

# A first principles approach to identifying polymers for use in two-phase partitioning bioreactors

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## Abstract

**BACKGROUND:** Two-phase partitioning bioreactors (TPPBs) employ an immiscible phase to partition toxic substrates/products to/away from cells to reduce cytotoxicity and improve bioprocess performance. Initially, immiscible organic solvents were used as the sequestering phase, and their selection included consideration of solute–solvent affinity, which can be predicted through first principles consideration of solute activity and phase equilibrium thermodynamics. Polymers can replace organic solvents in such systems, however, their selection has largely been via heuristic means, and a more fundamental approach is necessary for future success in rational polymer identification.

**RESULTS:** Material properties (polymer crystallinity, solubility parameter, and glass transition temperature  $T_g$ ) were examined across several polymers and polyaromatic hydrocarbons as target solutes. All were shown to influence solute–polymer affinity.

**CONCLUSION:** This first attempt at identifying physical/chemical properties that affect solute–polymer partitioning has been able to demonstrate some clear trends, and has allowed us to formulate a polymer selection guide, based on first principles, to facilitate the selection of solute–polymer pairs for solid–liquid TPPB applications.

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**Keywords:** biotransformation; reactor design; sorption; multiphase; thermodynamics

## INTRODUCTION

The introduction of a carefully selected second, immiscible phase to a bioreactor is an effective strategy to reduce cytotoxicity in microbial transformations. This approach, which relies on the partitioning of target molecules based on thermodynamic equilibria, improves the performance of biosynthetic transformations that generate inhibitory cell products, as well as biodegradative applications in which appropriate levels of toxic substrates are delivered to cells from the sequestering phase based on their metabolic demand. The history of this bioprocess technology has recently been reviewed.<sup>1</sup>

The first embodiment of this technology used immiscible organic solvents as the carrier phase. Although a prescriptive list of desirable solvent properties was formulated to aid in selecting appropriate organic solvents,<sup>2</sup> the most important are biocompatibility, non-biodegradability, and affinity for the target molecule. A strategy for predicting the biocompatibility of an organic solvent has largely been addressed by consideration of the log  $K_{o/w}$  (log $P$ ) of the solvent and the critical log $P$  of the organism under investigation,<sup>3</sup> however, no predictive tools are available for assessing biodegradability, and experimental testing is needed to determine the stability of a potential solvent under TPPB conditions.<sup>4</sup> The third solvent property, solute affinity, has been dealt with via a first-principles approach, namely that at thermodynamic equilibrium the activity of a solute is the same in both phases. Accordingly, we developed the Extractant Screening Program (ESP), which combines the UNIFAC Group Contribution Method to predict solute activity, and multiphase equilibria, for

a large database of solvents.<sup>5</sup> This approach has been used to identify appropriate organic solvents for a large number of biotransformations.<sup>6,7</sup>

As an alternative to the use of immiscible organic solvents several researchers have used low molecular weight poly(dimethylsiloxane), or silicone oil, as the sequestering phase, whose biocompatibility and non-biodegradability are advantages relative to many organic solvents.<sup>8</sup> While its low dielectric constant makes silicone oil well-suited for the extraction of hydrophobic solutes, its efficacy on more polar compounds is lacking, and its high cost makes it commercially unattractive. We have shown that inexpensive thermoplastics, usually in the form of small solid beads, can be used for a wide range of biosynthetic and biodegradative applications.<sup>9,10</sup> The variety of available polymer structures provides a virtually limitless array of material properties, but their use presents new questions regarding TPPB sorbent selection.<sup>11,12</sup> For example, quantitative measures of solute affinity must be determined for polymers of potential interest. Consideration must also be given to glass transition temperatures and polymer morphologies, since these affect the thermodynamic and transport properties of solutes in these materials.

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There have been many successful, albeit heuristic, examples of selecting polymers for biocatalytic applications, yet some studies have demonstrated relatively modest performance in polymer absorption of certain target molecules,<sup>12</sup> while others have demonstrated drastically different levels of absorption of relatively similar target molecules into different polymers.<sup>13</sup> Our aim was to gain insight into these findings by establishing a deeper understanding of the factors influencing polymer absorption through a systematic analysis of polymer properties and their effect on target molecule absorption.

