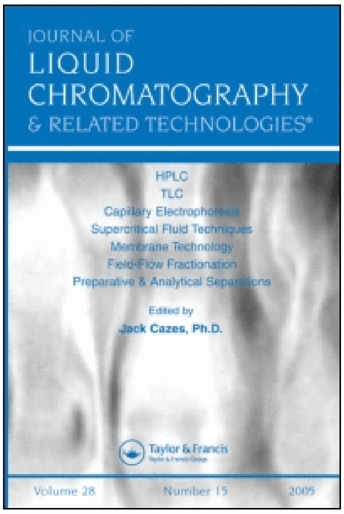

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MOLECULAR INTERACTIONS ON POLYSTYRENE STATIONARY PHASES

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ABSTRACT

The strength of the interactions between individual molecules and solvent-swollen polystyrene gels can be correlated using Lewis acid-Lewis base arguments. Polystyrene may be viewed as a Lewis base because it may serve as an electron-pair donor to a suitable electron-pair acceptor. Mobile phases such as toluene and tetrahydrofuran (THF) are also Lewis bases. The stationary phase gel and mobile phases such as toluene and THF will compete for a Lewis acid solute, with the stronger base always interacting preferentially. For a THF mobile phase, acidic solute-mobile phase interactions predominate and size exclusion chromatography (SEC) will be the only separation mechanism occurring. Polystyrene appears to be a stronger base than toluene, and acidic solutes always interact with the gel. Retention in this system includes contributions from both SEC and gel-solute interactions. Chloroform is a Lewis acid and will interact strongly with polystyrene. Acidic solute-gel interaction must then be stronger than the chloroform-gel interaction for non-SEC retention to occur. The relative strength of the Hydrogen-bonding interactions can be predicted using Drago's E and C constants. Dipole-dipole interactions can be estimated using simple solubility parameter theory. This approach unifies experimental data reported earlier and allows a qualitative prediction of the performance of other SEC mobile phases.

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INTRODUCTION

The existence of solvent-related non-exclusion effects on solvent swollen polystyrene gels has been recognized for many years. Size exclusion chromatography (SEC) on these gels is possible only if such non-exclusion effects are absent. Recent work in this laboratory (1,2) has proposed a scheme for determining when non-exclusion effects are occurring. Only when the slope of the van't Hoff plots (ln k vs 1/T) is zero, can the system be considered SEC. Although other procedures are available to indicate non-exclusion effects (cf. ref. 3-7), the van't Hoff plot approach offers a direct means to recognize such effects and determine their relative strengths.

In previously published work, three mobile phases were studied in detail--chloroform, toluene, and tetrahydrofuran (THF). With chloroform only phenols and carboxylic acids displayed non-SEC retention (1). For toluene, all tested solutes displayed non-SEC retention (2); every solute tested interacted with the gel (i.e.$\Delta H<0$). Using THF as mobile phase, only nitromethane showed these interactions (2).

Given the information available, it would be advantageous to be able to interpret these results in a more quantitative manner. Specifically, this involves the ability to predict when only SEC occurs ($\Delta H=0$) and when other enthalpic interactions ($\Delta H<0$) are occurring along with the SEC contribution to retention. Such a general predictive scheme would allow estimation of enthalpies for certain functional groups and, ultimately, for polymers containing those functional groups. In this way, one could more easily identify conditions where SEC is not likely to be the sole separation mechanism.

An ideal predictive scheme would be one which allowed an *a priori* calculation of the exact energy (or enthalpy) of interaction for solute molecules with mobile and stationary phase. Since existing theoretical models do not yet allow such calculations, procedures must be used which provide the relative energy of interaction. One such method involves the solubility parameter, δ. An excellent general review with an extensive list of solute parameters is available (8). The solubility parameter has been used in liquid chromatography mainly for the prediction of retention and selectivity (9,10). Predictions are fairly accurate for systems involving dispersion and dipole effects, but less successful when Hydrogen-bonding occurs. Expanded solubility parameter treatments also have been applied to chromatographic systems (11,12). Simple solubility parameter theory has been mentioned in discussing SEC systems (5,13,14), but mostly as a means for predicting overall retention and discussion of non-exclusion effects in very general terms.

