

Intramolecular versus Intermolecular Hydrogen Bonding in the Adsorption of Aromatic Alcohols onto an Acrylic Ester Sorbent

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Intramolecular hydrogen bonds influence intermolecular binding in adsorption and molecular recognition, but the interplay between intra- and intermolecular hydrogen bonding is poorly understood. In this study, a series of four aromatic alcohols, 2-phenylethanol, 3-phenyl-1-propanol, 2-phenoxyethanol, and 3-phenoxy-1-propanol, are examined to determine the effect of intramolecular hydrogen bond formation on the binding to ethyl propionate (EP), an analogue of an acrylic ester separation resin. A combination of infrared spectroscopy, molecular modeling, and *ab initio* calculations are used to investigate the conformational preferences of the alcohols and the alcohol:EP complexes in hexane. Without EP, 2-phenylethanol and 2-phenoxyethanol prefer intramolecularly hydrogen-bonded conformations, whereas 3-phenyl-1-propanol overwhelmingly favors a conformer without an intramolecular hydrogen bond. For 3-phenoxy-1-propanol, there is a smaller preference for conformers without an intramolecular hydrogen bond. These results agree qualitatively with the experimentally measured IR spectra. The conformational preferences are explained by examining the energy components of low-energy conformers. Electrostatic interactions favor the intramolecularly hydrogen-bonded species, whereas the dihedral energy term and entropic term favor conformers without an intramolecular hydrogen bond. The balance determines the most stable conformer. The calculations predict that all four alcohols bind EP weakly compared with *para*-methoxyphenol. This ranking is in good agreement with experimental adsorption measurements. The small calculated ΔG° values of ≈ -0.9 to -2.4 kJ/mol for the alcohols is explained in terms of hydrogen bond donating ability, entropy, and the competition between inter- and intramolecular hydrogen bonds.

Introduction

The competition between inter- and strong intramolecular hydrogen bonds influences the mechanism of a wide variety of processes: protein folding,¹ reversible CO₂ absorption to amino alcohols,^{2,3} binding of cyclitols to synthetic molecular receptors,⁴ and the adsorption of oxygenated aromatic compounds (OAC) by acrylic ester sorbents.^{5–7} In molecular recognition, intramolecular hydrogen bonds diminish the intermolecular binding constants. In principle, this competition can be exploited to enhance binding selectivities. This study aims to develop insight into the competition between inter- and intramolecular hydrogen bonds in systems where relatively weak intramolecular hydrogen bonds are expected.

In previous work,^{5–7} we used a combined molecular modeling/experimental approach to investigate how competition between intra- and intermolecular hydrogen bonding affects the adsorption of OACs onto an acrylic ester sorbent. A variety of OACs could be recovered from plant extracts or lignin wastes if separation operations were available for isolating individual components from the complex mixtures. This would permit plant phenols to become a useful source of specialty chemicals.

However, while adsorption offers potential for such separations, the molecular level interactions that confer selectivity are not completely understood. We have shown that the *para* isomers of three substituted phenols (methoxyphenol, methyl hydroxybenzoate, and hydroxyacetophenone) adsorb onto the acrylic ester resin from hexane primarily through an intermolecular hydrogen bond formed between the phenolic hydroxyl hydrogen and the sorbent's carbonyl oxygen. For the *ortho* isomers of these phenols, however, an intramolecular hydrogen bond competes with the intermolecular hydrogen bond, diminishing the adsorption to the acrylic ester resin. For these three OACs, the competition between intra- and intermolecular hydrogen bonding could be used to adsorb regioselectively the *para* isomers from *ortho/para* mixtures.

In all three of the previously studied systems, the *ortho* isomers have little conformational freedom, because the donating and accepting groups are in close proximity and are constrained energetically to lie in the plane of the ring. Additionally, the donating group is a phenolic hydroxyl, a good donating group. Thus, these structures form strong intramolecular hydrogen bonds. Compounds with more flexibility and weaker donating groups also form intramolecular hydrogen bonds.^{8–10} However, it is unclear whether these presumably weaker bonds can suppress adsorption.

In this work, we examine the competition between weak

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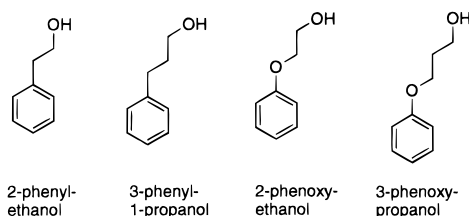


Figure 1. Structures of the four aromatic alcohols studied in this work.

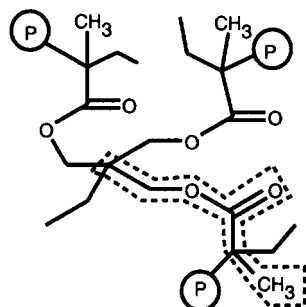


Figure 2. Partial structure of the acrylic ester sorbent XAD-7. The circled P refers to additional polymer units connecting at these points. The area inside the dashed outline corresponds to EP, the small molecule analogue used in modeling and IR studies.

intramolecular hydrogen bonding and intermolecular (i.e., adsorptive) hydrogen bonding. Specifically, we study four aromatic alcohols shown in Figure 1: 2-phenylethanol (PE), 3-phenyl-1-propanol (PP), 2-phenoxyethanol (POE), and 3-phenoxy-1-propanol (POP). All are able to form weak intramolecular hydrogen bonds. The effect of the intramolecular hydrogen bonding on intermolecular hydrogen bonding is evaluated by calculating the binding affinities of the four alcohols to ethyl propionate (EP), an analogue of the intermolecular hydrogen bonding site of the acrylic ester resin, XAD-7 (Rohm and Haas) shown in Figure 2.¹¹

The validity of using EP as an analogue for the resin has been tested for a series of phenols.¹² A correlation between the affinity of the phenol for the acrylic ester sorbent and the IR frequency shift ($\Delta\nu_{\text{OH}}$) for the solute:EP complex was observed for hydrogen-bonded complexes. The IR frequency shift to lower wavenumbers upon complexation with EP is consistent with the formation of an intermolecular hydrogen bond between the phenol and EP. The correlation between the $\Delta\nu_{\text{OH}}$ value and the adsorption affinity of the phenol for the acrylic ester sorbent suggests that EP is a good model for the adsorptive hydrogen-bonding mechanism. This correlation can only be directly established in the absence of intramolecular hydrogen bonding.