The present article examines these factors in the context of polyaromatic hydrocarbon (PAH) sorption from aqueous solution.<sup>14</sup> The influence of crystallinity, solubility parameter, and glass transition are demonstrated experimentally for PAH sorption by ethylene-rich homo and copolymers. Based on these observations, a polymer selection guide is developed for choosing materials for TPPB applications.

## EXPERIMENTAL

### Materials

Polyethylene (HDPE, LLDPE; Sigma Aldrich), poly(ethylene-co-vinylalcohol) (EVOH 957, EVOH 960, Scientific Polymer Products) and poly(ethylene-co-vinylacetate) (EVA 360, Elvax<sup>®</sup> 360; EVA 77, Elvax<sup>®</sup> 770, E.I. DuPont) were used as received. The polymer beads were roughly spherical with diameters of 2 to 5 mm. Pyrene, phenanthrene (Alfa Aesar) and fluoranthene (Sigma-Aldrich) were used without purification.

### Partitioning equilibrium experiments of PAHs between solid polymer and water

Scintillation vials were charged with water (10 mL) and polymer pellets (0.2 g) before adding aliquots (0–200  $\mu$ L) of stock PAH solutions (5.0 g L<sup>-1</sup> in methanol). The resulting polymer/water/PAH mixtures were equilibrated at room temperature for 1 week. The residual PAH concentration in the aqueous phase was measured by fluorescence spectroscopy, and a material balance provided the mass of PAH absorbed by the polymer, thereby allowing partition coefficients (PC values) to be calculated. For experiments conducted at 80 °C, vials were equilibrated in a temperature-controlled water bath.

### Crystallinity measurements

Differential scanning calorimetry (DSC) was used to measure degrees of crystallinity and glass transition temperatures using

a TA Instruments DSC Q100 apparatus operating at a heating rate of 10 °C min<sup>-1</sup> under a nitrogen purge. The melting endotherm recorded upon first sample heating was determined by integrating the heat flow measured over the melting transition, and the degree of crystallinity was calculated by dividing by this endotherm by the heat of crystallization of fully crystalline polyethylene (293 J g<sup>-1</sup>).<sup>15</sup>

### Analytical methods

PAH concentrations in aqueous solution were quantified via fluorescence spectroscopy using a QuantaMaster QM-2000-6 fluorescence spectrometer (Photon Technology International) equipped with a 72 W xenon arc lamp and Czerny–Turner excitation and emission monochromators. Excitation and emission slits were set to 2 nm bandpass, and solutions were held in 3H quartz cuvettes with a 10 mm path length. All samples were diluted by a factor of 10 000 in anhydrous HPLC-grade ethanol to be in the linear range of PAH detection. Synchronous scans were performed using the following detector conditions (change in wavelength ( $\Delta\lambda$ ), peak maximum, integration area, in nanometers): phenanthrene (53.0, 346.0, 343–351), pyrene (37.0, 371.5, 369–375), and fluoranthene (175.5, 460.0, 459–468).

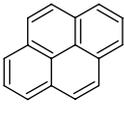
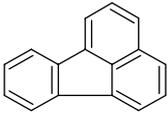
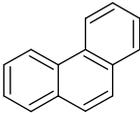
## RESULTS AND DISCUSSION

### Properties of PAH solutes and phase equilibrium considerations

PAHs are widespread contaminants of soil and sediments and are of concern due to their often toxic, mutagenic, teratogenic and/or carcinogenic properties. Their limited biodegradability has been ascribed to their aromatic chemical structure, and to their low water solubility, which reduces their availability to degrading organisms, leading to persistence in the environment. This has fueled interest in PAH biodegradation,<sup>16</sup> which has been studied widely in single-phase aqueous systems,<sup>17,18</sup> liquid-liquid TPPB processes<sup>19,20</sup> and polymer-water TPPBs.<sup>21</sup> Although the latter have been shown to outperform single-phase aqueous biodegradations, polymers used in these demonstrations were selected by trial and error, rather than via the rational strategy developed in this work. Table 1 provides a summary of key properties for the PAHs of present interest.

