with the help of eq 2 and the integration of the relevant host and guest signals in the spectrum, which gives the total concentration of G, ($[G]_{tot}$), and the total concentration of the aa conformer of **3c**, ($[aa]_{tot}$) (eqs 4 and 5).

$$[aa\cdot G] = [aa]_{tot} - [aa] \quad (4)$$

$$[G] = [G]_{tot} - [aa\cdot G] \quad (5)$$

Determination of Association Constants by UV Titrations. Stock solutions were prepared in $CHCl_3$, containing approximately 2 mM **3d** (stock solution A). From these stock solutions, new solutions containing also approximately 1 M guest were prepared (stock solution B). Stock solution A (1.7 mL) was placed in a 1-cm cuvette. For each successive data point, a 25-μL aliquot of stock solution B was added to the cuvette. K_as were calculated with the help of a computer program that evaluates K_a and ϵ in a way analogous to that described for the determination of the association constants from the ^1H NMR shift titrations.[25] Excellent fits were obtained assuming an experimental error of 0.0003 absorption units. The extinction coefficients of the free guests and **3d**, which are required for the calculations, were determined separately. The K_a values for binding to the aa conformer were obtained by dividing the calculated K_a values by the fraction of molecules **3d** that are in the aa conformation when no guest is present (0.027). This procedure is allowed if it is assumed that only the aa conformer of **3d** binds guest molecules (see text).

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Gas Chromatographic Study of Solute Hydrogen Bond Basicity

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Abstract: The purpose of the present work was to develop a scale of relative hydrogen bond basicity for a wide variety of solutes by means of their retention in gas chromatography. We used a powerful hydrogen bond donor (4-dodecyl-α,α-bis-(trifluoromethyl)benzyl alcohol) as an active hydrogen bond donor phase and a related ether (4-dodecyl-α,α-bis(trifluoromethyl)benzyl methyl ether) as a chemically similar but hydrogen bond inert reference stationary phase. The results are compared to a free energy based scale for the formation of 1:1 hydrogen bond complexes. In general, agreement is good, but a number of systematic discrepancies are found. FT-IR studies show that complexes with stoichiometries higher than 1:1 can be formed even for species as simple as THF in the presence of excess donor. Our results indicate that the use of hydrogen bond basicity scales based on the free energy of formation of hydrogen bond complexes to the rationalization of solvation-related phenomena must be used with discretion, at least in solvents which are very strong hydrogen bond acids.

Introduction

The phenomenon of hydrogen bonding is an immensely important topic in chemistry and biology.[1] The structure of bulk water[2] and the specific chemical and physical properties[3] of water are related to hydrogen bonding. The hydrophobic effect[4] and phenomena such as the self-assembly of micelles[4b-d] and vesicles[4c,d] and the folding of proteins[4e] are all partly a consequence of specific hydrogen bonding interactions in water. In addition, water is a strong hydrogen bond donor (acid). In fact, it is a better acid than it is a base.[5] Kamlet, Taft, and their collaborators have shown that solutes which are strong hydrogen bond bases are more soluble in water,[6] partition better from octanol into water,[7] and are less retained in reversed-phase liquid chromatography[8] than are otherwise similar but less basic solutes. Such important properties of a molecule as its toxicity to various organisms[9] and its partitioning between blood and various body tissues[10] correlate strongly with the species' ability to accept a hydrogen bond. For these reasons, we feel that empirical scales of solute hydrogen bond basicity are very significant.

Hydrogen bond complexation represents a specific type of donor–acceptor[11] interaction. There have been many efforts to establish scales of relative acidity and basicity.[12] One of the best known approaches is the dual parameter scale of Drago and Wayland.[12g] Maria and Gal[13] have analyzed a very wide variety of basicity-dependent properties (BDPs). Using principle components analysis, they have shown that virtually all BDPs can be described as the weighted sum of two uncorrelated abstract factors. These abstract factors are describable as being primarily electrostatic and covalent, in agreement with the concepts of Drago.[12g] Abraham has shown that hydrogen bond formation generally corresponds to a specific combination of these abstract factors

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and that hydrogen bonding is primarily, but not exclusively, an electrostatic interaction.[14a]

The solvatochromic comparison method[12a,b] can be used to develop scales of solvent hydrogen bond acidity and basicity. It has only been over the past several years that scales of solute hydrogen bond acidity and basicity have been developed. Primarily through the work of Abraham and his co-workers,[14] great strides have been made in developing a reasonably general scale of solute hydrogen bond strength. It should be recognized that scales of solvent and solute basicity and acidity are conceptually very different (see below). Abraham developed his solute scales based on measurements of the equilibrium constants (see eq 1) for

$$\text{A–H} + \text{B} \rightleftharpoons \text{A–H}\cdots\text{B} \qquad (1)$$

formation of 1:1 complexes in a relatively inert solvent, such as carbon tetrachloride, where A–H is a hydrogen bond acid and B is a hydrogen bond base. In Abraham's work, both A–H and B were present at low concentration to avoid self-association, particularly of the acidic species.

In order for a general scale of HB acidity to be set up, it is essential that a plot of log K for base B_1 against log K for base B_2 be a single straight line. There must be no family-dependent behavior, regardless of the type of acid or base used. Abraham and his co-workers have shown that for alcohols, phenols, and strong nitrogen acids, family independence does exist.[14] However, certain exceptions must be recognized. First, some specific combinations of donors and acceptors are subject to a great deal of front strain. These pairs must be excluded. Second, it is now established[14a] that hydrogen bonding involves both electrostatic and covalent factors. For most hydrogen bond donors and acceptors, the *relative* contribution of these factors to bond formation lies in a narrow range. When the proportion of these two factors is not in this range, deviations from the straight-line family-independent behavior are observed. Such pairs of acids and bases must also be excluded. Thus, for a large number of bases, plots of log K for a set of acids for a given base vs log K for the same set of acids for an arbitrary reference base are straight lines that intersect in a relatively narrow interval at log K equal to −1.1 (±0.1).

As will be seen, there are considerable differences between the basicity scale developed here and Abraham's β_2^H scale. In large measure, these differences were anticipated in Kamlet's parameter estimation scheme for solute π_2^*, β_2, and α_2 values[9a] and in Abraham's recent gas chromatographic studies,[14e-g] wherein the need for summing individual hydrogen bond acceptor site basicities ($\sum\beta_2^H$) was postulated for systems in which the donor is in excess. However, in this work, we show that a single atom such as oxygen in THF that has two lone pairs can serve as the site for 2:1 complexation. The same is true for multiheteroatom functional groups such as amides, sulfoxides, or nitriles.

In this work, we will present our study of a solute basicity scale based on retention in gas chromatography. Hydrogen bond formation can greatly influence retention and separability. This has engendered considerable interest in devising schemes for quantifying the contribution of hydrogen bond acidity and basicity to retention. Among such schemes are the multicomponent solubility parameter approach[15,16] and the Snyder solvent classification "triangle".[17]

Retention in chromatography can be so sensitive to hydrogen bond formation that measurement of retention volumes as a function of the type and composition of the stationary phase can be used for the study of complex formation processes.[18] We will use measurements of retention in gas–liquid chromatography to establish an empirical free energy based scale of the *relative* hydrogen bond acceptor basicities. We will also use the generalized free energy based scales of basicity and acidity developed by Abraham and his co-workers. The experimental methodology is based upon the ideas involved in work by Purnell[19] and Martire.[20]

In the approach of Purnell,[19] a series of columns were prepared in which the concentration of a hydrogen bonding active molecule dissolved in a hydrogen bond "inert" diluent is varied. Our methodology is closely related, but not identical, to that of the Martire group. Their approach involves the use of two columns, each prepared with a pure stationary phase. One stationary phase serves as a reference phase. The reference phase is generally a hydrogen bond inert hydrocarbon. In contrast, in our approach, the reference phase is closely matched in polarity to the donor phase (see below). The second phase, in Martire's method, is a hydrogen bonding active phase and is usually an acceptor. The capacity factor of the solute of interest (e.g., an alcohol) and an alkane of similar size and shape are measured on both phases. The contribution of complex formation to retention is then computed on the basis of all four retention measurements.

Clearly in Purnell's approach, one must assume that the hydrogen bond additive will have no effect on solute retention if no molecular complex is formed or, alternatively, that the effect of chemically nonspecific factors such as changes in dispersive and dipolar interactions between the solute and the stationary phase are incorporated into the equilibrium constant. This approach is most fruitful when the concentration of the additive is sufficiently low so that the solute environment is not perturbed. However, low additive concentrations can only produce measurable changes in retention when the equilibrium constants are quite large. In essence, Purnell chose the hypothetically infinitely dilute (Henry's law) reference state for the solute, cosolvent, and complex as the basis for computing the equilibrium constant. Abraham and his co-workers used the same approach. The effect of this choice of reference state on the equilibrium constants computed in this fashion relative to the use of compliance with Raoult's law as the standard state are very well summarized in studies by Eckert et al. of hydrogen bond association equilibria of dilute alcohols in

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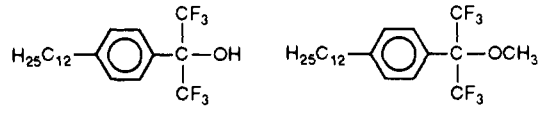
Chart I



I II

alkane solvents.[21] These effects can be very significant. In contrast, the Martire approach is based on the assumption that the test solute and its homomorph are retained in the same way and to the same extent on both phases when no molecular complex is formed. Thus, it offers an additional opportunity for cancellation of undesired effects. Even if dispersive interactions exactly cancel, one must still recognize that any test solute capable of forming a hydrogen bond complex is at least somewhat dipolar. Consequently, the Martire approach effectively subsumes the dipole–dipole and part of the dipole–induced dipole interactions into the equilibrium constant since the reference phase is nonpolar.