The ability of intramolecular hydrogen bonding to compete with and suppress adsorption is expected to depend on at least three factors. First, it depends on the nature of the intramolecular hydrogen bond acceptor, with a stronger acceptor leading to a stronger intramolecular bond. For the phenyl alcohols (PE and PP) the aromatic π electrons serve as weak hydrogen bond acceptors.⁸ For the phenoxy alcohols (POE and POP), the ether oxygen is the hydrogen bond accepting site.^{10,13,14}

Second, the geometry of the bonded conformer affects the strength of the intramolecular hydrogen bond. For compounds with little conformational flexibility, such as ortho-substituted phenols, intramolecular hydrogen bonding is generally favorable when planar, five- or six-membered rings are formed, with six-membered ring structures being the more stable.^{15,16} Likewise, for a series of flexible *N*-(*p*-nitrophenyl)alkylenediamines, it has been reported that intramolecular hydrogen bonds do form, and that the strongest bond occurs for the molecule that is able to

form a six-membered ring.¹⁷ The molecules in the present study all form either a five- or six-membered ring when in an intramolecularly hydrogen-bonded conformer.

Finally, we expect the stability of the intramolecularly hydrogen-bonded species to depend on the entropic cost associated with restricting the intervening dihedral angles. For a flexible chain, an intramolecular hydrogen bond that requires the formation of a six-membered ring has a greater entropic cost than the formation of a five-membered ring because of the additional degrees of freedom that must be constrained.

The interplay of these three factors makes it difficult to predict the relative populations of intramolecularly hydrogen-bonded species and thus their effect on intermolecular binding affinities. This study uses molecular modeling, *ab initio* calculations, and IR to evaluate the contributions of all three factors to the stability of the intramolecular hydrogen bond. Next, the binding free energies of the alcohol:EP complexes are calculated using a novel molecular modeling technique that efficiently identifies the stable conformers of a molecule or complex and uses these conformations as the basis for free-energy calculations.¹⁸ These binding free energies are compared with those of substituted phenols to elucidate the roles of entropy, hydrogen bond donating ability, and intramolecular hydrogen bonding on adsorptive bonding. Finally, the calculated alcohol:EP binding affinities are compared with experimental adsorption binding affinities of the alcohols onto the acrylic ester resin.

Methods

1. Experimental. *a. Materials.* The acrylic ester sorbent (Rohm and Haas Amberlite XAD-7), with a reported specific surface area of 450 m²/g, was purchased from Sigma Chemical Company (St. Louis, MO). Before use, the sorbent was washed sequentially with water, methanol, acetone, and hexane and dried in a vacuum oven overnight. The solvents (OPTIMA grade) were purchased from Fisher Scientific (Pittsburgh, PA). The solutes 2-phenylethanol and 2-phenoxyethanol were purchased from Sigma Chemical, and 3-phenyl-1-propanol (98%) and 3-phenoxy-1-propanol (97%) were purchased from Acros Chemical (Pittsburgh, PA). Ethyl propionate, the soluble analogue of the acrylic ester sorbent, was purchased from Aldrich (Milwaukee, WI). All chemicals were used without further purification.

b. Procedures. Adsorption studies were performed by contacting a predetermined amount of sorbent with a hexane solution containing solute of a known initial concentration (C_0). After 2 days of equilibration, the solute concentration (C) was determined by UV spectrophotometry using a Spectronic Genesys 20 spectrophotometer (Milton Roy Co., Rochester, NY). The amount of solute adsorbed per unit mass of sorbent (q) was determined from the difference between the initial and equilibrium solute concentrations by the following equation:

$$q = \frac{(C_0 - C)V}{M} \quad (1)$$

where V is the volume of solution and M is the mass of the sorbent. Adsorption affinities (q/C) are calculated from the slopes of the linear region of the adsorption isotherms. Adsorption enthalpies were determined from the temperature dependence of the adsorption affinities by means of a van't Hoff plot of $\ln(q/C)$ vs $1/T$. Uncertainties in the enthalpies (95% confidence level) were estimated using the uncertainties in the best fit lines of the van't Hoff plot.

IR spectra were collected for each of the alcohols in the presence and absence of EP. In the absence of EP, spectra were analyzed qualitatively to determine solute conformations in hexane solutions. In the presence of EP, IR spectra were used to demonstrate intermolecular hydrogen bonding between the alcohol and EP. In these cases, the spectrum of EP was subtracted from spectra of the alcohol:EP mixture. Spectra were collected (32 scans per spectrum) using a Nicolet Instrument Corporation (Madison, WI) 5DXC FTIR Spectrometer with a resolution of 4 cm⁻¹. The IR chamber was purged with N₂ before and during sampling to eliminate interference from CO₂ and H₂O. The IR cell used in these experiments had KBr windows and a 0.152-cm Teflon spacer. To determine peak areas, the IR spectra were deconvoluted using PeakFit 4.0 (SPSS Inc., Chicago, IL). The peaks were fit to the Voigt function in a manner analogous to that described by Brinkly and Gupta.¹⁰

2. Free-Energy Calculations. *a. Theory.* As described in previous work,^{6,7} free-energy calculations are used to calculate the standard free energy of binding, ΔG_b° , of an alcohol (A) to EP and to determine the lowest-energy conformations of the free species and bound complexes. The standard free energy of binding can be written as:¹⁹

$$\Delta G_b^\circ = -RT \ln \frac{Z_{A:EP}}{Z_A Z_{EP}} + RT \ln \frac{8\pi^2 \sigma_{A:EP}}{C^\circ \sigma_A \sigma_{EP}} \quad (2)$$

where R is the gas constant; T is the temperature; C° is the standard concentration; $\sigma_{A:EP}$, σ_A , σ_{EP} are symmetry numbers; and $Z_{A:EP}$, Z_A , and Z_{EP} are the configuration integrals of the complex, the alcohol, and EP, respectively. In eq 2 a factor of $P^\circ \bar{V}$ is omitted because it is very small at the standard temperature and pressure.¹⁹

The configuration integrals have the form:¹⁹

$$Z = \int e^{-\beta(U(\mathbf{r})+W(\mathbf{r}))} d\mathbf{r} \quad (3)$$

where $\beta = 1/kT$ and the Boltzmann factor is given as a function of $U(\mathbf{r})$ and $W(\mathbf{r})$, the gas-phase potential energy and the solvation energy, respectively. For the isolated molecules, the integral is calculated over \mathbf{r} , the full range of internal coordinates. For the complex, the configuration integral also extends over the six rotational and translational degrees of freedom of the alcohol molecule with respect to the EP molecule.²⁰

b. Algorithm. Evaluation of eq 3 was performed by the Mining Minima (MM) method which has been described previously.¹⁸ The MM method uses the predominant states approximation²¹ that the free energy is dominated by a small number of low-energy states. The free energy, or more properly the chemical potential, can therefore be computed from the contributions G_j of a finite number N of energy wells j :

$$G^\circ = -RT \ln \left(\sum_{j=1}^N e^{-G_j/RT} \right) \quad (4)$$

The algorithm proceeds by finding a minimum energy conformation, mapping out the extent of the potential energy well around this structure, and calculating the configuration integral for that well by Monte Carlo integration of the Boltzmann factor. The configuration integral is then approximated as the sum of the contributions of individual energy wells. New energy wells are included in the sum until for five successive minima either (a) contributions to the free energy drop to a fractional change of $<10^{-6}$ or (b) the cumulative average potential energy of the wells changes less than 0.004 kJ/mol.²⁰

TABLE 1: Atomic Charge Parameters in Units of Electrons^a

chemical group	atom	charge
aromatic -CH	C	-0.13
	H	0.13
	H	0.13
aromatic -CO-	C	0.16
	O	-0.23
aromatic -C - CH ₂ -	aromatic C	-0.02
	aliphatic C	-0.10
C-OH	C	0.17
	O	-0.65
-CH ₂ -	H	0.40
	C	-0.10
	H	0.05

^a One electron = 1.602×10^{-19} C.