Of the three PAHs used in this study, phenanthrene has the greatest affinity for water, as evidenced by its relatively high solubility limit, and low octanol/water partition coefficient,  $K_{o/w}$  (Table 1). Given that  $K_{o/w}$  values describe the equilibrium position of two-phase (water/octanol), three component (water/octanol/solute)

**Table 1.** PAH properties

			
Name	Pyrene	Fluoranthene	Phenanthrene
CAS number	129-00-0	206-44-0	85-01-8
Toxicity (acute, LD <sub>50</sub> Oral, Rat)	2700 mg kg <sup>-1</sup>	2000 mg kg <sup>-1</sup>	1800 mg kg <sup>-1</sup>
Aqueous solubility limit (mg L <sup>-1</sup> )	0.14	0.26	1.29
Octanol/water partition coefficient, $K_{o/w}$	151000	158000	28800
Half-life in soil and sediment <sup>33</sup> (days)	19.4–630	137–377	63
Solubility parameter, $\delta$ [MPa] <sup>1/2</sup>	20.8	19.3	20.1

systems, these parameters are cited widely in the TPPB literature as a measure of the ease of solute extraction. Irrespective of the absorbent used in a TPPB process, solutes with high  $K_{o/w}$  values are extracted from an aqueous solution more easily. However, from the standpoint of polymer selection, knowledge of how a solute partitions into octanol provides little guidance regarding an ideal polymeric sorbent. As noted above, polymer selection requires quantitative measures of solute–polymer interactions.

The partitioning of a PAH between aqueous and absorbent phases is an equilibrium condition that can be described by conventional thermodynamic principles. Equilibrium is achieved when the chemical potential of the solute is equal within the aqueous and organic phases. This state is described by

$$x_{\text{solute}}^{\text{aq}} \gamma_{\text{solute}}^{\text{aq}} = x_{\text{solute}}^{\text{organic}} \gamma_{\text{solute}}^{\text{organic}} \quad (1)$$

where  $x_{\text{solute}}$  are solute mole fractions and  $\gamma_{\text{solute}}$  are solute activity coefficients. The ratio of mole fractions gives the partition coefficient,  $PC$ ,

$$PC = \frac{x_{\text{solute}}^{\text{organic}}}{x_{\text{solute}}^{\text{aq}}} = \frac{\gamma_{\text{solute}}^{\text{aq}}}{\gamma_{\text{solute}}^{\text{organic}}} \quad (2)$$

which is dictated by the aqueous and organic phase activity coefficients. Efficient partitioning requires a high solute activity in water, and a low activity in the solvent. Therefore, the best absorbent for a TPPB processes is one that minimizes solute activity.

Activity coefficient models and model parameters for small molecule systems are ubiquitous, but data sets for polymeric systems are far less complete. Consider the widely used Flory–Huggins treatment of solute activity in a polymer phase:

$$\ln(\gamma_{\text{solute}}^{\text{polymer}}) = \ln\left(\frac{\phi_1}{x_1}\right) + \left(1 - \frac{1}{m}\right) \phi_2 + \chi_{12} \phi_2 \quad (3)$$

where  $\phi_1$  and  $\phi_2$  are the volume fractions of solute and polymer, respectively,  $m$  is the number of monomer units per chain segment, and  $\chi_{12}$  is the Flory–Huggins parameter.<sup>22</sup> The latter is an empirical constant that accounts for non-ideality in the enthalpy of mixing. Values of  $\chi_{12}$  are composition specific, and while they are available for a number of polymer–solvent mixtures, compilations are not comprehensive enough to support TPPB design. A simple method of estimating Flory–Huggins parameters is based on pure component, Hildebrand solubility parameters:

$$\chi_{12} = \chi_0 + \frac{V_{\text{seg}}(\delta_{\text{solute}} - \delta_{\text{polymer}})^2}{RT} \quad (4)$$

where  $\chi_0$  is a constant with a value between 0.3 and 0.34,  $V_{\text{seg}}$  is the molar volume of the solute ( $\text{cm}^3 \text{mol}^{-1}$ ),  $\delta_s$  is the solubility parameter of the solute ( $\text{MPa}^{1/2}$ ),  $\delta_p$  is the solubility parameter of the polymer ( $\text{MPa}^{1/2}$ ),  $R$  is the gas constant ( $\text{J mol}^{-1} \text{K}^{-1}$ ) and  $T$  is temperature (K).<sup>23</sup>