Previously we reported on a methodology for estimating dipolarity–polarizability (π_2^{*C}) and hydrogen bond acidity (α_2^C) parameters on the basis of gas chromatographic measurements.[22] In this work, we sought to develop a gas chromatographic method for estimating relative hydrogen bond basicities (β_2^C). This is a simpler and much more facile experiment than measuring the absolute equilibrium constant for hydrogen bond complexation, but it is conceptually more difficult. The stationary phase must be a good hydrogen bond donor. Thus, the stationary phase must have an active hydrogen. Virtually all good hydrogen bond acids are also reasonable hydrogen bond bases. For example, the Kamlet–Taft acidity (α) and basicity (β) of bulk butanol are 0.79 and 0.88, respectively.[23] Therefore, in the case of amphiprotic solutes such as alcohols and amines, one must deconvolve the solute acidity from its basicity. In contrast, it is easy to find very strong hydrogen bond bases which are not at all acidic. Hexamethylphosphorous triamide, one of the most powerful acceptors, has a β value of 1.05 and no measurable acidity. Kamlet, Taft, and their co-workers encountered this same problem in establishing the solvatochromic acidity scale for amphiprotic solvents.[12b]

We wanted to separate the contributions of dipolar interactions from the relative basicity. Clearly, we want one of the stationary phases to contain a very powerful hydrogen bond donor moiety which at the same time is a very weak hydrogen bond acceptor. This suggests the use of a highly fluorinated alcohol as the hydrogen bond donor. For example, hexafluoroisopropyl alcohol (α = 1.96[23]), due to the presence of the electron-withdrawing inductive effect of the two perfluoromethyl groups, is a far stronger hydrogen bond donor than is isopropyl alcohol (α = 0.76[23]). Trifluoroethanol is virtually as strong a hydrogen bond donor as is phenol, and hexafluoroisopropyl alcohol is a considerably stronger donor than phenol.[24,25] The solvent basicity of hexafluoroisopropyl alcohol has been estimated as 0.[23] For example, (trifluormethyl)acetone and *N,N*-dimethyltrifluoroacetamide are more than 10-fold weaker hydrogen bond bases than are acetone and *N,N*-dimethylacetamide.[24a] An additional major advantage of using a highly fluorinated alcohol is the fact that these species, in the bulk state, are far less self-associated than are other types of hydrogen bond donors. In order to cancel the contributions of dipolar interactions of a solute with the phase, we decided to assess the use of the methyl ether of the fluorinated alcohol as the reference phase.

Stationary phases for gas chromatography must be nonvolatile, and, consequently, low molecular weight highly fluorinated alcohols will not be useful. Based upon the above ideas and synthetic simplicity,[26] we decided to use 4-dodecyl-α,α-bis(trifluoromethyl)benzyl alcohol (Chart I, structure I) and its methyl ether (Chart I, structure II) as the donor and reference phases, respectively. We believe that it will mimic many of the properties of HFIPA. We expect it to be a very strong hydrogen bond donor and a very weak hydrogen bond base. Kivinen has measured the dimerization constant and heat of dimerization for HFIPA at 25 °C in carbon tetrachloride.[27] Extrapolation of his data to 80 °C (the temperature used in this study) and estimation of the concentration of the liquid as 3 M leads to an estimate of about 80% monomer. That is, this liquid is largely unassociated under the conditions used in this work.

There are two advantages to using a matched pair of stationary phases rather than a donor phase and a hydrocarbon reference of the same size and shape. First, we anticipate that dipolar contributions to retention will more completely cancel out with the use of a carefully matched reference phase (see below). Second, we expect that the effect of differential adsorption contributions to retention on the two phases will be minimized. In addition, we note that in many studies it has been shown that hydrocarbon phases do not completely wet even silanized supports.[28] Further, nonpolar stationary phases cannot compete very effectively for residual adsorption sites on the stationary phase when polar solutes are used, whereas a polar but hydrogen bond inert phase can compete to some extent. Finally, use of a polar reference phase will minimize the effect of gas–liquid interfacial adsorption.

The approach taken here to establishing the hydrogen bond basicity is founded upon the use of linear solvation energy relationships of the form developed by Kamlet, Taft, and their coworkers.[12a,b] Recently it has been explored as a method for examining retention in gas–liquid chromatography.[29,30] As shown by Abraham and ourselves, one of the most useful LSERs for gas to liquid transfer processes is

$$\log k' = SP_0 + l \log L^{16} + s\pi_2^* + d\delta_2 + a\alpha_2 + b\beta_2 \quad (2)$$

where L^{16} is the partition coefficient for transfer of the solute (by convention, solute parameters are denoted with a subscript 2, except for L^{16}) from the gas phase to hexadecane as measured at 25 °C. It simultaneously represents the contribution to retention from dispersive interactions and cavity formation in a given liquid phase (species denoted 1). π_2^* is the monomeric or solute dipolarity/polarizability parameter. Due to the significant differences in the mix of dipolarity and polarizabilities of aliphatic, polyhalogenated, and aromatic species, a polarizability correction factor (δ_2), taken as 0, 0.5, and 1.0, respectively, is usually required. α_2 is a solute hydrogen bond acidity parameter, and β_2 is a solute hydrogen bond basicity parameter.

Experimental Section

Preparation of 4-Dodecyl-α,α-bis(trifluormethyl)benzyl Alcohol. 4-Dodecyl-α,α-bis(trifluormethyl)benzyl alcohol was synthesized on the basis of an adaptation of a method given by Farah et al.[26] Seventeen grams of dodecylbenzene (Aldrich) was added to a 100-mL three-necked flask and diluted with 50 mL of carbon disulfide (Aldrich). Fifty milligrams of $AlCl_3$ catalyst, required for the Frieldel–Craft reaction, was added. A gas inlet tube was used to conduct the hexafluoroacetone (Columbia Organic Chemicals) from a lecture bottle via an airtight seal to the reactor, and a dry ice/acetone condenser was connected to the center neck of the reactor to return the gaseous hexafluoroacetone (bp −26 °C). A thermometer was inserted into the reactor. Two additional traps (hexylamine and water) were placed in-line with the reflux con-

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denser to remove any escaping hexafluoroacetone. The reaction was started at room temperature, and then the flask was placed in an ice bath at 0 °C after the reaction was underway. The gas inlet rate was controlled so that the input rate matched the reaction rate. If refluxing continued after the gas flow was stopped, we concluded that the reaction was complete. In any case, periodic TLC testing showed when the dodecylbenzene was consumed.

The reaction mixture was then shaken with deionized water to remove $AlCl_3$. The organic layer was washed twice with water and saturated sodium chloride and then dried over calcium sulfate. The dried solution was filtered, and the solvent was removed via distillation on a Rotovap at 100 °C. The product was then distilled at 159–161 °C under vacuum. Only a minor amount of viscous material was left after distillation. The product was identified by proton NMR and mass spectrometry. The final yield was about 90%.

Preparation of 4-Dodecyl-α,α-bis(trifluormethyl)benzyl Methyl Ether. The methyl ether was prepared by derivatization of the alcohol with methyl iodide by adapting a well-known method.[31] Fifteen grams of the alcohol was placed in a 100-mL flask, 20 mL of acetone was added as the solvent, and 40 g of methyl iodide was added with stirring. While the mixture was stirred in a water bath at room temperature, three 7-mL portions of 10 M sodium hydroxide were added. After each addition, the reaction mixture was heated in a water bath to reflux gently for 15 min. The reaction was monitored by TLC until the alcohol disappeared. Additional heating was performed until the reaction was complete. The organic layer was dried in a Rotovap. The contents of the flask were washed twice with saturated sodium chloride and then dried over molecular sieves. The product contained traces of the original alcohol, as shown by TLC. The alcohol was completely removed by dissolving the product in 60 mL of pentane and passing the solution through a column of activated alumina. Pentane was removed by rotoevaping. The final yield was 11.6 g. The product was identified by proton NMR and mass spectrometry.

Column Preparation. The alcohol was dissolved in *n*-pentane, and 60/80-mesh Chromosorb W HP was added. A vacuum was applied to fully wet the support and remove trapped air, and then the solvent was slowly removed on a Rotovap. The stationary-phase loading was 13.6% by weight. The coated support was packed in a clean 14-in. by $^1/_4$-in. (i.d.) stainless steel column. A similar column was used as a carrier gas saturator column to prevent loss of the stationary phase. The column was conditioned at 110 °C for 2 h and then left in the chromatograph at 80 °C overnight before any measurements were made. In some cases, retention on the 14-in. column were much too long to be useful. In this case a 3-in. long column was used. The ether column was similarly prepared. It had a phase loading of 18.3% (w/w).

Apparatus. All retention measurements were carried out with an F&M Scientific Model 5750 chromatograph from Hewlett-Packard, modified to achieve a temperature control of ±0.1 °C. Chromatograms and retention times were recorded with a Hewlett-Packard 3390 reporting integrator. Day-to-day variations in retention times were about 1%, and capacity factors could be reproduced to 0.5%. The chromatography was all carried out at 80 °C. Capacity factors were measured using methane as a dead time marker. However, when the 3-in. column was used, the extra column time delay was a substantial percentage of the overall dead time. Consequently, we used *sec*-butylbenzene and 1,2,3,5-tetramethylbenzene as calibration markers on both the long and the short columns and adjusted the data so that both of these species had the same k' on both columns. In general, the flow rate was about 60 mL/min.

Procedure. Most of the samples were injected as the head space vapor above the pure liquid or above a mixture of solutes. Generally, about 2–5 μL of sample was injected.

Infrared Measurements. All infrared spectroscopic studies reported here were carried out in carbon tetrachloride (Fisher, certified grade), purified by refluxing over calcium hydride for at least 3 h and then fractionally distilled and stored over a 4-Å molecular sieve (Baker, analyzed grade). All other chemicals used in the infrared studies were at least 99% pure. Each of them was statically dried with molecular sieves and stored in a sealed vial before use. In general, samples were made by adding specific weights of HFIPA to 5 mL of approximately 0.2 M of the hydrogen bond acceptor under study. These solutions were diluted with carbon tetrachloride to 10 mL. The molar ratio of donor (HFIPA) to acceptor (base) was varied from 1 to 6, as indicated in Table V. The infrared spectra were acquired at a resolution of 1.4 cm^{-1} on a Mattson Sirius-100 Fourier transform spectrometer at room temperature (22–24 °C). Sample solutions were contained between CaF_2 windows with a path length of 0.2 mm, as provided by a Teflon-brand spacer.

(31) Morrison, R. T.; Boyd, R. N. *Organic Chemistry*, 4th ed.; Allyn and Bacon Inc.: Boston, 1983.