We assume that the conformational distributions of bond lengths and angles are not changed significantly by complexation. This allows us to treat them as rigid.¹⁹ The integration is thus only over dihedral angles (and the previously mentioned translations and rotations of the complex). In this study, three rotatable dihedrals are included in the sampling for PE and POE and four for PP and POP. The EP molecule is treated as rigid. As described previously,⁶ to model surface adsorption, the sampling is restricted to only those conformations in which the aromatic carbon bonded to the alcohol chain remains above the EP carbonyl carbon.

Because bond lengths and angles are not varied in the sampling, it is possible that the calculations are biased by the bond lengths and angles used in the calculations. This is of particular concern because the molecules can possibly form intramolecularly hydrogen-bonded structures which may have different bond lengths and angles than structures in more extended nonintramolecularly hydrogen-bonded conformations. The bond lengths and angles might influence the strength of the hydrogen bond and thus affect the intermolecular bond to EP. To address this concern, two sets of calculations are performed for each alcohol and alcohol:EP complex. Equation 4 is then replaced by

$$G^\circ = -RT \ln \left(\sum_{j=1}^{N^h} e^{-G_j^h/RT} + \sum_{j=1}^{N^e} e^{-G_j^e/RT} \right) \quad (5)$$

where G_j^h refers to the free energy of well j for alcohol conformations that are derived from an initial structure that has been energy minimized with an intramolecular hydrogen bond, and G_j^e refers to the free energy of well j for alcohol conformers derived from an initial structure that has been energy minimized in the extended conformation (i.e., with the hydroxyl hydrogen at least 3 Å from the electron acceptor). During both MM calculations, it is possible for an intramolecular hydrogen bond to form during the free-energy calculation. Thus, the calculations include structures optimized to form intramolecular hydrogen bonds and structures more conducive to intermolecular hydrogen bonding.

c. Energy Model. The energy in eq 3 is separated into the potential energy, $U(\mathbf{r})$, and the solvation energy, $W(\mathbf{r})$. Here, the potential energy is calculated using the CHARMm 19²² force field with the all-hydrogen representation. The charges for all atoms are shown in Table 1.

The solvation model approximates the solvation energy as the sum of the contributions from a two-step solvation process.

The first step is the formation in the solvent of a Lennard–Jones cavity which has the shape of the solute. The second solvation energy term is due to the electrostatic charging of the atomic partial charges inside the cavity. These two terms are included in the manner described in ref 6. The nonpolar solvation energy associated with the first step, ΔG^{NP} , is approximated as linear in the solvent-accessible surface area of the solute with a coefficient of $-69.87 \text{ J}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-2}$ and an offset of -20.46 kJ/mol . The offset, although large, cancels when comparing binding affinities of two solutes in the same solvent. The electrostatic term is calculated using the computationally rapid generalized Born (GB) approximation^{23,24} in which the effective Born radius of each atom is computed via a charge-induced dipole interaction term.²⁵ The GB solvation term is included during the MM calculation, but the nonpolar solvation energy is added to the free energy of each minimum after all minima are found.²⁰ Also added after the MM calculation is a correction for the approximate nature of the GB approach. This correction is the difference between the electrostatic solvation energy as calculated by the GB method and the energy calculated using the more accurate, but computationally more demanding, Poisson–Boltzmann approach. The atomic radius of each atom is set to the average of its CHARMM van der Waals radius (R_{min}) and the solvent radius (2.0 \AA for hexane). The solvent dielectric constant is set to 1.89 for hexane.

d. Energy Component Analysis. The individual energy components are investigated to understand the reasons behind the conformational preferences of the individual alcohols. For each alcohol, the lowest free-energy conformer with and without an intramolecular hydrogen bond is identified. For each of these conformers, the Coulombic, E_{Coul} , van der Waals, E_{vdW} , and dihedral, E_{dih} , energies are calculated. Also for each conformer, the nonpolar contribution to the solvation energy, E_{np} , and the electrostatic contribution to the solvation energy after the correction mentioned above, E_{PB} are obtained. The difference for each component is taken as

$$\Delta E = E^{\text{intra}} - E^{\text{nonintra}} \quad (6)$$

where a negative value indicates that the conformer with an intramolecular hydrogen bond is favored for this energy component.

In addition to potential and solvation energy, entropy influences the ratio of intramolecularly to nonintramolecularly hydrogen-bonded conformations. To evaluate the entropic contribution, all conformations found during the calculation of the free energy by the MM algorithm are first divided into two sets: those with and those without an intramolecular hydrogen bond. This is done by calculating the distance between the hydroxyl hydrogen and the acceptor. If this distance was less than 2.3 \AA for the phenoxy alcohols or 2.55 \AA for the phenyl alcohols,²⁶ the conformer was binned as having an intramolecular hydrogen bond. The conformational entropy change upon breaking an intramolecular hydrogen bond is given by¹⁹:

$$\begin{aligned} -T\Delta S &= \Delta G^{\circ} \\ &+ \langle U(\mathbf{r}_{\text{hbond}}) + W(\mathbf{r}_{\text{hbond}}) \rangle \\ &- \langle U(\mathbf{r}_{\text{no hbond}}) + W(\mathbf{r}_{\text{no hbond}}) \rangle \end{aligned} \quad (7)$$

where the angle brackets indicate an ensemble average over either the intramolecularly hydrogen-bonded or nonintramolecularly hydrogen-bonded conformations, ΔG° is the relative stability of the nonintramolecularly hydrogen bonded conformations, U is the potential energy and W is the solvation energy.

TABLE 2: Energy Component Differences (kJ/mol) for the Formation of Intramolecular Hydrogen Bonds for PE, PP, POE, POP, and oMP^a

alcohol	ΔE_{vdW}	ΔE_{Coul}	ΔE_{Dih}	ΔE_{np}	ΔE_{PB}	$-T\Delta S$	ΔG°
PE	-2.8	-5.4	-3.6	0.4	1.3	2.7	-3.6
PP	-1.9	-11.3	8.9	1.9	1.8	8.9	6.5
POE	-1.8	-8.7	-1.6	0.2	1.4	2.4	-8.1
POP	-3.1	-9.6	8.0	0.9	1.3	5.7	2.1
oMP	-0.3	-28.2	0.0	-0.2	6.7	1.5	-19.7

^a E_{vdW} is the van der Waals energy, E_{Coul} is the electrostatic Coulombic energy, E_{Dih} is the dihedral or torsional strain energy, E_{Coul} is the nonpolar cavity solvation energy, and E_{PB} is the electrostatic solvation energy calculated using the Poisson–Boltzmann equation. Both the entropic contribution (cf. eq 7) and ΔG° include all energy wells. For all entries, a negative value favors the formation of an intramolecular hydrogen bond.