A successful general method for estimating the enthalpy of Hydrogen-bond adduct formation is that of Drago and coworkers (15-18). Using equation 1,

$$-\Delta H = E_A E_B + C_A C_B \tag{1}$$

the enthalpy of adduct formation (A•B) can be estimated, where E is a parameter related to electrostatic contributions, C is a parameter related to covalent contributions, and subscripts A and B refer to the acid and base (acceptor and donor), respectively. This scheme is based on interactions between model compounds in an inert solvent. Direct applications of this equation to chromatographic retention are limited (19,20).

An advantage of the E and C approach is that it quantitatively extends the definition of "acid", in the Lewis sense, to include species such as chloroform. Similarly, the definition of a "base", in the Lewis sense, can be extended to solutes such as benzene and toluene. These aromatic compounds have electrons available for donation to a suitable Lewis acid, but benzene and toluene are not usually considered bases, since their electron-pair donating ability is considerably less than that of, for example, aliphatic amines. The E and C approach provides a means for estimating relative interaction strengths for relatively weak Lewis bases.

These two predictive methods, solubility parameters and the E and C approach, are used in this work to independently estimate the overall enthalpy of interaction for solutes in toluene and chloroform mobile phases. These calculations are based on bulk solution properties, while experimental data are obtained from chromatographic retention measurements for a system involving a mobile-stationary phase interface. This method is therefore limited to the prediction of relative, not absolute, enthalpy changes. However, the calculations are in good agreement with observed values if the inherent limitations of the theories are considered. This general approach allows qualitative predictions about the performance of other systems not studied.

MATERIALS AND METHODS

Equipment

The chromatographic system was identical to that described earlier (2). Temperature control for the column was better than 0.2°C. All data were collected at 2 Hz and processed with semi-automatic software developed in this laboratory. Toluene data were collected at 10, 25, 40, and 55°C. Chloroform data were obtained at 10, 20, 30, 40, and 50°C. Retention times were reproducible to better than 2% RSD.

Chemicals

Toluene was HPLC grade and used as received. Chloroform was obtained as reagent grade and purified as in (1) to remove ethanol.

Test solutes were chosen to reflect a variety of functional groups. The number of specific solutes chosen was limited by the availability of a complete set of solute parameters (solubility parameter, E and C constants, solvatochromic parameter) for each solute. Complete van't Hoff plot data were obtained for the following solutes - benzyl alcohol, chloroform, ethanol, hexafluoro-2-propanol, 2-methyl-2-propanol, phenol, water, acetonitrile, benzene, dimethylsulfoxide, diethyl ether, ethyl acetate, pyridine.

RESULTS AND DISCUSSION

The strength of the interaction of a solute molecule with the stationary phase may be measured by employing the van't Hoff relationship in its chromatographic form,

$$\ln k = -(\Delta H/R)\ (1/T) + [\Delta S/R - \ln\beta]$$

where k is the partition ratio, T the absolute temperature, β the phase ratio, ΔH the energy change, and ΔS the associated entropy change for the interaction. The slope of a plot of ln k vs. 1/T provides the enthalpy change for this process. If no net interaction occurs between solute and stationary phase, then $\Delta H=0$ and the slope of the van't Hoff plot is zero; retention does not change with temperature for this situation. If a net attractive interaction occurs, the enthalpy change is negative and a positive van't Hoff plot slope is observed; retention decreases with increasing temperature. Net repulsive interactions would result in a negative slope (positive enthalpy change), but this has not been observed with the systems under study. A non-SEC contribution to retention is therefore identified by a negative enthalpy change (positive slope). This situation is distinguished from a pure SEC system (zero slope) by a statistical evaluation of the regression data, as described in (1). All enthalpy changes reported here are indeed obtained from statistically non-zero slopes.

The interaction of a solute with the stationary phase gel may be described by the following equilibrium,

$$X{\cdot}M + M{\cdot}S \rightleftarrows X{\cdot}S + M{\cdot}M$$

where X, M, and S represent solute, mobile phase, and stationary phase, respectively. The change in energy for this process is the sum of the individual enthalpies associated with each interaction, as given in equation 2.

$$\Delta H = H_{X\cdot S} + H_{M\cdot M} - H_{X\cdot M} - H_{M\cdot S} \qquad (2)$$

Note that this model does not presume a specific type of displacement mechanism, but merely measures the relative strengths of the individual interactions for the overall displacement. The overall enthalpy change, ΔH, from equation 2 will be negative if the solute prefers the stationary phase over the mobile phase. This means that the equilibrium is shifted to the right. If this represents a valid model for the systems under study, then any enthalpy changes calculated from equation 2 should follow the same trends as the experimental data obtained from van't Hoff plots.