It is clear from this analysis that the activity of a solute within a polymer is minimized when the solubility parameters of the solute and polymer are identical. This is a quantitative expression of the common adage that ‘like dissolves like’ wherein  $(\delta_{\text{solute}} - \delta_{\text{polymer}})$  quantifies the affinity of a polymeric sorbent toward a given PAH. Indeed, differences less than  $\pm 2 \text{ MPa}^{1/2}$  generally result in miscibility in polymer–solute mixtures, while differences greater than this threshold often result in immiscible systems.

The  $K_{o/w}$  values for pyrene, fluoranthene and phenanthrene listed in Table 1 are quite large, indicating that octanol is a good solvent for PAH extraction from water. This is not surprising, since the solubility parameter for n-octanol ( $\delta = 21.1 \text{ MPa}^{1/2}$ ) is comparable to those of our solutes. However, this simple two-component (solute/octanol) analysis does not account for the relatively low  $K_{o/w}$  value of phenanthrene, since it does not consider the aqueous phase. Being the least hydrophobic PAH of the three, phenanthrene is expected to have the lowest activity in water and, as such, to produce the lowest partition coefficient, irrespective of the absorbent.

### Polymer selection criteria

At first glance, selecting a polymeric sorbent appears to be relatively simple, since polymers are generally not bioavailable (biodegradable) and are biologically inert (non-toxic). However, additional complexity is introduced upon moving from small molecules to macromolecules. Unlike organic solvents, many polymeric sorbents of practical interest are semi-crystalline materials comprised of a non-ordered amorphous phase intermingled with a crystalline phase. Additionally, the amorphous phase can be glassy or rubbery, depending on the polymer’s glass transition temperature ( $T_g$ ). Therefore, our studies focused on three variables that relate to PAH absorption: degree of crystallinity, absorption affinity, and  $T_g$ .

### Effect of crystallinity

Uncross-linked thermoplastics operating above their  $T_g$  derive their rigidity and creep resistance from the presence of a crystalline phase. However, crystalline domains are impenetrable by even the smallest of gases, with the solubility depending on the degree of crystallinity, as follows:

$$PC = \alpha PC^* \quad (5)$$

where  $PC$  is the partition coefficient of the semi-crystalline polymer,  $\alpha$  is the volume fraction of amorphous polymer, and  $PC^*$  is the partition coefficient for completely amorphous material.<sup>24</sup> Therefore, polymers with the smallest crystalline fraction, while still possessing adequate handling characteristics (strength, abrasion resistance, etc.), are expected to perform best in TPPB applications.

Our study of the relationship between polymer crystallinity and PAH uptake examined two grades of polyethylene (Fig. 1). HDPE is a linear polymer comprised solely of ethylene mers, whose stereoregular structure promotes chain crystallization to a relatively high degree. Our sample was 63 wt% crystalline, as determined by differential scanning calorimetry (DSC). The linear low-density polyethylene (LLDPE) used in this work was a random copolymer comprised of ethylene and a small amount of 1-hexene (Fig. 1). Since mers proximal to the branch points created by the  $\alpha$ -olefin monomer cannot crystallize, the amorphous phase within LLDPE was more abundant, as evident from a degree of crystallinity of just 39 wt%. The  $T_g$ s of both materials were well below  $25^\circ\text{C}$ , resulting in a rubbery amorphous phase with a high degree of polymer chain mobility.