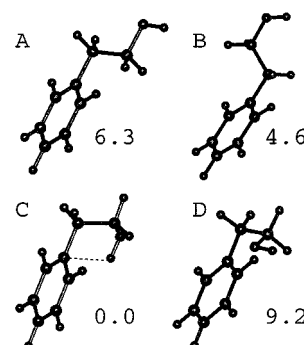


Figure 3. Representative conformers of PE found by the MM algorithm including the lowest-energy conformations with and without an intramolecular hydrogen bond. The free-energy relative to the minimum-energy conformation of each conformer is given in kJ/mol. The intramolecular OH... π hydrogen bond in conformer C, marked by a dashed line, is 2.52 \AA long.

A negative value for $-T\Delta S$ indicates that entropy favors the intramolecularly hydrogen-bonded conformations.

Results and Discussion

First, we describe the conformational preferences of the phenyl and phenoxy alcohols in hexane in the absence of EP. IR, *ab initio* calculations, and free-energy calculations make it possible to assess the relative stabilities of the free and intramolecularly hydrogen-bonded species. Next we use free-energy calculations to evaluate the possible binding mechanisms of the phenyl and phenoxy alcohols to EP. Finally, we compare the calculated binding affinities of the alcohols for EP to the binding affinities of the same compounds for the acrylic ester sorbent XAD-7.

1. Free Alcohols. a. Conformational Preferences. The conformations of the aromatic alcohols in hexane may be divided into two categories: those with and those without intramolecular hydrogen bonds. Although neither PE nor PP has an oxygen available to form an OH...O intramolecular hydrogen bond, the aromatic ring presents a hydrogen bond accepting site as shown previously.^{8,9,27} More traditional OH...O intramolecular hydrogen bonds are possible for phenoxy alcohols. The relative stabilities, ΔG° , are given in Table 2. Each alcohol is now discussed individually.

Representative conformers of PE obtained by the MM algorithm are shown in Figure 3. The free-energy calculations rank structure C as the lowest energy conformer. In this conformer, the distance between the hydroxyl hydrogen and the closest aromatic carbon is 2.52 \AA . Although this is considerably longer than a standard hydrogen bond, previous experimental

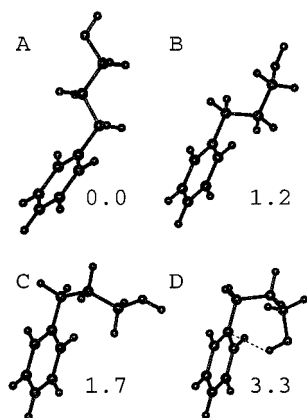


Figure 4. Same as Figure 3 for PP. The intramolecular hydrogen bond in conformer D is 2.27 Å long.

work^{8,28} on PE suggests that at least part of the preference for conformer C is due to the presence of an intramolecular OH $\cdots\pi$ hydrogen bond and not merely the repulsion between the π electrons and the lone-pair electrons of the hydroxyl oxygen. Thus, the results are consistent with previous work⁸ suggesting that structure C is stabilized by an intramolecular OH $\cdots\pi$ hydrogen bond, and that this structure will be the major conformer in a nonpolar solvent.

To confirm the preference for structure C, all four structures in Figure 3 were minimized using HF/6-31G(d,p) gas-phase *ab initio* methods. Potential energies were then calculated at the MP2 level for each optimized structure. These calculations predict that structure C is 6.9 kJ/mol more stable than the lowest-energy conformer without an intramolecular hydrogen bond, in good agreement with the free-energy calculations.

Representative conformers and their relative energies for PP are shown in Figure 4. For PP, the most stable conformation (conformer A) does not have an intramolecular hydrogen bond. That a conformation with an intramolecular hydrogen bond is calculated to be the most stable conformer for PE but not for PP is somewhat surprising, because the geometry would seem to favor hydrogen bonding in PP to a greater extent than in PE. Specifically, conformer D of PP has a shorter (2.27 Å vs 2.52 Å) and more linear (130.9° vs 105.7°) intramolecular hydrogen bond than conformer C of PE. The issue is discussed in the energy component analysis below. The conformational ranking is again confirmed by *ab initio* calculations which predict that a conformer with an intramolecular hydrogen bond is 2.5 kJ/mol less stable than the lowest-energy nonintramolecularly hydrogen-bonded conformer.

Figures 5 and 6 show the lowest free-energy conformers for POE and POP, respectively. The intramolecular hydrogen bond distances are 2.29 and 2.01 Å for POE and POP, respectively. Both the free-energy and *ab initio* calculations predict that a hydrogen-bonded conformer is the single most stable conformer for POE and POP. However, for POP, the overall free energy for forming a hydrogen bond is weakly unfavorable (2 kJ/mol). The basis for this preference is discussed below.

b. IR Spectroscopy. The calculations above were used to interpret the IR spectra of hexane solutions containing the individual alcohols. For PE, Figure 7 shows two peaks in the OH stretching region at 3643 cm⁻¹ and 3608 cm⁻¹, whereas PP shows three peaks of very different magnitudes in the OH stretching region. There is a large peak at 3649 cm⁻¹ with a second shoulder peak at 3633 cm⁻¹ and a third smaller peak at 3611 cm⁻¹. Consistent with Bakke and Chadwick,⁸ the high-frequency peaks of PE and PP (3643, 3649, and 3633 cm⁻¹)

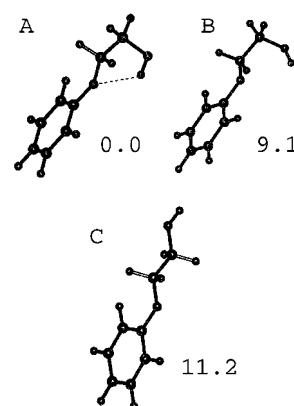


Figure 5. Same as Figure 3 for POE. The OH \cdots H intramolecular hydrogen bond in conformer A is 2.29 Å long.

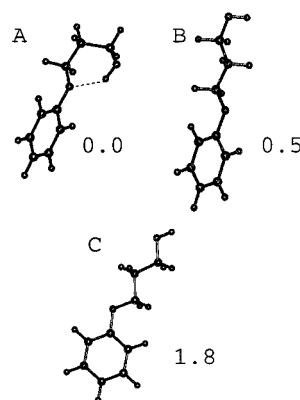


Figure 6. Same as Figure 3 for POP. The intramolecular hydrogen bond in conformer A is 2.01 Å long.

are assigned to the OH stretching of non-hydrogen-bonded conformations. Hydrogen bonds lengthen and weaken the O—H bond causing shifts to lower wave numbers. Thus, the lower-frequency peaks at 3608 cm⁻¹ and 3611 cm⁻¹ are assigned to OH stretches distorted by hydrogen bonds.