The thermodynamic interaction model requires that the three components of the system (mobile phase, stationary phase, solute) be first qualitatively classified according to their Lewis acid/Lewis base properties. The following solutes are considered "acids" (electron acceptors): benzyl alcohol, chloroform, ethanol, hexafluoro-2-propanol, 2-methyl-2-propanol, phenol, and water. The remaining solutes are considered "bases" (electron donors): acetonitrile, benzene, dimethylsulfoxide, diethyl ether, ethyl acetate, and pyridine.

The Polystyrene/Toluene System

Because of its electron-rich aromatic rings, the polystyrene gel may be considered a "base". Like many other aprotic aromatic hydrocarbons, the actual electron-donating ability is not large. However, in the presence of a suitable Lewis acid, a donor-acceptor adduct can indeed be observed. By a similar argument, toluene may be viewed as a Lewis base. The polystyrene/toluene system, therefore, consists of a weak base stationary phase and a weak base mobile phase. The most interesting interactions should be observed for Lewis acid solutes, which will have a choice of bases with which to interact (toluene and polystyrene). The interaction with the stronger base will be preferred.

The ranking of toluene and polystyrene is possible using arguments developed with the E and C concept. Because of the weak electron-donating ability of alkyl substituents, toluene may be considered a slightly stronger base than benzene. Similarly, ethylbenzene (a polystyrene surrogate) is a slightly stronger base than toluene in the Drago model (21). Thus the acid-base interactions should always be stronger with the gel than toluene and it is easy to see why acidic solutes in this system exhibit negative enthalpies from the van't Hoff plots (2).

This explanation can be further rationalized by the terms in equation 2. Compared to the magnitude of Hydrogen-bonding interactions one would expect $H_{M \cdot M}$ and $H_{M \cdot S}$ contributions to be small (base-base, or dipole-dipole interactions). The difference, H_{MM}-H_{MS}, should then be negligible. Equation 2 reduces to

$$\Delta H = H_{X \cdot S} - H_{X \cdot M} \qquad (3)$$

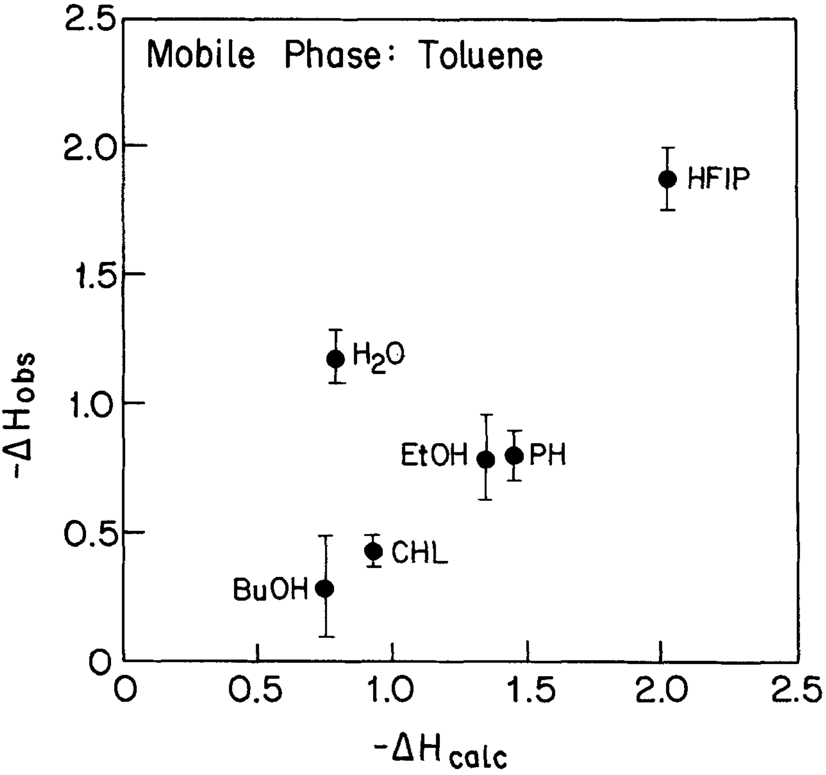

FIGURE 1. Calculated vs observed enthalpy changes (in kcal/mol) for acidic solutes with toluene mobile phase. Values were calculated using E and C constants for the interaction of each solute with benzene. Solutes: HFIP - hexafluoro-2-propanol, PH-phenol, EtOH-ethanol, CHL-chloroform, BuOH-2-methyl-2-propanol. The error bars indicate the 95% confidence interval for the observed enthalpy change.