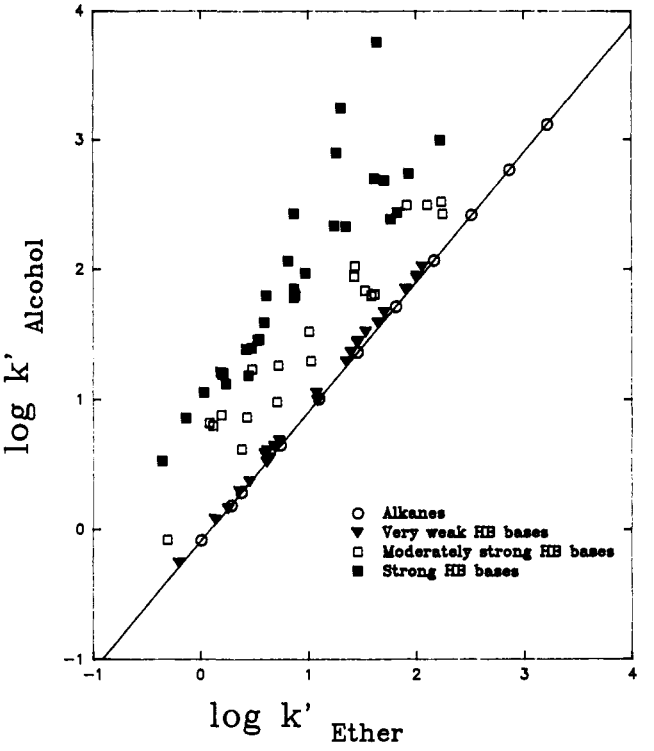

Figure 1. Plot of log k' on the alcohol phase vs log k' on the ether phase: (○) alkanes ($\beta_2^C = 0$); (▼) very weak hydrogen bond bases ($\beta_2^C = 0$–0.15), (□) moderately strong hydrogen bond bases ($\beta_2^C = 0.15$–0.39); (■) strong hydrogen bond bases ($\beta_2^C > 0.4$).

Molecular graphics studies were carried out using Insight II Discover Molecular Mechanics run on an IRIS Silicone Graphics Personal Workstation (Mountain View, CA).

Results and Discussion

Evaluation of the Ether Phase. Measured log k' values, along with the solvatochromic parameters, are summarized in Table I. Comparison of retention on the fluoro alcohol phase to retention on any other stationary phase indicates a remarkable sensitivity to solute basicity. For example, the capacity factor of acetone was a factor of 10 larger on the alcohol phase relative to the ether phase, whereas *n*-pentane, which is about as volatile as acetone, has essentially the same capacity factor on both columns. The data are illustrated graphically in Figure 1. The strongly basic solutes are much more retained on the alcohol phase than are the nonbasic alkanes. The solid line in this figure is a least-squares line through the saturated alkanes (see below). Since the ether phase is chemically simpler than the alcohol, we examined it first. As recommended by Kamlet,[7b] the final regression was built up in a stepwise fashion, so as to guard against incorporating any chemically invalid explanatory variables. The final least-squares regression equation is

$$\log k'_{ether} = (-1.39 \pm 0.03) + (0.697 \pm 0.01) \log L^{16} + (0.742 \pm 0.05)\pi_2^{*,C} + (0.153 \pm 0.06)\beta_2^H + (-0.131 \pm 0.03)\delta_2 \quad (3)$$

$$n = 87,\ SD = 0.084,\ r = 0.9942$$

A plot of the measured data against eq 3 is shown in Figure 2. Overall, this correlation is quite satisfactory. The regression coefficients were robust, that is, independent of subsets of the data. For example, the intercept and the l and s coefficients did not change upon deleting all the hydrogen bond donor solutes. This fit is actually better, because the carboxylic acids are now not included (see below).

$$\log k'_{ether} = (-1.40 \pm 0.02) + (0.697 \pm 0.01) \log L^{16} + (0.692 \pm 0.03)\pi_2^{*,C} + (0.179 \pm 0.04)\beta_2^H + (-0.09 \pm 0.02)\delta_2 \quad (4)$$

$$n = 59,\ SD = 0.043,\ r = 0.9978$$

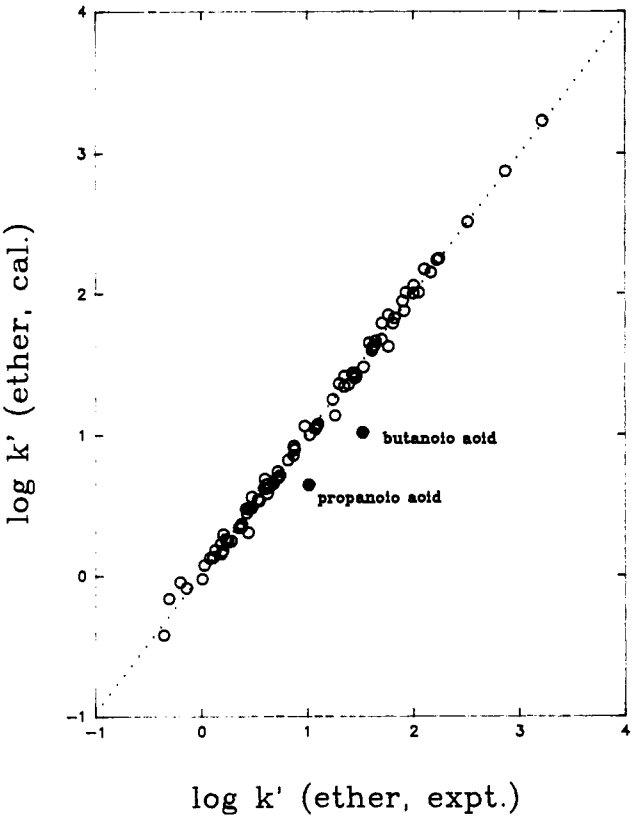

Figure 2. Plot of calculated log k' values vs experimental values for the ether phase (see eq 10).

The coefficients of the fit make chemical sense. The coefficient of log L^{16} (0.697) is similar to that of a moderately polar phase at 80 °C.[29] The coefficient of $\pi_2^{*,C}$ (0.825) is intermediate between that of squalane (0.14) and TCEP (2.18), a very polar liquid.[29] The ether phase is clearly moderately dipolar. No dependence on solute hydrogen bond donor acidity was found, thereby indicating that the ether phase is at most only weakly basic. The coefficient of solute basicity (0.153) is small but statistically real, even though the ether phase should have negligible acidity. We attribute this dependence to interactions of the solutes with the support particle surface. Finally, we note that the largest deviations seen in Figure 2 are due to carboxylic acids. These are due to either dimerization of the acids or, more likely, to their interactions with Lewis acid (metal) sites in the support.

Comparison of the Ether and Alcohol Phases. The relative retentions on the alcohol and ether phases are most simply compared in terms of the saturated hydrocarbons. There is an excellent linear correlation of the capacity factors of the linear, branched, and cyclic hydrocarbons (see solid line and open circles in Figure 1). This relationship is expected because the hydrocarbons are

$$\log k'_{\text{alcohol}} = (-0.092 \pm 0.001) + (0.9970 \pm 0.0008) \log k'_{\text{ether}} \quad (5)$$

$$n = 14,\ \text{SD} = 0.003,\ r = 0.999\,996$$

not able to donate hydrogen bonds and there is only a small systematic variation in $\pi_2^{*,C}$ from *n*-pentane (−0.18) to tetradecane (−0.07). The small average deviation is a good measure of the reproducibility of retention measurements on both columns. Note that the slope of the regression is very close to 1. The intercept, which we believe is primarily due to the difference in phase ratios, is fairly small. The average difference in logarithmic capacity factors for the alkanes on the two phases is −0.096 ± 0.0042 for the 14 saturated alkanes. We assume that any compound whose log k' on the alcohol column is more positive by 2 standard deviations than the average difference for the alkanes is a hydrogen bond acceptor. As shown in Figure 1, the vast majority of the solutes examined are at least slightly hydrogen bond basic molecules.

There is a very great difference in the average standard deviations found in correlations 3 and 5. This is obviously not due to the experimental precision in measurement of k' and indicates that we certainly have not achieved the level of exhaustive fit[7b] in explaining retention on the ether phase.

The straight-line portion of the data set shown in Figure 1 is very reminiscent of the solvatochromic comparison method developed by Kamlet and Taft when they first reported on measurements of solvent hydrogen bond basicity.[12a,b] We see that the deviations are all in the expected positive direction and the magnitude of the deviation is much larger for those species that are good hydrogen bond bases.

The ratio of capacity factors on the two phases is moderately well-correlated with Abraham's hydrogen bond basicity parameter (β_2^H).[14] The slope of the dependence on the HB basicity is clearly

$$\log (k'_{\text{alcohol}}/k'_{\text{ether}}) = (0.21 \pm 0.04) + (2.38 \pm 0.10)\beta_2^H \quad (6)$$

$$n = 84,\ \text{SD} = 0.20,\ r = 0.930$$

quite strong and consistent with our goal in designing the two phases. In this regression, propanoic acid and butanoic acid were excluded. We attempted to improve the quality of the fit by adding additional explanatory variables including a dependence on solute $\pi_2^{*,C}$ and on log L^{16}. The only additional dependence that had any measurable influence on the goodness of fit was the polarizability correction factor:

$$\log (k'_{\text{alcohol}}/k'_{\text{ether}}) = (-0.13 \pm 0.04) + (2.30 \pm 0.10)\beta_2^H + (-0.17 \pm 0.05)\delta_2 \quad (7)$$

$$n = 84,\ \text{SD} = 0.19,\ r = 0.941$$

As in our previous work on the development of a chromatographically based scale of solute hydrogen bond acidity and dipolarity/polarizability,[22] we felt that it should be possible to use the above regression as a mechanism for computing a chromatographically based hydrogen bond basicity. In the present instance, this was particularly straightforward due to the fact that the ratio of capacity factors did not appear to depend on anything but the solute basicity and polarizability correction factor. In addition, the dependence on β_2^H is quite strong and, consequently, errors in log k' would not propagate heavily. As in our previous work,[22] we used both a zero-lag adaptive Kalman filter and a least-median regression technique to minimize the effect of outliers on the final fitting coefficients. Our final best estimate of the relationship between retention on the two columns and the Abraham basicity parameter is

$$\log (k'_{\text{alcohol}}/k'_{\text{ether}}) = (-0.089 \pm 0.02) + (2.15 \pm 0.05)\beta_2^H + (-0.23 \pm 0.02)\delta_2 \quad (8)$$

$$n = 84,\ \text{SD} = 0.22,\ r = 0.967$$

We can now compute a value of β_2^C as follows:

$$\beta_2^C = (\log (k'_{\text{alcohol}}/k'_{\text{ether}}) + 0.089 + 0.23\delta_2)/2.15 \quad (9)$$

This scheme produced the set of β_2^C given in Table I.