The sorption capacities of HDPE and LLDPE were assessed by PAH uptake measurements involving the equilibration of various water/polymer/PAH mixtures for 7 days, and measuring the residual PAH concentration in the aqueous phase. Figure 2 illustrates typical data for pyrene, fluoranthene, and phenanthrene partitioning between HDPE and water. The slope of each line,

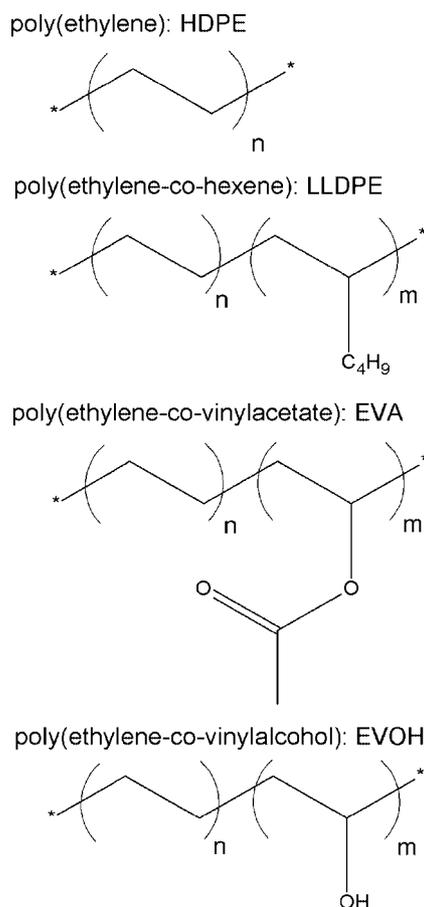


Figure 1. Polymers used in this study.

as determined by least-squares linear regression, provided the dimensionless partition coefficient over the concentration range of interest.

The data presented in Table 2 show that the partition coefficients measured for HDPE and LLDPE demonstrate an inverse relationship between a polymer's degree of crystallinity and its PAH absorption capacity. According to our DSC measurements, our LLDPE sample was 61% amorphous, while our HDPE material was 37% amorphous. As such, the amount of material capable of absorbing a given PAH should be 1.6 times greater for LLDPE than for

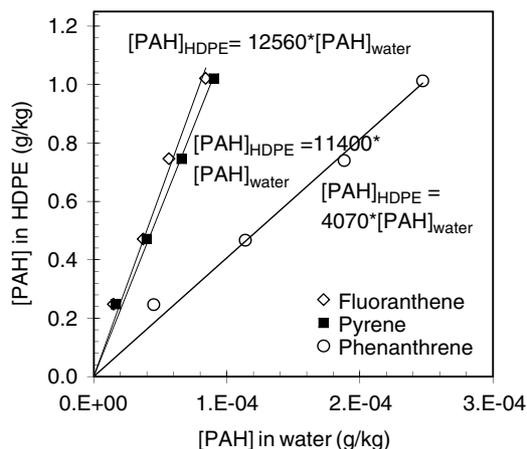


Figure 2. PAH partitioning between HDPE and water at room temperature.

HDPE. This value is comparable with the ratio of LDPE/HDPE partition coefficients, confirming that the crystalline fraction of a thermoplastic does not contribute significantly to PAH uptake. We conclude, therefore, the best thermoplastics for TPPB applications contain only as much crystallinity as is needed to provide acceptable mechanical properties.

#### Thermodynamic affinity

We have shown that ethylene-rich copolymers contain less crystallinity, thereby improving PAH uptake. The inclusion of a comonomer is also a simple means of tailoring the thermodynamic affinity of a polymer for a given solute, irrespective of crystallinity. Our investigation of the effect of polar comonomers on PAH sorption capacity focused on two grades of poly(ethylene-co-vinylacetate) (EVA, Fig. 1). EVA 770 contained 12 mole% of vinylacetate that was randomly distributed among ethylene mers, resulting in a  $T_g$  of  $-35^\circ\text{C}$  and a degree of crystallinity of 32%. The data listed in Table 2 show that, when compared with LLDPE of a similar degree of crystallinity, EVA 770 provided much larger partition coefficients. Since these improvements cannot be attributed to reduced crystallinity, they must be a function of differing thermodynamic affinity. Further improvements were realized by increasing the vinylacetate content to 25 mole%, as EVA 360 provided the highest partition coefficients recorded in this study.