To determine whether these lower-frequency peaks result from intramolecular interactions or intermolecular self-association, IR spectra were collected at various concentrations of both PE and PP. As the concentrations of PE and PP increase, peaks due to intermolecular hydroxyl/hydroxyl self-association are expected to grow in. For PE, the ratio of peak area for the 3608 cm⁻¹ relative to the peak at 3643 cm⁻¹ is independent of PE concentration, which indicates that the peak at 3608 cm⁻¹ is due to intramolecular hydrogen bonding. When PE concentrations were increased to greater than 8 mmol/L, a broad peak at 3530 cm⁻¹ was observed in the spectra, and the area of this peak increased relative to the area of the non-hydrogen-bonded peak. This observation indicates that the peak at 3530 cm⁻¹ peak is due to the intermolecular self-association of PE. For PP, from similar arguments, the peak at 3611 cm⁻¹ is due to intramolecular hydrogen bonding, whereas the broad peak present for concentrations greater than 5 mmol/L at 3530 cm⁻¹ is due to intermolecular self-association.

The IR spectra for POE and POP in hexane are shown in Figures 7c and 7d. For POE, there is only one peak at 3620 cm⁻¹. Consistent with Spassov et al.¹³ and Brinkley and Gupta¹⁰ who studied hydrogen bonding in alkoxy ethanols, this peak is assigned to an OH stretch distorted by an intramolecular hydrogen bond with the ether oxygen. In the spectrum of POP, there are two peaks of similar area at 3649 cm⁻¹ and 3596 cm⁻¹. The higher-frequency peak is assigned to OH stretches associ-

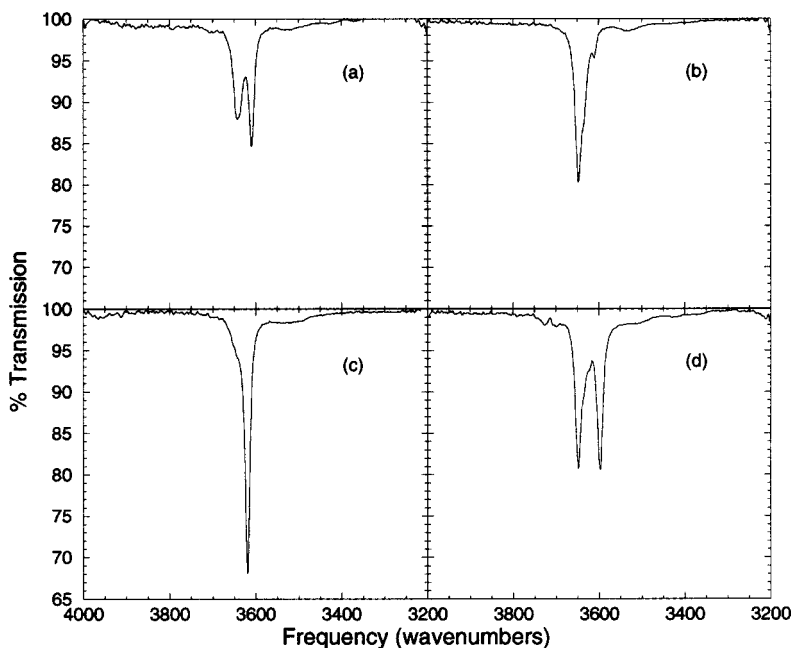


Figure 7. IR spectra of (a) 11.6 mmol/L solution of PE, (b) 11.8 mmol/L solution of PP, (c) 11.6 mmol/L solution of POE, and (d) 11.9 mmol/L solution of POP in hexane. Spectra were obtained at room temperature.

ated with conformations that lack an intramolecular hydrogen bond. The lower-frequency peak is assigned to the OH stretch for intramolecularly hydrogen-bonded conformations.

Because absorption coefficients are unavailable, it is impossible to compare IR quantitatively with calculations. Thus, only a qualitative comparison between experimental peak areas and the computed conformational population is possible. Figure 7a shows that PE exists in hexane in both intramolecularly and non-hydrogen-bonded conformations at similar concentrations. The free-energy calculations also predict both types of conformations, but the hydrogen-bonded conformations are computed to be significantly more stable (3.6 kJ/mol) than the non-hydrogen-bonded conformations. This would predict approximately a 5-fold difference in peak areas. This suggests that the calculations may overestimate free-energy differences between the conformers with and without intramolecular hydrogen bonds. For PP, Figure 7b indicates that non-hydrogen-bonded conformers predominate. Indeed the sum of the areas associated with the non-hydrogen-bonded peaks is 8 times the area for the intramolecularly hydrogen-bonded conformations. The calculations shown in Table 2 are in good agreement. The non-hydrogen-bonded conformers are calculated to be 6.5 kJ/mol more stable than intramolecularly hydrogen-bonded conformations, which results in a prediction of a 12-fold difference in peak areas.

The IR spectra for POE in Figure 7c show that the intramolecularly hydrogen-bonded conformation predominates in hexane. This observation is consistent with calculations which predict that intramolecularly hydrogen-bonded POE conformations are 8.1 kJ/mol more stable than non-hydrogen-bonded conformers. The calculated 25-fold preference for intramolecularly hydrogen-bonded conformations corresponds favorably with experiments in which only the intramolecular peak is observed. For POP, the difference in calculated stabilities is only 2 kJ/mol, suggesting that the intra- and nonintramolecularly hydrogen-bonded species should exist in a ratio of 1:2. This compares well with the spectrum in Figure 7d, which shows that the peak areas due to hydrogen-bonded and non-hydrogen-bonded conformations have similar proportions.

c. Energy Component Analysis. The individual energy components of conformations with and without an intramolecular hydrogen bond are compared to provide insight into the physical basis of the conformation preference of PE, PP, POE, and POP. Table 2 shows energy component differences between the lowest free energy hydrogen-bonded conformers (conformer C for PE, D for PP, and A for both POE and POP) and the lowest free energy non-hydrogen-bonded conformers (conformers B for PE, A for PP, and B for both POE and POP). Here, a negative value indicates that, for this energy component, the energetics are more favorable for the intramolecular species than for the conformer without an intramolecular hydrogen bond.