Based on the goodness of fit for the alkanes on the two columns, the random measurement error is about 0.003 for a pair of k' values. Based on the variations in β_2^C between species with the same functional group, we can estimate that the random experimental error in β_2^C is probably not larger than about 0.03. The large standard deviation in eq 8 is mainly due to the lack of fit by using β_2^H and not due to experimental error in the ratio of log k' values on the two phases.

We were surprised to see the small but significant dependence of the log k' ratio (see eq 8) on the δ_2 polarizability correction factor. We had thought that it, like the L^{16} and $\pi_2^{*,C}$ dependencies, should cancel out in the ratio. Note that the capacity factors for all nonpolar aromatic solutes on the alcohol phase are actually less than those on the ether phase. The average difference for the alkyl-substituted benzenes is 0.038 (±0.0051). This difference is smaller than that observed for the saturated alkanes, so we conclude that the basicity of even the nonpolar aromatics is detectable. In previous work,[22,29] we observed that the $d\delta_2$ term was

Table I. Solute Retention Data and Descriptive Parameters

no.	compd name	log k'^a alcohol	log k'^b ether	log L^{16c}	$\pi_2^{*C\,c}$	$\alpha_2^{C\,c}$	$\beta_2^{H\,d}$	$\beta_2^{C\,e}$	class[f]
1	pentane	−0.086	0.007	2.163	−0.18	0.00	0.00	0.00	1
2	hexane	0.284	0.378	2.668	−0.16	0.00	0.00	0.00	1
3	2-methylpentane	0.183	0.284	2.507	−0.14	0.00	0.00	0.00	1
4	heptane	0.648	0.742	3.173	−0.14	0.00	0.00	0.00	1
5	octane	1.006	1.101	3.677	−0.12	0.00	0.00	0.00	1
6	nonane	1.361	1.456	4.176	−0.12	0.00	0.00	0.00	1
7	decane	1.714	1.810	4.685	−0.11	0.00	0.00	0.00	1
8	undecane	2.068	2.167	5.191	−0.10	0.00	0.00	0.00	1
9	dodecane	2.419	2.516	5.696	−0.09	0.00	0.00	0.00	1
10	tridecane	2.769	2.870	6.200	−0.08	0.00	0.00	0.00	1
11	tetradecane	3.116	3.221	6.705	−0.07	0.00	0.00	0.00	1
12	cyclopentane	0.162	0.251	2.426	−0.06	0.00	0.00	0.00	1
13	cyclohexane	0.519	0.613	2.906	0.00	0.00	0.00	0.00	1
14	cycloheptane	0.996	1.087	3.543	−0.01	0.00	0.00	0.00	1
15	1-hexane	0.295	0.355	2.571	−0.07	0.00	0.07	0.02	2
16	chlorobutane	0.609	0.621	2.716	0.19	0.00	0.10	0.08	3
17	1,2-dichloroethane	0.585	0.592	2.572	0.39	0.05	0.05	0.08	3
18	dichloromethane	0.079	0.129	1.997	0.34	0.06	0.06	0.06	3
19	chloroform	0.370	0.452	2.478	0.27	0.16	0.02	0.04	3
20	carbon tetrachloride	0.552	0.642	2.822	0.16	0.00	0.00	0.04	3
21	fluorobenzene	0.686	0.728	2.785	0.36	0.00	0.07	0.10	4
22	chlorobenzene	1.290	1.349	3.630	0.44	0.00	0.07	0.09	4
23	bromobenzene	1.588	1.644	4.022	0.51	0.00	0.06	0.10	4
24	iodobenzene	1.946	2.005	4.505	0.59	0.00	0.05	0.09	4
25	*o*-dichlorobenzene	1.934	2.001	4.453	0.56	0.00	0.03	0.09	4
26	*p*-dichlorobenzene	1.849	1.899	4.404	0.53	0.00	0.03	0.10	4
27	benzene	0.644	0.683	2.792	0.29	0.00	0.14	0.10	5
28	toluene	1.050	1.075	3.343	0.29	0.00	0.14	0.11	5
29	ethylbenzene	1.361	1.393	3.785	0.30	0.00	0.15	0.11	5
30	propylbenzene	1.669	1.702	4.239	0.30	0.00	0.12	0.11	5
31	butylbenzene	2.019	2.054	4.714	0.30	0.00	0.12	0.11	5
32	*o*-xylene	1.520	1.530	3.947	0.31	0.00	0.17	0.12	5
33	*m*-xylene	1.448	1.461	3.868	0.29	0.00	0.17	0.12	5
34	*p*-xylene	1.438	1.451	3.867	0.28	0.00	0.17	0.12	5
35	nitromethane	0.620	0.378	1.839	0.67	0.06	0.25	0.16	6
36	nitroethane	0.981	0.712	2.313	0.66	0.00	0.25	0.17	6
37	nitropropane	1.297	1.023	2.773	0.65	0.00	0.25	0.18	6
38	anisole	1.810	1.615	3.916	0.52	0.00	0.26	0.22	8
39	nitrobenzene	2.427	2.245	4.433	0.91	0.00	0.30	0.21	9
40	phenol	1.799	1.585	3.641	0.77	0.69	0.22	0.23	10
41	ethyl ether	0.819	0.079	2.066	0.03	0.00	0.45	0.40	11
42	propyl ether	1.262	0.720	2.971	0.03	0.00	0.46	0.30	11
43	butyl ether	1.944	1.426	3.954	0.04	0.00	0.45	0.29	11
44	isopropyl ether	0.867	0.429	2.561	0.03	0.00	0.47	0.25	11
45	tetrahydrofuran	1.803	0.615	2.521	0.27	0.00	0.51	0.61	24
46	dioxane	2.430	0.872	2.788	0.45	0.00	0.47	0.79	24
47	aniline	2.386	1.762	3.934	0.76	0.20	0.38	0.42	12
48	*N*-methylaniline	2.500	2.106	4.492	0.70	0.14	0.47	0.31	12
49	*N*,*N*-dimethylaniline	2.523	2.237	4.753	0.57	0.00	0.35	0.26	12
50	propionaldehyde	0.797	0.112	1.770	0.35	0.00	0.40	0.37	13
51	benzaldehyde	2.440	1.822	3.935	0.75	0.00	0.42	0.42	
52	acetonitrile	0.882	0.191	1.537	0.62	0.05	0.44	0.37	14
53	propionitrile	1.232	0.477	1.978	0.64	0.00	0.43	0.41	14
54	benzonitrile	2.496	1.913	3.913	0.85	0.00	0.42	0.40	15
55	acetone	1.195	0.201	1.766	0.38	0.01	0.50	0.52	21
56	2-butanone	1.462	0.547	2.269	0.39	0.00	0.48	0.48	21
57	2-pentanone	1.785	0.869	2.726	0.40	0.00	0.48	0.48	21
58	acetophenone	2.999	2.224	4.458	0.80	0.00	0.51	0.49	18
59	cyclopentanone	2.333	1.240	3.093	0.58	0.00	0.52	0.57	23
60	cyclohexanone	2.701	1.612	3.580	0.59	0.00	0.52	0.56	23
61	methyl acetate	1.120	0.231	1.946	0.33	0.00	0.40	0.47	19
62	ethyl acetate	1.458	0.532	2.359	0.31	0.00	0.45	0.49	19
63	propyl acetate	1.804	0.881	2.861	0.32	0.00	0.45	0.48	19
64	methanol	0.522	−0.356	0.916	0.35	0.35	0.41	0.46[g]	22
65	ethanol	0.858	−0.141	1.462	0.27	0.29	0.44	0.52	22
66	1-propanol	1.204	0.208	1.975	0.30	0.32	0.45	0.52	22
67	butanol	1.593	0.599	2.539	0.30	0.31	0.45	0.52	22
68	isobutyl alcohol	1.396	0.475	2.381	0.28	0.31	0.45	0.48	22
69	pentanol	1.972	0.978	3.057	0.32	0.32	0.45	0.52	22
70	hexanol	2.329	1.350	3.550	0.33	0.34	0.45	0.51	22
71	heptanol	2.686	1.705	4.067	0.35	0.33	0.45	0.51	22
72	2-propanol	1.052	0.027	1.750	0.21	0.29	0.47	0.53	22
73	*sec*-butyl alcohol	1.387	0.423	2.322	0.22	0.28	0.51	0.50	22
74	*tert*-butyl alcohol	1.210	0.184	1.994	0.19	0.25	0.49	0.53	22
75	isopentanol	1.851	0.871	2.885	0.28	0.34	0.45	0.51	22
76	cyclohexanol	2.025	1.433	3.594	0.37	0.31	0.51	0.33[g]	22
77	benzyl alcohol	2.742	1.930	4.162	0.71	0.43	0.42	0.51	22

Table I (Continued)

no.	compd name	log k'^a alcohol	log k'^b ether	log $L^{16\,c}$	$\pi_2^{*C\,c}$	$\alpha_2^{C\,c}$	$\beta_2^{H\,d}$	$\beta_2^{C\,e}$	class[f]
78	trifluoroethanol	−0.080	−0.306	1.315	0.37	0.66	0.18	0.15	7
79	HFIPA	−0.259	−0.200	1.370	0.47	1.11	0.03	0.02	
80	pyridine	2.899	1.264	2.969	0.60	0.00	0.62	0.90	27
81	triethylamine	2.066	0.818	3.008	0.02	0.00	0.67	0.64	26
82	dimethylformamide	3.247	1.302	2.922	0.81	0.00	0.66	0.97	28
83	dimethylacetamide	3.761	1.634	3.357	0.80	0.00	0.74	1.06	28
84	dimethyl sulfoxide	n.d.[h]	1.766	3.110	1.00	0.00	0.78	1.54[i]	30
85	acetic acid	1.183	0.444	1.750	0.54	0.72	0.43	0.40[g]	20
86	propanoic acid	1.522	1.012	2.290	0.52	0.54	0.43	0.29[g]	20
87	butanoic acid	1.838	1.525	2.830	0.54	0.57	0.42	0.19[g]	20

[a] log capacity factors on the alcohol column. [b] log capacity factors on the ether column. [c] From ref 22. [d] From ref 14d. [e] This work. [f] Solute class number as shown in Table III. [g] The β_2^C values for these compounds were found significantly different from results we obtained from other donor stationary phases (ref 32). We recommend the following β_2^C values: methanol (0.52), cyclohexanol (0.53), acetic acid (0.50), propionic acid (0.50), butanoic acid (0.48). [h] Did not elute, no data. [i] Estimated from using a phenolic donor stationary phase (ref 32).

most often small and positive (0.0–0.2) for all but a few of the nearly 100 phases that were examined. As shown in eqs 3 and 8, both the ether and the alcohol phases have negative *d* coefficients. Previously we saw that the *d* term was negative for stationary phases that are very strong hydrogen bond base liquids such as trioctylphosphine oxide (TOPO) and 4-butylpentylpyridine (BPP).[22] In addition, the *d* coefficient was negative for highly fluorinated liquids such as QF-1[29] and Zonyl-E 7.[22] Nonetheless, we still expected that complete cancellation would occur. It clearly did not, and substantially different β_2^C values were obtained for the aromatic solutes when $d\delta_2$ was not included as an explanatory variable in the regression. Since the *d* coefficient is negative and indicates a lessening of retention, we conjecture that a repulsion takes place between the electron-rich fluorine atoms of the two perfluoromethyl groups and the π electrons of the aromatic solutes. On average, this effect must be greater for the alcohol phase than for the ether phase. However, as assessed by separately regressing the aliphatic and aromatic solutes, the magnitude of the effect seems to be independent of the solute basicity. No significant difference in the coefficient of β_2^C was observed.