Table 2. Polymer properties and PAH partition coefficients

	Polymer properties					Polymer/water partition coefficient		
	Polar monomer content [mole%]	Reported $T_g$ [ $^\circ\text{C}$ ]	$T_m$ [ $^\circ\text{C}$ ]	Crystallinity [%]	Solubility parameter, $[\text{MPa}]^{1/2}$	Pyrene	Fluoranthene	Phenanthrene
HDPE	0	$< -100$	132	63	15.8	11 400	12 560	4070
LLDPE	0	$< -100$	126	39	15.8	18 750	21 060	8970
EVA 770	12	$-35$	96	32	17.8	36 530	28 810	20 850
EVA 360	25	$-36$	78	19	18.8	39 740	37 370	36 770
EVOH 960	56	55	–	0	21.4	190	150	60
EVOH 960 at $80^\circ\text{C}^a$						6630	2880	1240
EVOH 957	72	72	–	0	23.1	520	370	130
EVOH 957 at $80^\circ\text{C}^a$						6080	3870	990

<sup>a</sup> PAH partitioning measurements made at  $80^\circ\text{C}$ .

The solubility parameters for the PAHs used in this work fall in a narrow range of 19.3 to 20.8 MPa<sup>1/2</sup> (Table 1). The solubility parameter of LLDPE ( $\delta = 15.8$  MPa<sup>1/2</sup>) is considerably lower, indicating that polymers comprised of simple aliphatic hydrocarbon functionality have poor thermodynamic compatibility with the PAHs of interest. The solubility parameters of our EVA samples ( $\delta \approx 17.8, 18.8$  MPa<sup>1/2</sup>)<sup>25</sup> are significantly closer to the target value of 20 MPa<sup>1/2</sup>, owing to the polarity of their acetate functionality, and are near the solubility parameter difference of 2 MPa<sup>1/2</sup> noted earlier for predicting polymer-solute miscibility. Thus, improved thermodynamic compatibility, as gauged by solubility parameters, results in higher PAH partition coefficients.

Based on these observations, it is reasonable to assume that a polymer with an overall solubility parameter approaching 20 MPa<sup>1/2</sup> (i.e. the approximate solubility parameter of the PAHs tested here) would be more effective than EVA. However, since only the amorphous fraction of the polymer engages in solute absorption, overall solubility parameters are less relevant than amorphous phase solubility parameters. Consider EVA 360, which contained an overall vinylacetate content of 25 mole%. Since the crystalline phase comprising 19 wt% of the sample contained no vinylacetate, the amorphous phase comprising 81 wt% of the material must have a vinylacetate content of 35 mole%. This is the composition that is relevant for TPPB material selection. Using the solubility parameters of poly(ethylene) ( $\delta = 15.8$  MPa<sup>1/2</sup>) and poly(vinylacetate) ( $\delta = 22.0$  MPa<sup>1/2</sup>), the interpolation method used by Matsuyama and coworkers<sup>26,27</sup> suggests that the solubility parameter of the amorphous phase within EVA 360 is at least 0.6 MPa<sup>1/2</sup> greater than its overall value. This brings the material significantly closer to our PAH solubility parameter target of 20 MPa<sup>1/2</sup>.

#### Effect of glass transition temperature ( $T_g$ )

The materials discussed above had  $T_g$  values well below TPPB operating temperatures. Therefore, their amorphous phases had the long-range molecular motion needed for relatively fast PAH permeation. For polymers operating below their  $T_g$ , there is insufficient thermal energy to allow significant chain mobility or even chain segmental motion. Only cooperative motion of a few atoms of the main chain or side-groups is present, as well as atomic vibrations. This inhibited segmental motion results in permeabilities several orders of magnitude less than those provided by rubbery materials, which can have implications for TPPB performance. For example, the room temperature diffusivity of oxygen through low density polyethylene ( $T_g < -100$  °C) is 9.99E-16 (mol m)/(m<sup>2</sup> s Pa), while the value recorded for poly(ethylene-co-vinylalcohol) (EVOH, Fig. 1, 23% ethylene,  $T_g \approx 70$  °C) is only 6.02E-20 (mol m)/(m<sup>2</sup> s Pa).<sup>28</sup>

