy of solution and $\ln \gamma_{i,w}$ are positive and linearly related to V , which is illustrated in Fig. 2(d) and by the observed correlation:

$$\Delta G_{s,i} = RT \cdot \ln \gamma_{i,w} = 0.10 (\pm 0.03) \cdot V + 18.91 (\pm 4.21) \quad (31)$$

$$(n = 12, r = 0.93)$$

From Fig. 2 it can be concluded that the relationship between the free energy of solution and molar volume, within the homologous series of PCDDs, is largely due to the increase of the free energy of vaporization with molar volume and it is virtually independent of the solvation of the solute. This indicates that the drop of the aqueous solubility with increasing molecular size is due to the phenomenon that larger size molecules require more free energy to leave the subcooled liquid phase.

RELATIONSHIP WITH MOLECULAR STRUCTURE

Correlations between the aqueous solubility (or activity coefficient) and molar volume, TSA or TMV, are generally based on the assumption that these structural characteristics play an important role in solute-water interactions. For example, it has been proposed that the introduction of a hydrophobic chemical into water is associated with a large unfavourable free-energy change due to either unfavourable hydrophobic interaction between solute and water molecules, or the formation of a cavity in the water matrix, or "iceberg" formation of the water molecules, which are believed to be directly related to the TSA or TMV or V of the solute [1-7]. This hypothesis is supported by the observation that the dissolution of a hydrophobic chemical in water is associated with a loss of entropy, which tends to become larger with increasing molecular size, and which is predominantly due to the entropy loss associated with the incorporation of the solute in the water (i.e. solvation). However, the entropy of solvation should not be viewed independently from the enthalpy

of solvation. This is illustrated in Fig. 2(b), which demonstrates that, when a gaseous hydrophobic molecule enters the water, the loss of entropy is compensated by a gain in enthalpy. This enthalpy-entropy compensation indicates that the order increase (loss of entropy) in the water, due to solvation, is associated with an enthalpy gain of similar magnitude, thus resulting in a free-energy change, which, within the homologous series of PCDDs, is independent of molecular size. The formation of order among the water molecules, as a result of the entry of a solute, thus results in a release of heat which tends to outweigh the entropy loss.

It thus appears that, although there is a large loss of entropy due to the entry of the hydrocarbon into the water, this loss has little effect on the actual solution process because of the enthalpy-entropy compensation in the water. Consequently, the effect of the hydrocarbon-water interaction, which is modelled by V , TSA or TMV, on the aqueous solubility is small. The drop of the aqueous solubility with increasing molar volume, TSA or TMV is, therefore, largely due to the increase of the free energy of vaporization with increasing molecular size and thus reflects the interactions between the solute molecules in the pure (subcooled) liquid state, rather than solute-water interactions. The satisfactory correlations between the aqueous solubility and molecular descriptors such as V , TSA or TMV indicates that the solute-solute interactions in the (subcooled) liquid phase are successfully modelled by either V , TSA or TMV. However, to improve correlations between molecular properties and aqueous solubility it is important to model the solute-solute interactions, rather than the solute-water interactions.

HYDROPHOBICITY

This study shows that the loss of entropy of solvation is the only "force" of the aqueous system that drives the solute out of the aqueous solution. This contribution to the free energy of solution reflects the solute's "phobia" toward water and is the chemical's "hydrophobicity". However, for the chemicals in this study, the "hydrophobic" effect, which increases with molar volume or solute size, is largely offset by a compensating favourable enthalpy effect that tends to eliminate a major energy barrier for solvation. This suggests that, although many hydrophobic organic chemicals, such as PCDDs, may experience a large hydrophobic effect when present in water, this may have relatively little influence on the chemical's activity in the water.

CONCLUSION

The thermodynamic analysis of the aqueous solubility of PCDDs demonstrates that, due to enthalpy-entropy compensation in the water, the solvation

of PCDDs in water is virtually independent of the molecular size characteristics (e.g. TSA, TMV or V) of the dissolving chemical. Solute-water interactions of PCDDs, in particular those characterized by the free energy of solvation, thus appear to be independent of TSA, TMV or V . The observed relationships between the aqueous solubility of PCDDs in water and structural characteristics such as TSA, TMV or V , is the result of the phenomenon that, with increasing molar volume, molecules require more energy to leave the pure (subcooled liquid) phase. This indicates that the relationship between the (biological) activity of PCDDs in water and molecular structure reflects molecular interactions between the solute molecules in the pure subcooled liquid phase rather than solute-water interactions.

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