Given the simplicity of the methodology and the fact that we do not need values of either $\pi_2^{*,C}$ or the hydrogen bond acidity α_2^C, we measured the retention of an additional 60 hydrogen bond bases on both the ether and alcohol columns (see Table II). The relationship between the two types of hydrogen bond solute basicity parameters is shown in Figure 3. A number of significant differences exist between the two scales. The overall correlation between β_2^C and β_2^H is as follows:

$$\beta_2^C = (-0.06 \pm 0.02) + (1.29 \pm 0.05)\beta_2^H \qquad (10)$$

$$n = 147,\ \mathrm{SD} = 0.13,\ r = 0.908$$

The intercept of this regression, although not statistically 0, is small enough to be of minimal concern. This correlation is considerably poorer than our previously obtained relationship between α_2^C and α_2^H,[22] which showed an average standard deviation of 0.04 and a correlation coefficient of 0.976.

In order to determine how the chromatographically derived scale relates to other scales of basicity, we carried out a correlation of our data with the F_1 and F_2 basicity parameters developed by Maria and Gal.[13,14a] We have only 15 species in our data set for which these parameters are available. The correlation is shown in eq 11. Abraham's β_2^H values were regressed against F_1 and

$$\beta_2^C = (0.78 \pm 0.01) + (0.65 \pm 0.02)F_1 + (1.41 \pm 0.07)F_2 \qquad (11)$$

$$n = 13,\ \mathrm{SD} = 0.033,\ r = 0.995$$

F_2 for the same 13 solutes with the following result:

$$\beta_2^H = (0.58 \pm 0.01) + (0.26 \pm 0.02)F_1 + (0.51 \pm 0.07)F_2 \qquad (12)$$

$$n = 13,\ \mathrm{SD} = 0.031,\ r = 0.974$$

We excluded dioxane, triethylamine, and DMSO. We can estimate a β_2^C for DMSO on the basis of its retention on other phases,[32] but we could not estimate its β_2^C value using the fluoro alcohol phase, since it was simply too well retained to observe elution. Dioxane was excluded for the reasons given in the literature.[14a] Triethylamine most definitely does not fit the correlation. Based on the work of others[14a] and our observations, we are convinced that there is a great deal of front strain between this base and the bulky trifluoromethyl groups of our donor. It is not clear to us whether proton transfer took place with triethylamine in the stationary-phase alcohol. However, IR data (see below) clearly show that in carbon tetrachloride proton transfer does take place between HFIPA and this solute.

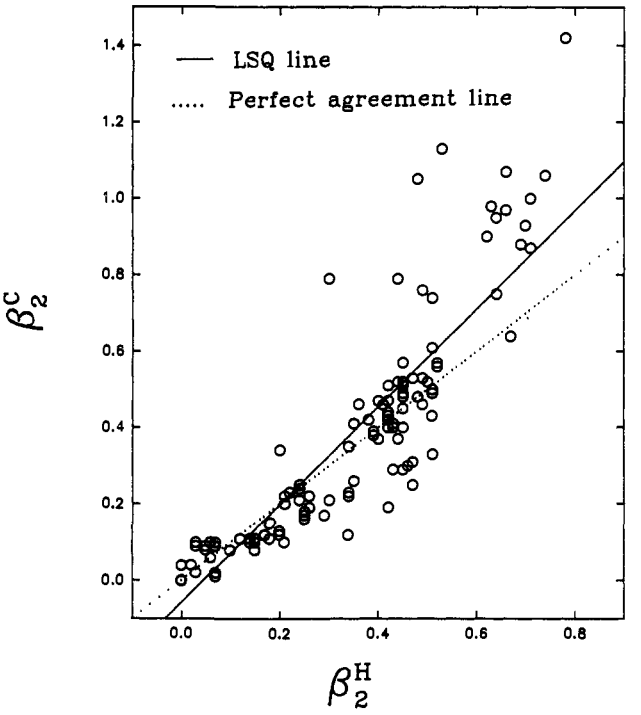

Figure 3. Plot of β_2^C vs β_2^H for all solutes.

The coefficients of F_1 and F_2 lead to an estimate of an angle θ equal to 65.3°. θ is a measure of the relative electrostatic and covalent energy contributions to a basicity-dependent property.[13,14a] Many hydrogen bond formation processes have θ values between 53° and 86°. In order for family independence to be observed, Abraham[14a] states that θ should lie between 64° and 73°. Our value of 65.3° indicates that we are dealing with a simple hydrogen bonding process. The same analysis carried out on Abraham's β_2^H scale for the same 13 species gives a θ of 62.6° and a correlation coefficient of 0.974, which is slightly poorer than that observed here. We believe that our β_2^C scale fits within the general family of hydrogen bonding basicity scales. It has the advantage of being very easily and precisely measurable.

In order to compare the two hydrogen bond solute basicity scales in a less abstract fashion, we summarized our results by averaging

(32) Li, J.; Zhang, Y.; Carr, P. W. Manuscript in preparation.

Table II. Additional Solute Retention Data and Parameters

no.	compd name	log k'^a alcohol	log k'^b ether	$\beta_2^{H\,c}$	$\beta_2^{C\,d}$	class[e]
88	2,3,4-trimethylpentane	0.863	0.957	0.00	0.00	1
89	2,4-dimethylpentane	0.412	0.511	0.00	0.00	1
90	ethylcyclohexane	1.146	1.238	0.00	0.00	1
91	2,5-dimethylhexane	0.765	0.861	0.00	0.00	1
92	pentene	−0.079	−0.024	0.07	0.02	2
93	heptane	0.659	0.715	0.07	0.02	2
94	octene	1.021	1.072	0.07	0.02	2
95	chloropentane	0.976	0.985	0.15	0.08	3
96	chlorohexane	1.331	1.343	0.15	0.08	3
97	chloroheptane	1.687	1.697	0.15	0.08	3
98	benzyl bromide	2.170	2.168	0.34	0.12	
99	*p*-chlorotoluene	1.697	1.753	0.14	0.10	4
100	*p*-bromotoluene	1.998	2.049	0.14	0.10	4
101	styrene	1.489	1.522	0.18	0.11	
102	phenylacetylene	1.424	1.432	0.20	0.12	
103	naphthalene	2.485	2.524	0.21	0.10	
104	1,2,4,5-tetramethylbenzene	2.347	2.321	0.20	0.13	5
105	*tert*-butylbenzene	1.815	1.843	0.15	0.11	5
106	isopropylbenzene	1.574	1.602	0.15	0.11	5
107	*sec*-butylbenzene	1.840	1.885	0.15	0.10	5
108	1,3,5-trimethylbenzene	1.844	1.837	0.20	0.13	5
109	phenyl ether ether	2.013	1.866	0.26	0.19	8
110	thioanisole	2.250	2.158	0.29	0.17	
111	*o*-nitrotoluene	2.692	2.479	0.34	0.22	9
112	*m*-nitrotoluene	2.856	2.632	0.34	0.23	9
113	*p*-nitrotoluene	2.905	2.696	0.34	0.22	9
114	*m*-creol	2.218	1.972	0.24	0.24	10
115	*o*-cresol	2.078	1.903	0.24	0.21	10
116	*p*-cresol	2.231	1.969	0.24	0.25	10
117	4-fluorophenol	1.864	1.655	0.21	0.22	10
118	*p*-ethylaniline	3.135	2.399	0.42	0.47	12
119	*p*-chloroaniline	2.958	2.489	0.34	0.35	12
120	hexanal	1.908	1.200	0.39	0.38	13
121	heptanal	2.270	1.554	0.39	0.39	13
122	octanal	2.631	1.905	0.39	0.39	13
123	*p*-tolunitrile	2.962	2.337	0.42	0.42	15
124	propiophenone	3.144	2.509	0.51	0.43	18
125	3-methylbutanol	1.857	0.867	0.45	0.52	22
126	2-phenylethanol	3.166	2.230	0.45	0.57	22
127	2-phenyl-2-propanol	2.872	2.167	0.49	0.46	22
128	trichloroethanol	1.550	1.309	0.21	0.20	7
129	2-methylpyridine	3.056	1.261	0.63	0.98	27
130	2,6-dimethylpyridine	2.812	1.499	0.64	0.75	27
131	4-picoline	3.453	1.469	0.66	1.07	27
132	diethylamine	2.426	0.572	0.70	0.93	26
133	butylamine	2.867	0.865	0.71	1.00	26
134	hexylamine	3.473	1.714	0.69	0.88	26
135	dibutylamine	3.429	1.692	0.71	0.87	26
136	methyl benzoate	2.918	2.277	0.42	0.43	17
137	ethyl benzoate	3.208	2.539	0.42	0.44	17
138	ethyl propionate	1.718	0.860	0.45	0.45	
139	2-fluoroethanol	0.836	0.041	0.36	0.46	16
140	2-chloroethanol	1.297	0.603	0.35	0.41	16
141	2-bromoethanol	1.573	0.892	0.35	0.41	16
142	3-cyanopyridine	3.346	1.957	0.44	0.79	25
143	3-chloropyridine	2.862	1.533	0.49	0.76	25
144	3-bromopyridine	3.140	1.847	0.51	0.74	25
145	pyrimidine	3.107	0.993	0.53	1.13	29
146	pyrazine	2.889	0.943	0.48	1.05	29
147	pyridazine	3.549	1.822	0.64	0.95	29

[a] log capacity factors on the alcohol column. [b] log capacity factors on the ether column. [c] From ref 14d. [d] This work. [e] Solute class number as shown in Table III.

over all solutes in a class of a given functional group (see Table III). On this basis, there is really very good agreement, at least in the *relative* order of basicities, between the present approach and that of Abraham.