It is well known that permeability ( $P$ ) is the product of diffusivity and solubility coefficient,

$$P = D \cdot PC \quad (6)$$

where  $D$  is the solute diffusivity in the polymer matrix and  $PC$  is the partition coefficient, described above, which relates the solute concentration in the external solution to its concentration in the polymer. The limited diffusivity of solutes within glassy materials is the main contributor to their low permeation rates. This has led researchers working with macroporous poly(styrene-co-divinylbenzene) resins to treat solute uptake as a surface adsorption phenomenon, owing to the high  $T_g$  of these cross-linked copolymers.<sup>29,30,31</sup> We note, however, that high  $T_g$  materials

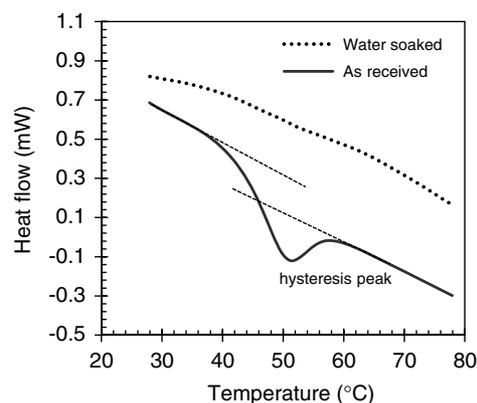


Figure 3. DSC analysis of EVOH 960 as received and after water immersion.

are capable of solute absorption in the unplasticized state,<sup>32</sup> but particularly under conditions where the polymer gains molecular mobility from the presence of a small molecule. Consider oxygen permeability through an EVOH sample containing 32% ethylene, which increases more than two orders of magnitude from 1.20E-20 (mol m)/(m<sup>2</sup> s Pa) at 0% relative humidity to 1.18E-18 (mol m)/(m<sup>2</sup> s Pa) at 100% relative humidity.<sup>27</sup> In this case, water plasticizes the glassy polymer, thereby providing the molecular mobility needed to increase oxygen permeation.

Material properties and PAH absorption data for two samples of poly(ethylene-co-vinylalcohol) are summarized in Table 2. As expected, the introduction of a substantial amount of polar functionality ( $-OH$  versus  $-alkyl$ ,  $-OCOCH_3$ ) raised solubility parameters slightly above those of our PAHs, and increased  $T_g$  values well above room temperature. PAH uptake measurements showed that neither material performs well at 25 °C, as partition coefficients were two orders of magnitude less than those recorded for EVA. We attribute this poor performance to the glassy state of the polymer as opposed to a lack of polymer-solute affinity, since the solubility parameters of EVOH matched those of our PAHs more closely than for polyethylene.

Given the obvious influence of the glass transition on solute uptake, we have examined phase behavior of EVOH 960 more closely. Whereas the manufacturer's reported  $T_g$  of this material was 55 °C, differential scanning calorimetry (DSC) analysis of 'as received' material stored at ambient humidity revealed a slightly lower value of 48 °C (Fig. 3). More importantly, measurements on a sample that was immersed in water for 1 week revealed little evidence of any glass transition, owing to the lowering and broadening of  $T_g$  brought on by water plasticization. We suggest that the EVOH chain mobility provided by absorbed water assists PAH uptake, and similar phenomena are likely to affect other absorption systems involving high  $T_g$  polyamides.<sup>9,12</sup> Of course, the simplest means of increasing EVOH chain mobility is to raise the PAH sorption temperature above  $T_g$ , and the data listed in Table 2 show an order of magnitude improvements in partition coefficients upon moving from 25 °C to 80 °C.

#### Implications of physical/chemical properties

In our view, solute-absorbing, low  $T_g$  polymers have advantages over adsorbing macroporous resins, including mechanical toughness, adjustable selectivity, reduced bio-fouling, and lower cost. Since the partition coefficient provided by a semi-crystalline polymer is inversely proportional to its degree of crystallinity, an ideal

TPPB material would be completely amorphous. However, low  $T_g$  amorphous polymers are elastomeric, and require crosslinking to provide resistance against particle agglomeration. Thermoplastics, on the other hand, derive their mechanical strength from the rigid domains that prevent cold flow. These domains may be crystallites comprised of random copolymer chain segments as found in the homopolymer LLDPE, or block copolymer chain segments as found in Hytre<sup>®</sup>. They may also be glassy domains as found in segmented polyurethanes and poly(butadiene-block-styrene) copolymers. It should be noted that the physical property improvements afforded by these rigid domains come at the cost of solute uptake capacity, and they should be present only to the extent needed to provide the desired mechanical integrity.