The Coulombic energy, dihedral strain energy, and entropy show the largest energy component differences. It is not surprising that for all of the molecules, electrostatics favors the hydrogen-bonded conformation, because molecular mechanics force fields such as CHARMM treat hydrogen bonds as purely electrostatic. This energy difference is larger for PP than PE because of the shorter, more linear hydrogen bond in PP. The same trend is observed for POP relative to POE. However, in contrast to PP where a 0.25 Å shorter OH \cdots π distance has a large effect on ΔE_{Coul} , only a small difference is noticeable for the 0.28 Å shorter OH \cdots O bond of POP. This can be explained by noting that PP and POP have different hydrogen bond acceptors. Shortening the intramolecular hydrogen bond in POP brings the hydroxyl oxygen 0.2 Å closer to the negatively charged ether oxygen. This results in a repulsive interaction greater in magnitude than that which results from bringing the hydroxyl oxygen of PP closer to an aromatic carbon.

In contrast to the Coulombic term, entropy favors the nonintramolecularly hydrogen-bonded conformer for all four alcohols. This difference is much larger for the more flexible PP and POP. Both POP and PP form six-membered rings, yet the entropic difference is largest for PP. This again may be explained by the difference in hydrogen bond acceptors. The formation of an intramolecular hydrogen bond in PP constrains the entire benzene ring, whereas for POP the hydrogen bond is formed with the ether oxygen. This leaves the benzene ring free to rotate, which results in a smaller entropic penalty.

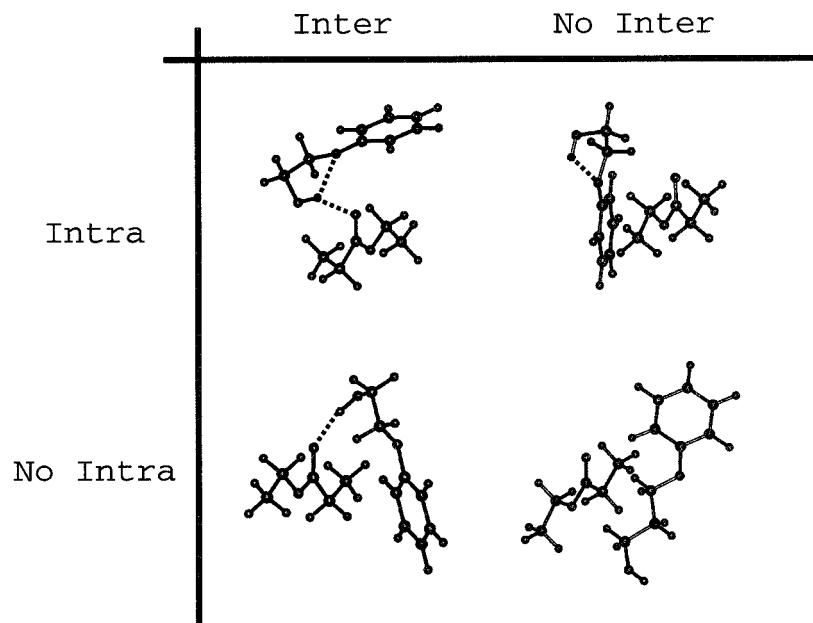


Figure 8. The four types of alcohol:EP complexes found by the MM algorithm.

The greatest difference between PE and PP or POE and POP lies in the dihedral strain energy. For PE and POE, the intramolecularly hydrogen-bonded conformer is less strained than the conformer without a hydrogen bond, whereas the formation of an intramolecular hydrogen bond in PP and POP causes a large increase in E_{dih} . For PP, this dihedral strain, combined with the entropy penalty, overwhelms the favorable Coulombic interaction making intramolecular hydrogen bonding unfavorable. For POP, neither the entropy nor the dihedral energy makes as large a destabilizing contribution as they do for PP, which results in the intra- and nonintramolecular conformations being approximately equal in stability. The net result is that PE and POE more strongly favor the hydrogen-bonded species. This is despite the fact that PP and POP are able to form six-membered intramolecular hydrogen bonds which are customarily regarded as more stable, whereas PE and POE only form five-membered rings.

The complicated balance of entropy, Coulombic energy, and dihedral strain energy means that prediction of the most stable conformer of each of these species is difficult. As shown in Table 2, the free-energy calculations predict that, for PE, intramolecularly hydrogen-bonded conformations are more stable by 3.6 kJ/mol, whereas for PP, non-hydrogen-bonded conformers are more stable by 6.5 kJ/mol. A similar pattern is shown for the phenoxy alcohols studied here. The intramolecularly hydrogen-bonded species is favored by POE by 8.1 kJ/mol, whereas non-hydrogen-bonded conformers are more stable for POP by a modest 2.1 kJ/mol.

The strongest intramolecular hydrogen bond found among the four alcohols studied here is that of POE. The present calculations suggest that the intramolecular hydrogen bonds of the alcohols examined are weak in comparison with that of *o*-methoxyphenol (oMP), where intramolecularly hydrogen-bonded conformers are favored by 20 kJ/mol.⁶ There are three reasons for the greater stability of the intramolecular hydrogen bond in oMP. First, oMP has a better donating group, as is apparent from its much more negative ΔE_{Coul} (Table 2). Second, the formation of an intramolecular hydrogen bond in oMP does not require the distortion of any dihedral angles, whereas significant dihedral distortions are required for two of the alcohols (Table 2). Finally, the more rigid structure of oMP

imposes a smaller entropic cost for the formation of an intramolecular hydrogen bond, relative to the more flexible alcohols.

2. Complexes with Ethyl Propionate. *a. Low-Energy Conformers of Complexes.* The alcohol:EP conformations identified by the MM algorithm can be categorized on the basis of presence or absence of an intermolecular hydrogen bond and the presence or absence of an intramolecular hydrogen bond. The resulting four possibilities are illustrated in Figure 8.

To categorize the complexes, we define intermolecular hydrogen bonds as those with an $\text{OH}\cdots\text{O}$ distance of less than 2.0 Å, because the calculated distribution of the intermolecular hydrogen bond distances has a natural break point in this region: most complexes have an $\text{OH}\cdots\text{O}$ distance of either less than 2.0 Å or greater than 3 Å. Although some higher-energy complexes have distances in the 2.0–2.5 Å range, the $\text{OH}\cdots\text{O}$ angle of these complexes is considerably less linear: 125° compared with 140–160° for those with distances less than 2.0 Å. The range of lengths for intramolecular hydrogen bonds is determined also by setting distance maxima. For complexes that did not have an intermolecular hydrogen bond, cutoffs of 2.3 and 2.55 Å are used for $\text{OH}\cdots\text{O}$ and $\text{OH}\cdots\pi$ bonds, respectively. For complexes with intermolecular hydrogen bonds, the data have natural separations at 2.4 and 2.65 Å for $\text{OH}\cdots\text{O}$ and $\text{OH}\cdots\pi$ intramolecular bonds, respectively. The use of longer cutoff distances for defining intramolecular hydrogen bonds involved in simultaneous intermolecular hydrogen bonding is consistent with previous work on OMP.⁶ In that work, the intramolecular hydrogen bond is lengthened by about 0.1 Å upon formation of the three-centered hydrogen bond.⁶ Although the exact values of the stabilities change if the inter- and intramolecular cutoff distances are varied, the overall preference of a complex for a particular type of bound structure does not.