The classwise results are presented in Figure 4. The broken line is the line of perfect correspondence, and the solid line is a conventional least-squares line. We see that there is a reasonable linear correlation up to β_2^C of about 0.5. This encompasses the vast bulk of the data. However, there are significant discrepancies when β_2^C is greater than about 0.5. We note that the strongest acceptors (DMF, DMA, the diazines, and DMSO) show the biggest differences among all classes of solutes. Note that the β_2^C parameter for DMSO (1.54) was estimated from retention measurements on a phenolic stationary phase.[32]

In order to examine the data in more detail, we show the results within each class (see Table IV). First, we note the excellent agreement of β_2^C and β_2^H for the phenols, aldehydes, nitriles, alkyl benzoates, and aliphatic ketones. Second, note the less significant halogen substitution effect on the β_2^C scale, as is observed in the solute classes of halogenated alkanes, halogenated benzenes, and halopyridines. Third, alkyl substitution has a significant effect on the β_2^C scale, as is observed in the solute classes of aliphatic ethers, anilines, aliphatic amines, and alkylpyridines. Finally, β_2^C are greater than the β_2^H values when β_2^C is greater than about 0.5.

Table III. Comparison of Average β_2^C and β_2^H by Class

no.	solute class[a]	β_2^C[b]	SD[c]	β_2^H[d]	SD[e]	no.	solute class[a]	β_2^C[b]	SD[c]	β_2^H[d]	SD[e]
1	alkanes	0.000	0.000	0.000	0.000	16	2-haloethanols	0.429	0.025	0.353	0.005
2	alkenes	0.020	0.000	0.070	0.000	17	alkyl benzoates	0.435	0.007	0.420	0.000
3	halogenated alkanes	0.068	0.016	0.085	0.057	18	aromatic ketones	0.459	0.033	0.510	0.000
4	halogenated benzenes	0.100	0.009	0.103	0.092	19	alkyl acetates	0.480	0.008	0.433	0.024
5	alkylbenzenes	0.113	0.008	0.156	0.024	20	aliphatic carboxylic acids	0.493	0.009	0.427	0.005
6	nitroalkanes	0.170	0.007	0.250	0.000	21	aliphatic ketones	0.494	0.017	0.487	0.009
7	trichloro(fluoro)ethanol	0.176	0.023	0.195	0.015	22	aliphatic alcohols	0.516	0.022	0.458	0.027
8	aromatic ethers	0.204	0.012	0.260	0.000	23	cycloketones	0.565	0.001	0.520	0.000
9	nitroaromatics	0.222	0.007	0.330	0.017	24	cyclic ethers	0.700	0.088	0.490	0.020
10	phenols	0.228	0.014	0.230	0.013	25	halopyridines	0.761	0.019	0.480	0.029
11	aliphatic ethers	0.312	0.053	0.458	0.008	26	aliphatic amines	0.865	0.121	0.696	0.015
12	anilines	0.362	0.077	0.392	0.048	27	alkylpyridines	0.925	0.117	0.638	0.015
13	aldehydes	0.382	0.008	0.392	0.004	28	DMF/DMA	1.017	0.043	0.696	0.015
14	alkyl nitriles	0.390	0.015	0.435	0.005	29	diazines	1.043	0.076	0.550	0.067
15	aromatic nitriles	0.410	0.010	0.420	0.000	30	DMSO	1.540		0.780	

[a] The solutes included in each class are identified in the last column of Tables I and II. [b] Average β_2^C within the solute class. [c] Standard deviation of β_2^C within the solute class. [d] Average β_2^H within the solute class. [e] Standard deviation of β_2^H within the solute class.

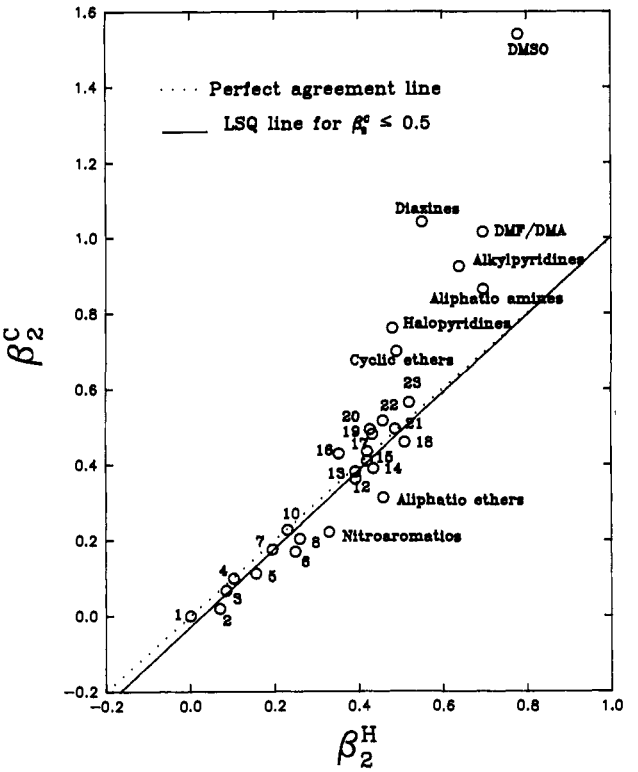

Figure 4. Plot of average β_2^C vs average β_2^H for all classes of compounds. The class number is the same as in Table III.

When viewed as a whole, Figures 3 and 4 seem to suggest a nonlinear relationship between the two types of parameters. While we observed excellent agreement for many solutes, there are also a large number of compounds for which there is considerable discrepancy. Thus, we believe that the differences are real and are not due to random experimental errors.

Many, but not all, of the differences between the two scales can be rationalized using two concepts: formation of 2:1 and higher complexes in some cases and steric impedance to hydrogen bond formation in others. Another possible source of discrepancy is proton transfer. Such reactions have been reported for some strong Bronsted acids, including 3-nitrophenol, *p*-nitrophenol, 2,4-dinitrophenol, and bromophenol blue, with bases such as amines and pyridines in a variety of solvents of low dielectric constant.[33] In order to simplify the comparison, we will temporarily disregard the influence of proton-transfer and ion-pair complex formation as a contributing factor for our differences. However, we realize that proton transfer could be one of the important factors which has an effect on linear solvation energy relationships.[34]

Although almost all studies of hydrogen bond complexation, including IR[35] and many calorimetric studies,[36] are carried out under conditions where there is a large excess of the base relative to the acid, there is little or no driving force for greater than 1:1 complexes to form. Nonetheless, there is a great deal of evidence for the formation of two hydrogen bonds to small acceptors such as water and acetone.[37] The formation of 2:1 complexes between acetone and chloroform and between carbonyl compounds (such as aldehydes, ketones, and esters) and *p*-cresol is strongly supported by IR spectroscopy.[38] Indeed, Kivinen and Murto[24b] report that the formation constant for the 2:1 complex between HFIPA and dioxane is in agreement with the statistically based prediction. Furthermore, even when the base is present in great excess over the acid, the formation of two distinct 1:1 hydrogen complexes has been reported for such species as phenylacetylene, arylfulvenes, and azulenes.[35c] These were observable because the two base sites have very similar basicities and the donor partitioned nearly evenly between them. We infer that in the presence of excess acid it should not be at all unusual for some fraction of the solute to be simultaneously hydrogen bonded to two or more hydrogen bond acids.

In Abraham's work there was little or no excess of donor relative to the acceptor, and, consequently, there was little possibility for formation of anything but a 1:1 complex. In contrast, in our work the test solutes were present at infinite dilution in the pure bulk donor. The effective concentration of OH groups in the fluoro alcohol phase is about 3 mol/L. Consider the β_2^C values for the heterocyclic amines. Pyridine has the smallest discrepancy among these heterocyclic amines. In contrast, for the three dinitrogen heterocycles, the value of β_2^C is much greater than the β_2^H value. The same is evident when we compare results for THF and dioxane. In fact, for virtually all compounds where one can rea-

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Table IV. Comparison of β_2^C and β_2^H within Solute Classes

compd name	β_2^C	β_2^H	compd name	β_2^C	β_2^H
			Alkanes		
pentane	0.00	0.00	tridecane	0.00	0.00
hexane	0.00	0.00	tetradecane	0.00	0.00
2-methylpentane	0.00	0.00	cyclopentane	0.00	0.00
heptane	0.00	0.00	cyclohexane	0.00	0.00
octane	0.00	0.00	cycloheptane	0.00	0.00
nonane	0.00	0.00	2,3,4-trimethylpentane	0.00	0.00
decane	0.00	0.00	2,4-dimethylpentane	0.00	0.00
undecane	0.00	0.00	ethylcyclohexane	0.00	0.00
dodecane	0.00	0.00	2,5-dimethylhexane	0.00	0.00
			Alkenes		
1-hexene	0.02	0.07	1-heptene	0.02	0.07
1-pentene	0.02	0.07	1-octene	0.02	0.07
			Halogenated Alkanes		
1,2-dichloroethane	0.08	0.05	chlorobutane	0.08	0.10
dichloromethane	0.06	0.06	chloropentane	0.08	0.15
chloroform	0.04	0.02	chlorohexane	0.08	0.15
carbon tetrachloride	0.04	0.00	chloroheptane	0.08	0.15
			Halogenated Benzenes		
fluorobenzene	0.10	0.07	*o*-dichlorobenzene	0.09	0.03
chlorobenzene	0.09	0.07	*p*-dichlorobenzene	0.10	0.03
bromobenzene	0.10	0.06	*p*-chlorotoluene	0.10	0.14
iodobenzene	0.09	0.05	*p*-bromotoluene	0.10	0.14
			Alkylbenzenes		
benzene	0.10	0.14	*p*-xylene	0.12	0.17
toluene	0.11	0.14	1,2,4,5-tetramethylbenzene	0.13	0.20
ethylbenzene	0.11	0.15	*tert*-butylbenzene	0.11	0.15
propylbenzene	0.11	0.12	isopropylbenzene	0.11	0.15
butylbenzene	0.11	0.12	*sec*-butylbenzene	0.10	0.15
o-xylene	0.12	0.17	1,3,5-trimethylbenzene	0.13	0.20
m-xylene	0.12	0.17			
			Nitroalkanes		
nitromethane	0.16	0.25	nitropropane	0.18	0.25
nitroethane	0.17	0.25			
			Trifluoro(chloro)ethanol		
trifluoroethanol	0.15	0.18	trichloroethanol	0.20	0.21
			Aromatic Ethers		
anisole	0.22	0.26	phenyl ethyl ether	0.19	0.26
			Nitroaromatics		
nitrobenzene	0.21	0.30	*m*-nitrotoluene	0.23	0.34
o-nitrotoluene	0.22	0.34	*p*-nitrotoluene	0.22	0.34
			Phenols		
phenol	0.23	0.22	*p*-cresol	0.25	0.24
m-creol	0.24	0.24	4-fluorophenol	0.22	0.21
o-cresol	0.21	0.24			
			Aliphatic Ethers		
ethyl ether	0.40	0.45	butyl ether	0.29	0.45
propyl ether	0.30	0.46	isopropyl ether	0.25	0.47
			Anilines		
aniline	0.42	0.38	*p*-ethylaniline	0.47	0.42
N-methylaniline	0.31	0.47	*p*-chloroaniline	0.35	0.34
N,*N*-dimethylaniline	0.26	0.35			
			Aldehydes		
propanal	0.37	0.40	heptanal	0.39	0.39
hexanal	0.38	0.39	octanal	0.39	0.39
			Alkyl Nitriles		
acetonitrile	0.37	0.44	propionitrile	0.41	0.43
			Aromatic Nitriles		
benzonitrile	0.40	0.42	*p*-tolunitrile	0.42	0.42
			2-Haloethanols		
2-fluoroethanol	0.46	0.36	2-bromoethanol	0.41	0.35
2-chloroethanol	0.41	0.35			
			Alkyl Benzoates		
methyl benzoate	0.42	0.42	ethyl benzoate	0.44	0.42
			Aromatic Ketones		
acetophenone	0.49	0.51	propiophenone	0.43	0.51