Thus, the relative enthalpy changes for a set of solutes are controlled by the differences in acid-base interaction energies; i.e. mobile and stationary phase compete for an acidic solute. In this system $H_{X \cdot S}$ will always be more negative than $H_{X \cdot M}$, and ΔH will always be negative.

Figure 1 demonstrates fair agreement between observed enthalpies and those calculated from the E and C constants. Since no constants are available for toluene or polystyrene, equation 3 cannot be used directly. The calculated enthalpies are obtained from a single calculation using benzene as a donor for each of the acids. The model proposes that the observed enthalpies are a result of various acid-base interactions in the system. Equation 3 predicts that the total energy change results from a difference in individual interaction strengths. However, the magnitude of this difference follows the magnitude of a single interaction, so the benzene calculations represent a valid approximation. The satisfactory trend in Figure 1 supports this approach and the validity of the E and C concept in estimating the relative strength of adduct formation. The concept of non-SEC retention by acid-base adduct formation is also supported by these results.

Note that water does not follow the same trend. Drago's constants underestimate the strength of the interaction. This may mean the constants are in error because other effects are contributing in a way which is not accounted for in the calculation of the constants.

It has now been established that acidic solutes should always interact with the gel. The question remains as to why the basic solutes also prefer the get. A reasonable suggestion would be that dipole-dipole effects are responsible. Solubility parameter theory is useful for such systems, and individual enthalpy changes can be estimated using equations 4a-d.

$$\Delta H_{X \cdot S} = V_X (\delta_X - \delta_S)^2 \tag{4a}$$

$$\Delta H_{M \cdot M} = V_M (\delta_M - \delta_M)^2 = 0 \tag{4b}$$

$$\Delta H_{X \cdot M} = V_X (\delta_X - \delta_M)^2 \tag{4c}$$

$$\Delta H_{M \cdot S} = V_M (\delta_M - \delta_S)^2 \tag{4d}$$

where V represents the molar volume. The δ-values used are chosen from the same set (8) to avoid problems with the underlying assumptions used in obtaining the values. The actual parameter chosen represents a combination of dispersion, dipole, and Hydrogen-bonding effects. The value for polystyrene (9.31) is obtained from (14).

Following the general approach outlined by Karger et al (12), the overall change in enthalpy (or energy) for the retention process may be calculated from the enthalpy changes associated with each interaction [cf. equation 7 of reference (12)]. This approach is required here because the individual (absolute) enthalpies of interaction cannot be obtained from solubility parameter theory. Substitution of the enthalpy changes in equations 4a-d for the appropriate enthalpies in equation 2 is valid because the absolute enthalpies of individual species associated with equations 4a-d (H_X, H_M, and H_S) will all cancel if substituted into equation 2. The result is that either absolute enthalpies or enthalpy changes may be used in equation 2.

The results are shown in Figure 2. Considering the assumptions and limitations inherent in solubility parameter theory, the trend for the bases is acceptable. All bases, except acetonitrile, fall on the same line. All acids are below the line, indicating that the calculations overestimate the interactions. Solubility parameter theory is less useful for Hydrogen-bonding species, and an error in the parameter values for these solutes is a likely explanation for the deviations. Although water apparently falls on the line, this is probably a fortuitous coincidence, since the errors in the values for water are larger than for any other solutes. The bases, which do not form adducts in this system, exhibit excellent linearity. There is no obvious explanation for the acetonitrile anomaly.

With the trend for proposed model now established, it should be possible to predict relative enthalpies for other solutes, or perhaps oligomers containing specific functional groups, if the appropriate solubility parameters are available. It should be noted that the use of expanded solubility parameter equations (9,12) did not improve the correlations. In fact, these equations produced poorer results, probably due to Hydrogen-bonding limitations and a lack of suitable parameters for the stationary phase.

The Polystyrene/Chloroform System

This system consists of an acidic mobile phase and a basic stationary phase. There is now a strong acid-base interaction between mobile and stationary phase ($H_{M\cdot S}$ large), and a change in selectivity will result, compared to toluene.