The relative stabilities of the four types of conformations for all four alcohol:EP complexes are given in Table 3. The stability of PE complexes with and without intermolecular hydrogen bonding is similar as long as the intramolecular hydrogen bond is retained. For PP, the primary mechanism for PP:EP complexation appears to be the formation of two-centered hydrogen bonds. Indeed, no intermolecularly hydrogen-bonded complexes possess intramolecular hydrogen bonds. The calculations suggest

TABLE 3: Free Energies (kJ/mol) of the Conformational Categories Shown in Figure 9 of Alcohol:EP Complexes Relative to the Lowest Free-Energy Conformer as Calculated by Mining Minima

alcohol	inter		no inter	
	intra	no intra	intra	no intra
PE	0.0	1.3	1.0	3.4
PP	—	0.0	16.2	12.0
POE	0.0	5.9	3.9	5.3
POP	19.6	0.0	7.1	9.1

that POE, which forms the strongest intramolecular hydrogen bond (Table 2), retains this preference upon complexation with EP. Thus, the lowest-energy POE:EP complex forms a three-centered hydrogen bond. In fact, the preference for retaining the intramolecular hydrogen bond is so strong for POE that complexes with no intermolecular hydrogen bond but with an intramolecular hydrogen bond are more favorable than two-centered intermolecularly hydrogen-bonded complexes. In contrast, POP is calculated to bind to EP through the formation of two-centered hydrogen bonds. In summary, PP, POE, and POP primarily bind through the formation of an intermolecular hydrogen bond, whereas PE exhibits a weaker preference for the formation of intermolecular hydrogen bond formation.

b. Infrared Spectra of Phenyl Alcohols and Phenoxy Alcohols with EP. Figure 9 shows the IR spectrum for each aromatic alcohol in hexane solutions with 200 mmol/L of EP. In all four spectra, a broad OH stretching peak appears which increases in amplitude with increasing EP concentration (data not shown). This new peak is centered at 3566 cm^{-1} for the PE:EP, PP:EP, and POP:EP spectra and at 3552 cm^{-1} for the POE:EP spectrum. Although the lack of fine structure makes detailed analysis impossible, the appearance of the new lower-frequency stretching peak upon addition of EP confirms that an intermolecular hydrogen bond is formed between the alcohols and EP.

3. Binding Affinities. Table 4 presents the calculated binding affinities for all four alcohol:EP complexes. Previously reported data for *p*-methoxyphenol:EP (pMP:EP) and oMP:EP complexes are also given. All four alcohols bind with similar small changes in free energies of -0.9 kJ/mol to -2.4 kJ/mol . These affinities are substantially weaker than that obtained for the pMP:EP complex, even though all five molecules appear to bind primarily by formation of an intermolecular hydrogen bond involving a hydroxyl donor and a carbonyl acceptor. If EP is a good model for the sorbent resin XAD-7, a similar pattern of affinities should be obtained in experimental adsorption measurements. This is observed, as shown by the experimental adsorption affinities (q/C) in Table 4. The calculations are now used to analyze the molecular basis of the experimental observation that pMP binds more strongly than any of the four alcohols.

One reason that pMP binds more strongly is because phenol hydroxyls are more acidic than alcohol hydroxyls and are thus better hydrogen bond donors. The difference in donating ability is accounted for in the calculations, because the CHARMm force field assigns a slightly less positive charge to an alcohol hydroxyl hydrogen and a slightly more negative charge to the hydroxyl oxygen, relative to phenol. These changes in the charge distribution decrease the strength of the Coulombic interaction of an alcohol hydroxyl with the partial negative charge of the carbonyl oxygen acceptor. The significance of this change may be examined by calculating the change in energy ($U + W$ in eq 7) when the most stable single conformer of the POE:EP or POP:EP complex is pulled apart, relative to the corresponding change for the pMP:EP complex. The resulting energy changes indicate that the phenolic hydrogen bond is stronger by about 2.4 kJ/mol .

This difference in intermolecular hydrogen bond strength is reflected in the measured adsorption enthalpies of phenols and alcohols onto XAD-7. Previous studies using calorimetric²⁹ and van't Hoff¹² methods demonstrate that phenol derivatives have adsorption enthalpies approximately 8 kJ/mol more negative than phenyl alcohols. A similar analysis was performed for the alcohols studied here using the van't Hoff method as shown in Figure 10. As shown in Table 4, the adsorption enthalpy of pMP is -35 kJ/mol , 10 kJ/mol more negative than the adsorption enthalpies of phenylpropanol. Such adsorption enthalpies provide information on the strengths of the intermolecular hydrogen bonds, so long as the molecules studied do not form significant intramolecular hydrogen bonds and are not sterically hindered from forming intermolecular hydrogen bonds. These results support the conclusion that phenol hydroxyls form intrinsically stronger intermolecular hydrogen bonds than do alcohol hydroxyls.

Competition between inter- and intramolecular hydrogen bonds represents another possible cause of the difference between the binding affinities of pMP and the alcohols. The present calculations (cf. Table 2) suggest that the intramolecular hydrogen bonds of the examined alcohols are rather weak compared with oMP, where intramolecularly hydrogen-bonded conformers are favored by 20 kJ/mol . Nonetheless, the competition between intramolecular and intermolecular hydrogen bonds does influence the calculated binding affinities for alcohol:EP complexes. When all conformers with an intramolecular hydrogen bond were removed hypothetically from both the free and complexed states, the calculated free energies of binding become more negative by 1.4 , 0.1 , 2.0 , and 0.8 for PE, PP, POE, and POP, respectively. These calculations indicate that, for these alcohols, the formation of intramolecular hydrogen bonds suppresses intermolecular EP binding by only 0.1 – 2.0 kJ/mol .

The calculations suggest that the cost in configurational entropy for forming an intermolecular hydrogen bond is higher for the phenyl alcohols examined here than for pMP. All four alcohols experience an entropic penalty of 27 – 30 kJ/mol upon binding to EP. In contrast, the entropic cost of binding for pMP is approximately 22 kJ/mol . This difference is traceable to the fact that, even when hydrogen-bonded to EP, the phenyl alcohols have enough flexibility to contact and be excluded by the sorbent surface as modeled here by an excluded region (see Methods). However, pMP, once hydrogen-bonded to EP, cannot adopt any conformations that would bring it into contact with the plane that represents the sorbent. Thus, binding to the EP analogue may cause a significant conformational restriction for the alcohols but not for pMP.