Table IV (Continued)

compd name	β_2^C	β_2^H	compd name	β_2^C	β_2^H
		Alkyl Acetates			
methyl acetate	0.47	0.40	propyl acetate	0.48	0.45
ethyl acetate	0.49	0.45			
		Aliphatic Carboxylic Acids			
acetic acid	0.50	0.43	butanoic acid	0.48	0.42
propanoic acid	0.50	0.43			
		Aliphatic Ketones			
acetone	0.52	0.50	2-pentanone	0.48	0.48
2-butanone	0.48	0.48			
		Aliphatic Alcohols			
methanol	0.52	0.41	*sec*-butyl alcohol	0.50	0.51
ethanol	0.52	0.44	*tert*-butyl alcohol	0.53	0.49
1-propanol	0.52	0.45	isopentanol	0.51	0.45
butanol	0.52	0.45	cyclohexanol	0.53	0.51
isobutyl alcohol	0.48	0.45	benzyl alcohol	0.51	0.42
pentanol	0.52	0.45	3-methylbutanol	0.52	0.45
hexanol	0.51	0.45	2-phenylethanol	0.57	0.45
heptanol	0.51	0.45	2-phenyl-2-propanol	0.46	0.49
2-propanol	0.53	0.47			
		Cyclo Ketones			
cyclopentanone	0.57	0.52	cyclohexanone	0.56	0.52
		Cyclic Ethers			
tetrahydrofuran	0.61	0.51	dioxane	0.79	0.47
		Halopyridines			
3-cyanopyridine	0.79	0.44	3-bromopyridine	0.74	0.51
3-chloropyridine	0.76	0.49			
		Aliphatic Amines			
triethylamine	0.64	0.67	hexylamine	0.88	0.69
diethylamine	0.93	0.70	dibutylamine	0.87	0.71
butylamine	1.00	0.71			
		Alkylpyridines			
pyridine	0.90	0.62	2,6-dimethylpyridine	0.75	0.64
2-methylpyridine	0.98	0.63	4-picoline	1.07	0.66
		DMF/DMA			
Dimethylformamide	0.97	0.66	Dimethylacetamide	1.06	0.74
		Diazines			
pyrimidine	1.13	0.53	pyridazine	0.95	0.64
pyrazine	1.05	0.48	dimethyl sulfoxide	1.54	0.78

sonably suppose that there are two acceptor sites (each site may accept more than one active hydrogen), the β_2^C value is larger than the β_2^H value. This supposition will be demonstrated below in the section on IR spectroscopy. We believe that this explains the results for the amides and DMSO. That is, the amides are accepting active hydrogens at their carbonyl group, the usual site for hydrogen bond acceptance,[39] and at their nitrogen functionality.

The second postulated effect relates to differences in the extent of front strain between the fluorinated alcohol donor used in this work and the more conventional OH and NH donors used to develop the β_2^H scale. As pointed out by Abraham and his coworkers,[14] certain pairs of donors and acceptors do not fit their generalized scheme of solute acidity and basicity due to strong front strain. In this work, we note that 2,6-dimethylpyridine has a much lower relative basicity by our approach than that based on its β_2^H value. The same trend can be seen when comparing the two scales for primary, secondary, and tertiary aliphatic amines and noncyclic ethers. The perfluoromethyl alcohol moiety is certainly bulkier than is perhydroisopropyl alcohol and should be more sensitive to front strain. However, a molecular graphics study of the complexes of HFIPA with THF indicate that the extent of front strain is not particularly large, even when two HFIPA molecules complex with a single THF acceptor. The structural energy minimization routine of the molecular graphics software gave a distance of 1.65 Å between the O of the alcohol and the O of the THF when the 1:1 complex was optimized. As expected, the distance increased to 1.71 Å for the 2:1 complex. Both of these distances are well within the range of length of normal O–H···O hydrogen bonds.

Finally, we note the large differences in β_2^C and β_2^H values for pyridine. This solute has only one lone pair of electrons and should exhibit little front strain. Thus, the poor agreement between β_2^C and β_2^H cannot be explained by either of the above postulates. Furthermore, this discrepancy between β_2^C and β_2^H for pyridine is probably not due to the effect of proton transfer on the β_2^H scale, since β_2^H for pyridine was determined in part from data obtained with HB acids, such as ethanol, where proton transfer cannot happen. However, the donor used in this work is a much stronger Bronsted acid, and IR data (see below) indicate a great deal of proton transfer.

Infrared Studies. The infrared studies reported here were initially performed to test our conjecture that in the presence of excess donor a number of the hydrogen bond bases, such as DMSO, DMA, DMF, and dioxane, form complexes with stoichiometries that exceed 1:1. HFIPA was used as the donor to model the complex, difficult-to-handle liquid stationary phase. Carbon tetrachloride was chosen as the solvent because it is the most commonly used solvent in hydrogen bond studies[14] and it did not present any spectroscopic problems. Infrared spectra of HFIPA in CCl_4 at concentrations ranging from 0.05 to 0.5 M are shown in Figure 5. The OH stretch region shows two partially

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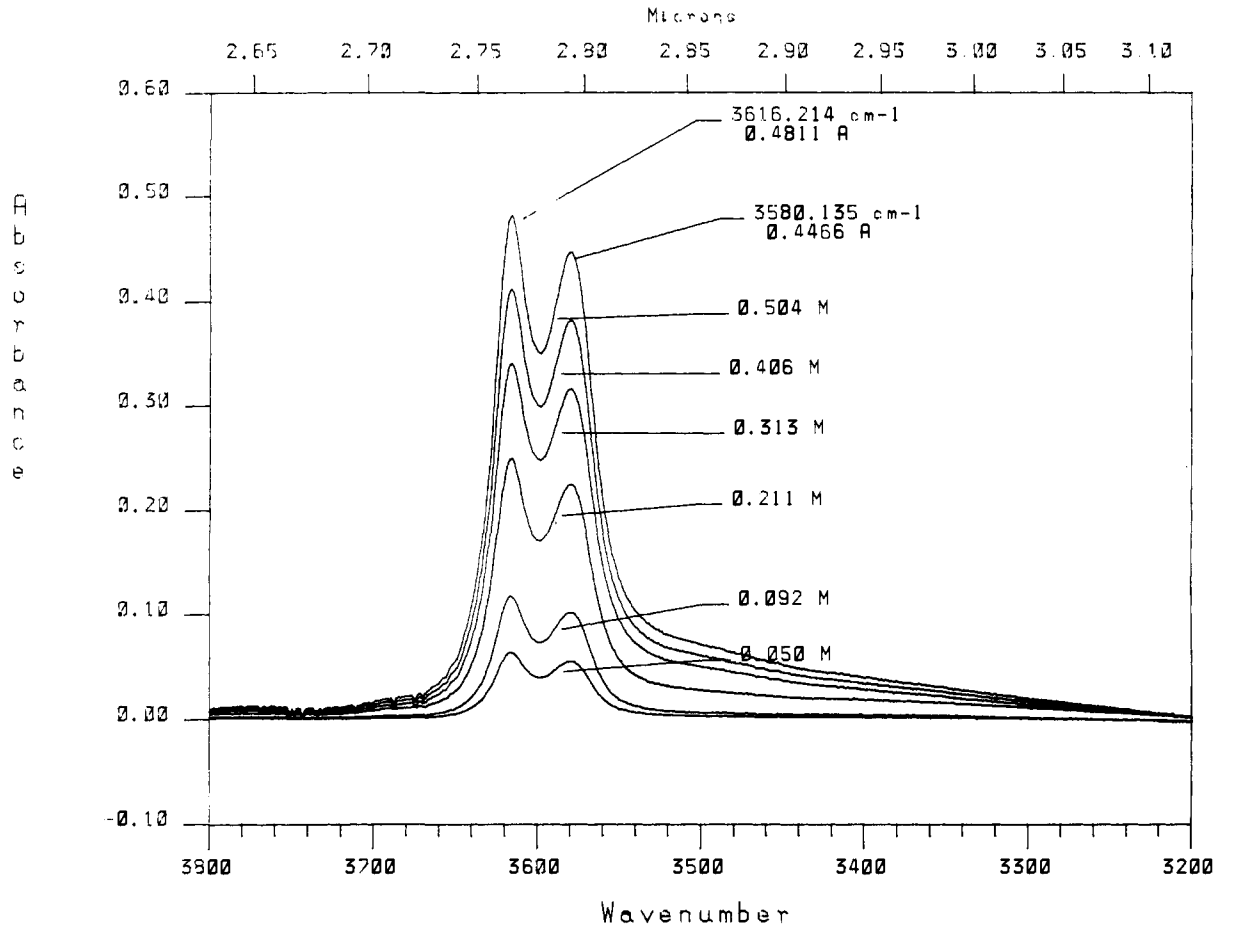

Figure 5. Plot of the effect of concentration on the infrared spectra of HFIPA in CCl_4.

overlapped, sharp peaks at 3616 and 3580 cm^{-1}. These two bands have been attributed to the OH stretching modes of free and/or rotational isomers of intramolecular hydrogen bonded HFIPA molecules.[24,25a,40] It should be noted that the ratio of the absorbances is essentially independent of concentration. This rules out the possibility that the two bands are due to intermolecular hydrogen bond effects. Drago has shown that this intramolecular hydrogen bonding process is the source of some lack of fit in correlations of the enthalpy of adduct formation between HFIPA with various bases and his dual parameter "C–E" acid–base scale.[40]

An absorbance calibration curve for HFIPA in CCl_4 is shown in Figure 6. The plot is curved at concentrations above 0.1 M. Kivinen has examined this curvature and assigns it to formation of an HFIPA dimer.[24b] The dimerization constant for HFIPA is about 0.13 L/mol, and it is considerably smaller than the dimerization constant for trifluoroethanol. Our data give an equilibrium constant of 0.23 L/mol. We believe that the curvature in all of the plots is a consequence of dimer formation.