The uptake of hydrophilic solutes by polymeric sorbents can be particularly challenging, since polar and/or hydrogen bonding functionality is needed to minimize differences between solute and polymer solubility parameters. The introduction of these functional groups, however, reduces polymer mobility, thereby raising  $T_g$  to the point that it may exceed TPPB operating temperatures. In these cases, plasticization by the solute or, more likely, by water may provide the polymer chain mobility required for solute diffusion. In such circumstances, we therefore suggest that polymer selection be based on  $T_g$  measurements on plasticized materials, as opposed to the values provided by polymer manufacturers.

The factors discussed above shed light on previous anomalous findings in several polymer TPPB studies. For example, the relative absorption of benzaldehyde (solubility parameter,  $\delta = 21.4 \text{ MPa}^{1/2}$ ) and benzyl alcohol ( $\delta = 23.8 \text{ MPa}^{1/2}$ ) differs drastically among different polymers.<sup>13</sup> In this case, the vinylacetate-rich ( $\delta \approx 18.8 \text{ MPa}^{1/2}$ ) and butadiene-rich ( $\delta \approx 17.0 \text{ MPa}^{1/2}$ ) polymers tested in the study absorbed significantly less benzyl alcohol relative to benzaldehyde than the butylene oxide-rich polymer ( $\delta \approx 19.4 \text{ MPa}^{1/2}$ ), a result of the larger difference between the polymers' solubility parameters and that of benzyl alcohol. Selecting a polymer whose solubility parameter lies closer to the target molecule to be absorbed provides control over multiple compounds' aqueous concentrations, demonstrating a basis for selectivity between similar target molecules.

As is the case with all TPPB process development exercises, the affinity of potential absorbents toward the target molecule weighs heavily in material selection. Unfortunately, assessing polymer–solute affinity is complicated by a lack of thermodynamic data for solute–polymer mixtures. We have shown that a simple comparison of Hildebrand solubility parameters can serve as an initial means of screening candidate polymers. The value of these pure-component parameters stems from their widespread availability, as opposed to their accuracy in describing polymer–solvent compatibility. An expanded solubility parameter approach wherein dispersive, dipole and hydrogen-bonding contributions are handled explicitly is recommended if Hansen parameters are available for the polymers of interest.<sup>33</sup> Ultimately, a complete thermodynamic treatment of two-phase, three-component systems is required for rigorous assessments of polymer performance. Group contribution models designed from the UNIFAC approach may have value in this regard, but they have yet to find use for TPPB design.

### Polymer selection guide

The purpose of an informed selection strategy is to aid in identifying candidate polymers for each specific TPPB application. This guide to polymer selection can provide insight into unexpected or anomalous observations found in previous polymer

TPPB studies in which information about a polymer's composition is known; however, in some cases these details are proprietary. We have demonstrated the influence of the following polymer properties on target molecule partitioning as an initial guide to polymer selection:

#### Accessibility

Polymers for TPPB applications should contain minimal glassy, crystalline, or tightly crosslinked domains, only sufficient to provide acceptable mechanical properties, because these do not participate in target molecule absorption.

#### Thermodynamic affinity

Higher mutual thermodynamic affinity is achieved by selecting a polymer whose amorphous phase solubility parameter is similar to that of the target molecule. However, the target molecule's affinity for the aqueous phase limits the extent of uptake, irrespective of the absorbent.

#### Glass transition temperature

Selecting a polymer whose amorphous phase glass transition temperature is well below the TPPB operating temperature confers the coordinated chain mobility required for target molecule uptake. Glass transition is also affected by plasticization in water-swallowable polymers, such that  $T_g$  should be evaluated under conditions representing the application.

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