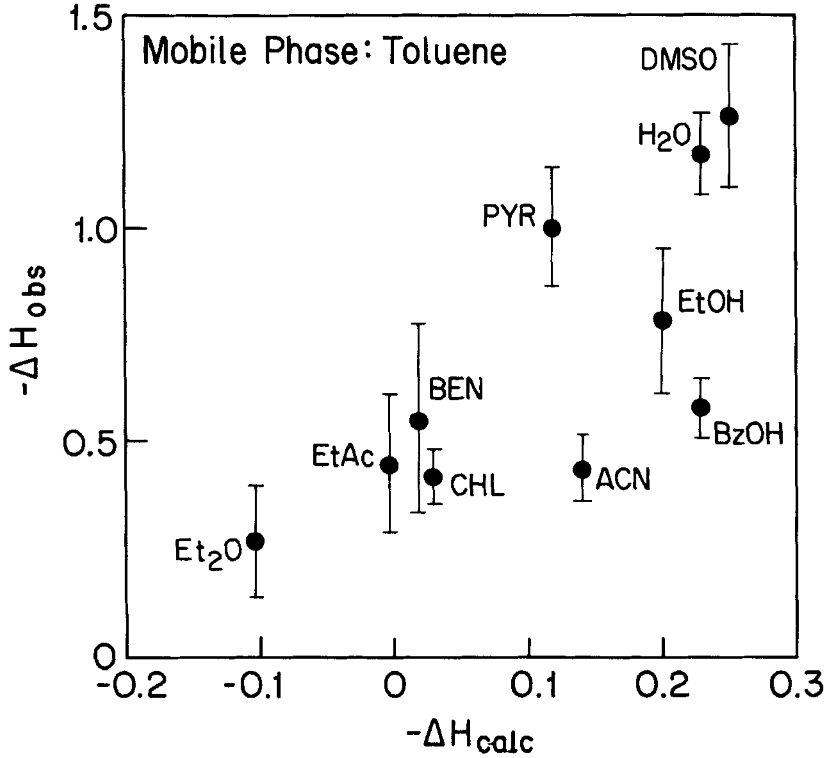

FIGURE 2. Calculated vs observed enthalpy changes (in kcal/mol) for toluene mobile phase using solubility parameter theory. Values were calculated using equations 2 and 4 a-d, and values from reference (8). Solutes: DMSO-dimethylsulfoxide, PYR-pyridine, BzOH-benzylalcohol, ACN-acetonitrile, BEN-benzene, EtAc-ethylacetate, Et_2O-diethylether. Other abbreviations as in Figure 1.

For an acidic solute, we can assume that the magnitudes of $H_{M \cdot M}$ and $H_{X \cdot M}$ (acid-acid interactions) are small, and the difference, $H_{M \cdot M} - H_{X \cdot M}$, will be negligible, compared to the magnitude of the Hydrogen-bonding interactions. This reduces equation 2 to

$$\Delta H = H_{X \cdot S} - H_{M \cdot S} \qquad (5)$$

Now the overall enthalpy change will result from a competition between two acids (solute and mobile phase) for the only available base