Conclusion

The stability of the intramolecular hydrogen bonds in the four aromatic alcohols studied depends on an interplay of electrostatics, steric strain, and entropy. The conformational analysis performed predicts that for PE intramolecularly hydrogen-bonded conformers are more stable by 3.6 kJ/mol , whereas for PP, extended conformers are more stable by 6.5 kJ/mol . For the phenoxy alcohols studied, POE favors intramolecularly hydrogen-bonded conformers by 8.1 kJ/mol , whereas POP favors nonintramolecularly hydrogen-bonded species by 2.1 kJ/mol . These conformational preferences are in good agreement with the observed IR spectra.

The agreement with IR spectroscopy allows a detailed examination of the individual energy components of intra- and nonintramolecularly hydrogen-bonded conformers to investigate

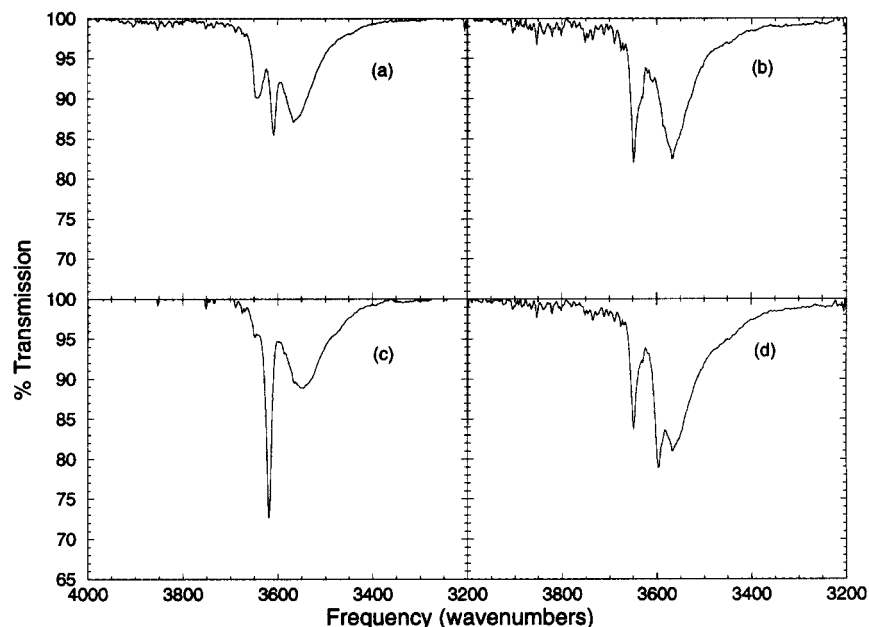


Figure 9. Infrared spectra of (a) 11.8 mmol/L PE, (b) 12.0 mmol/L PP, (c) 11.8 mmol/L POE, and (d) 12.1 mmol/L POP complexed with 200 mmol/L of EP.

TABLE 4: Comparison of Calculated Binding Affinities of Alcohol:EP Complexes to Experimental Adsorption of Alcohols onto an Acrylic Ester Sorbent^a

alcohol	ΔG°	K_b	q/C	$\Delta H^\circ_{\text{expt}}$
PE	-0.9	1.4	0.05 ± 0.001	-26 ± 2
PP	-1.7	2.0	0.07 ± 0.001	-28 ± 3
POE	-2.2	2.4	0.08 ± 0.003	-25 ± 1
POP	-2.4	2.6	0.10 ± 0.004	-26 ± 1
oMP ^a	-2.6	2.8	0.039	-27 ± 3
pMP ^a	-9.2	39	0.82	-35 ± 2

^a The experimental adsorption affinities, q/C , are in L/g and the experimental enthalpy changes, ΔH° , and computed free energies, ΔG° , are in kJ/mol. ^b Error estimates are not provided because these values were interpolated from data given in ref 12.

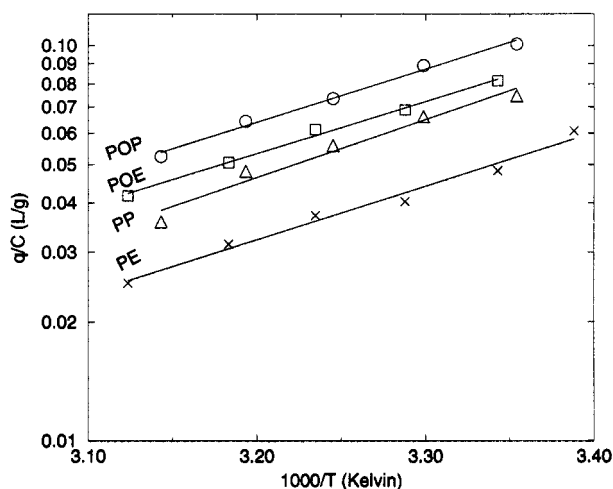


Figure 10. Experimental binding affinities as a function of temperature for the four studied alcohols adsorbing onto the acrylic ester resin XAD-7 from hexane.

the physical basis for the conformational preferences. The calculations suggest that three factors are important. First, as expected, the Coulombic energy favors the formation of an intramolecular hydrogen bond in all four alcohols. In fact, this energy term results in a surprisingly strong $\text{OH}\cdots\pi$ intramolecular hydrogen bond for PE. Comparisons with IR spectra

suggest that the calculations may overestimate the $\text{OH}\cdots\pi$ bond strength. Additionally, the Coulombic energy term is more favorable for the formation of an intramolecular hydrogen bond for PP and POP, which form six-membered rings, and consequently shorter hydrogen bonds, than for PE and POE, which form five-membered rings. However, the increase in Coulombic stabilization from five- to six-membered rings is smaller for the alkoxy alcohols than the aliphatic alcohols because of the greater repulsive interaction of the ether oxygen acceptor as compared with the aromatic carbon acceptor.

Second, entropy opposes the formation of intramolecularly hydrogen-bonded conformers. This opposition increases with increasing flexibility, with the formation of six-membered rings being less favorable than the formation of five-membered rings. Also, $\text{OH}\cdots\pi$ intramolecular hydrogen bonds are more entropically disfavored than $\text{OH}\cdots\text{O}$ bonds because additional benzyl ring degrees of freedom are constrained by the formation of the $\text{OH}\cdots\pi$ bonds. Third, for PP and POP, the dihedral strain energy strongly favors the nonintramolecularly hydrogen-bonded conformers.

All four alcohols are calculated to bind to EP with small changes in free energies of -0.9 to -2.4 kJ/mol. This is much weaker than the binding calculated for pMP to EP which has a ΔG° of -9.2 kJ/mol. These relative binding affinities are in good agreement with the experimental adsorption affinities of the alcohols and pMP to the acrylic ester resin. The calculations suggest that the alcohols bind more weakly than pMP for several reasons. One reason is the reduced hydrogen bond donating ability of the alcoholic hydrogen compared with the phenol hydrogen. The calculations also suggest that phenyl and phenoxy alcohols suffer a larger entropic penalty upon intermolecular hydrogen binding compared with pMP. Finally, the formation of weak intramolecular hydrogen bonds diminishes intermolecular hydrogen bonding for PE, POE, and POP.

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