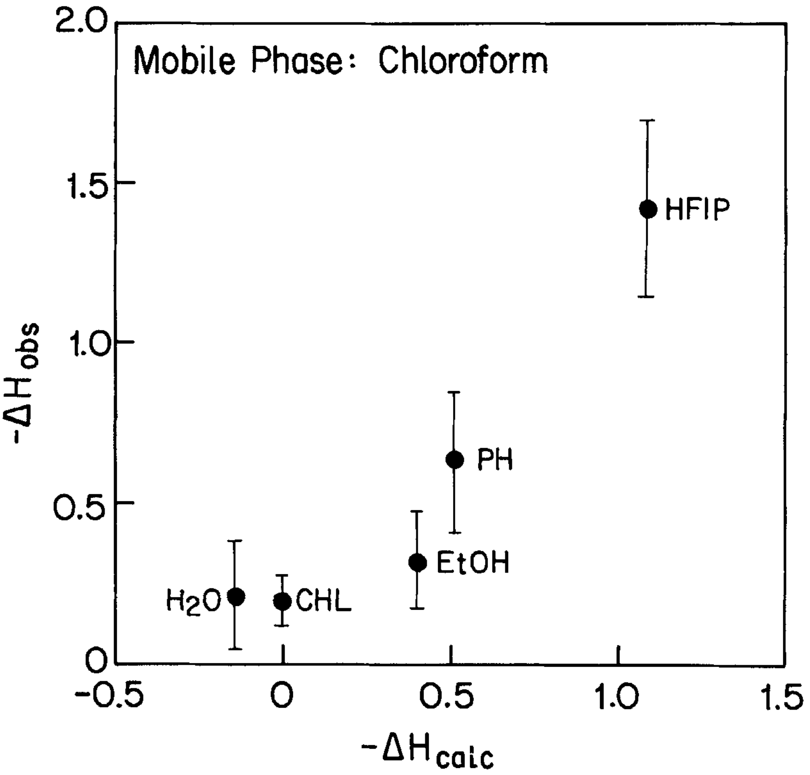

FIGURE 3. Calculated vs observed enthalpy changes (in kcal/mol) for chloroform mobile phase. Values were calculated using E and C constants and equation 5. Abbreviations as in Figure 1.

(polystyrene). Since the stronger acid will win this competition, a solute molecule must be a stronger acid than chloroform to be able to interact with the gel. This was suggested earlier (1), and is clearly justified, especially in light of the fact that the interaction between chloroform and aromatic rings has been measured spectroscopically (22).

A comparison of calculated enthalpy changes, using equations 1 and 5, with observed enthalpy change is shown in Figure 3. Again, the calculations correctly predict the proper order of interaction strength. For 2-methyl-2-propanol (not shown) a positive enthalpy was calculated; the observed slope was indeed zero, indicating additional agreement with the proposed model. As with the toluene data, Drago's constants underestimate the value for water.

For basic solutes, a different situation exists. A strong complex will form with the mobile phase ($H_{X \cdot M}$ large). The value for $H_{X \cdot S}$ will be small compared to $H_{X \cdot M}$ and $H_{M \cdot S}$ will remain unchanged. The overall enthalpy will always be positive. Indeed no statistically significant solute-stationary phase interaction has been observed for a basic solute in this system, and SEC effects will be the only contributions to retention.

The value of the solubility parameter for chloroform (9.3) is so close to that for polystyrene that calculations involving equations 4a-d are meaningless. Fortunately, the system can be described adequately using qualitative acid-base arguments. The only solutes which can interact with the gel are those which are stronger acids than chloroform (phenols, carboxylic acids, etc.). Finally given the fact that ethanol interacts with the gel even in the presence of chloroform it is important that this additive be removed from the chloroform before use if the results are to be properly interpreted.

CONCLUSIONS

A general trend which supports the proposed model has been demonstrated for a variety of functional groups. In general, discussions of retention mechanisms on solvent-swollen polystyrene gels must consider donor-acceptor adduct formation when the appropriate acid/base components are present. The model also provides some insight into the actual polymer swelling process, indicating that the structure of the "gel" may be different for each solvent.

The general trends discussed allow qualitative predictions to be made about other systems. The polystyrene/THF system is a variation of the toluene system, except that the mobile phase is a stronger base. All acidic solutes will prefer the mobile phase, producing van't Hoff plots with zero slopes, as is observed (2). Basic solutes will only interact if their dipole-dipole interactions with the gel are stronger than interactions between THF and the gel. This is apparently the case for nitromethane only.

Hexane or cyclohexane can interact with the gel through dispersion interactions only. This is a considerably weaker interaction than any other discussed here. As a result, acidic solutes will easily interact with the gel, and basic solutes will probably also shown non-zero slopes due to dipole effects. This system should not be considered SEC; it is more likely conventional normal phase chromatography. Methylene chloride (CH_2Cl_2) is a weaker acid than chloroform and possesses a significantly smaller dipole. It should behave like chloroform, except that even weaker acids will interact with the stationary phase, and some bases with large dipoles may interact with the gel. This system is probably not SEC either, except for less polar, non-Hydrogen-bonding solutes.

Finally, the discovery that water interacts with the gel, even in the presence of toluene or chloroform, is significant because of the interest in using polystyrene stationary phases for reverse phase applications. Selectivity effects may then be partially explained by considering the acid-base properties of the mobile phase. The well-known observation that polystyrene gels will swell in alcohols, or even water, is readily rationalized by acid-base arguments.

The model presented here should be viewed as qualitative. The prediction of enthalpy changes using the approach outlined will be most useful in identifying the relative magnitudes of such phenomena. Undoubtedly, exceptions will occur when a particular interaction dominates a molecule to an extent which is not reflected in the value of the solute parameters (e.g. induced dipoles). However, the approach proposed should provide a general, qualitative understanding of mobile phase effects until a more rigorous theoretical explanation is developed.

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