The essential idea of the present study was to examine the decrease in the intensity of the OH stretching bands of the HFIPA upon addition of a deficient amount of hydrogen bond acceptor. Through the use of the calibration curve (Figure 6), we estimated the number of moles of donor consumed per mole of base added (see Table V). These results were based on the shorter-wavelength OH stretching band because it is better resolved from bands due to residual water and new bands that form upon making the complexes (see below). Very similar results are obtained when the longer wavelength band is used. The last column gives an estimate of the amount of donor consumed per mole of base added. In the case of DMA, DMF, and DMSO it is clear that the "apparent stoichiometry" is much greater than 1:1. Deviations from integer values are due to the formation of two or more

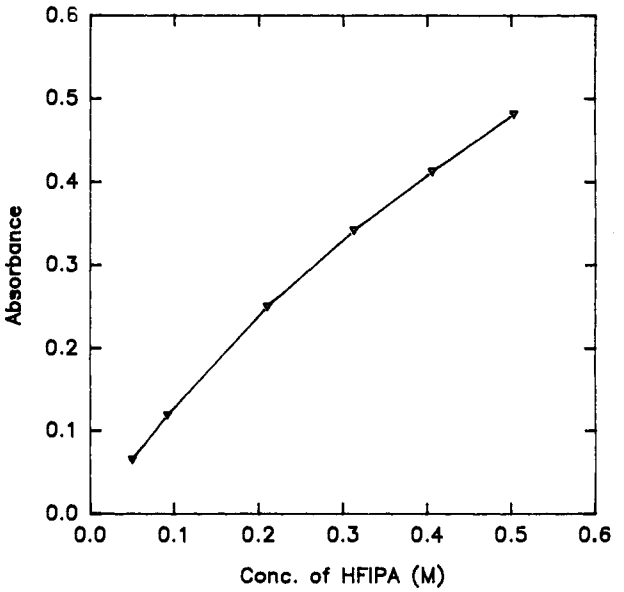

Figure 6. Plot of absorbance vs concentration of HFIPA at 3616.21 cm^{-1} in CCl_4.

complexes and incomplete reaction.[24] The spectra clearly show that even the strong acceptors did not react completely, even when an excess of donor was present. If we were to correct for the amount of unreacted base, the apparent stoichiometries would be higher.

It is very interesting that a considerable deviation from a stoichiometry of 1:1 was obtained for tetrahydrofuran and tetrahydropyran, even though these species have only a single oxygen. It appears that the extremely strong donor (HFIPA) can access

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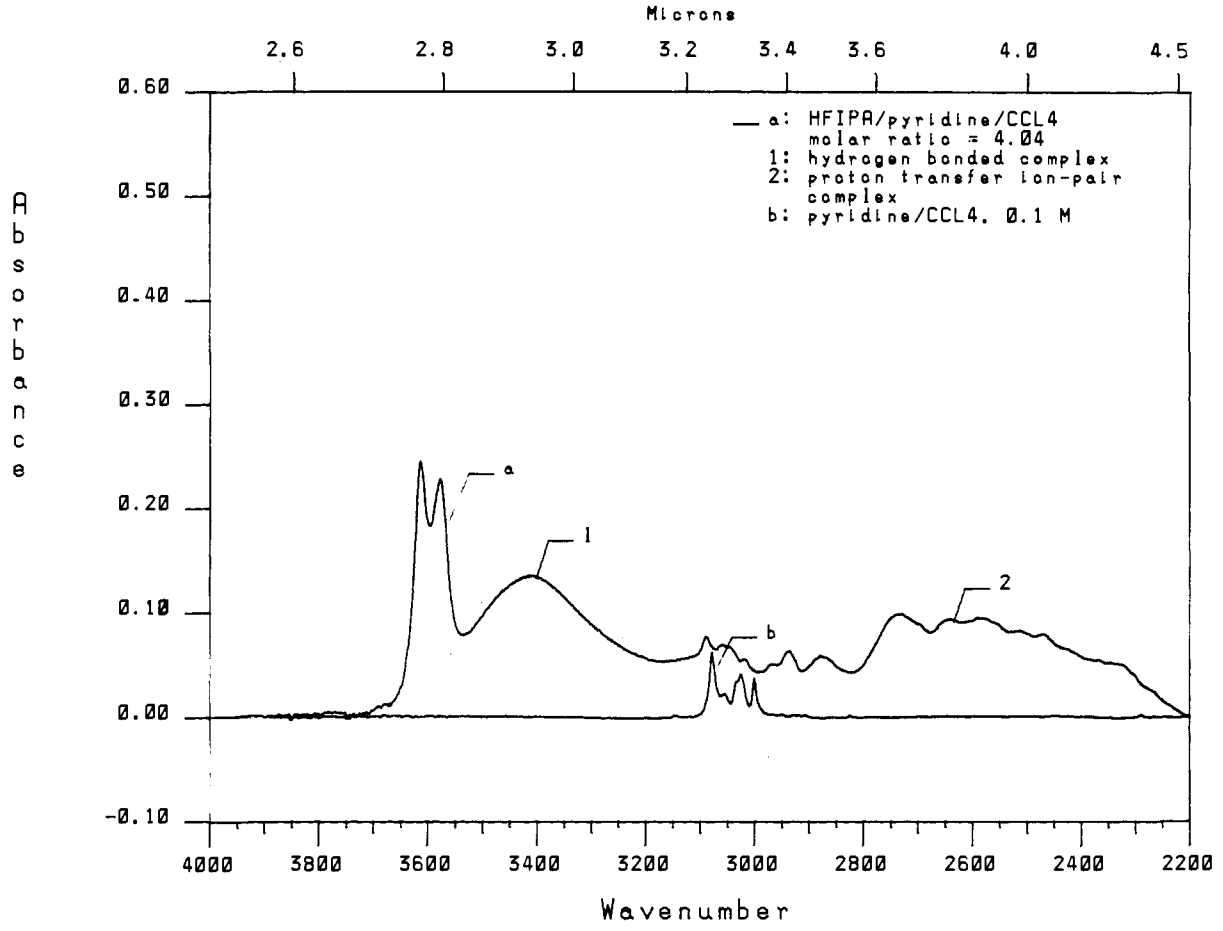

Figure 7. Infrared spectra of HFIPA/pyridine mixture and pyridine in CCl_4. Curve a shows a mixture of HFIPA/pyridine in molar ratio of 4.04 in CCl_4. There were two new bands shown in the spectra: band 1 is due to the hydrogen bonded complex and band 2 results from the proton transfer ion-pair complex. Curve b shows 0.1 M pyridine in CCl_4.

both lone pairs of electrons on the oxygen. Propionitrile also had a stoichiometric ratio equal to that of dioxane. This may be attributed to the interaction of the lone pair of electrons at the nitrogen atom and the π electrons of the nitrile triple bond with the donor. As expected,[35a,b] 1-octyne and 1-octene both have a stoichiometry close to 1 and octane has an apparent stoichiometry close to 0. We conclude that in the presence of an excess very strong donor, each accessible lone pair of electrons on a heteroatom is a potential site for formation of a hydrogen bond.

We were surprised that hydrogen bonding to octene and octyne could be observed in the presence of the solvent (CCl_4). However, in both cases, the decrease in the intensity of the O–H stretch bands was confirmed by the development of new bands in the IR spectrum. Despite our surprise, the finite β_2^C value observed for octene is in good accord with Abraham's β_2^H value. Inspection of Table V shows that we did not observe any hydrogen bond between HFIPA and benzene. It is difficult to rationalize this result.

The formation of complexes higher than 1:1 was confirmed by the appearance of additional spectroscopic bands. In a solution prepared by mixing nearly equal molar amounts of donor and acceptor, the OH stretching bands of the HFIPA are only about 12% (DMA) or 30% (THF) as large as we expect on the basis of the calibration curve (see Figures 7 and 8). Similarly, there is a significant decrease in bands due to the presence of the acceptor, such as the CH stretching band in DMSO (2940 cm^{-1}). When the donor/acceptor ratio was approximately 1:1, the spectra show a broad and quite symmetric H-bonding band, that is, a band which is absent in the pure donor and pure acceptor, with its maximum located near 3250 cm^{-1}. As the acid/base ratio is increased to about 4:1, the H-bonding band broadens, and, at a sufficiently high ratio of donor to acceptor, a new maxima appears at 3450 cm^{-1} (see Figures 8 and 9). We believe that this, along with the apparent stoichiometries given in Table V, strongly supports our view that in the presence of excess donor most acceptors listed in Table V form higher complexes, although their formations are quite incomplete.[1b,33a]

There are some minor problems involved in interpreting the above stoichiometric results, due to the presence of trace water in the solutions. The presence of small amounts of water is apparent in several of the spectra. We believe this to be unimportant for several reasons. First, we added known amounts of water. The total amount of water represented by its spectroscopic signature proved to be very small relative to the amounts of both HFIPA and the acceptor. Second, we saw almost no effect of added water on the apparent stoichiometry (see Table V). Third, water is a relatively weak hydrogen bond acceptor compared to species such as DMA, DMF, and DMSO. Finally, we performed several experiments where the water was very scrupulously removed. There was essentially no change in the results.

If higher hydrogen bonded complexes form in these dilute solutions in CCl_4, we ought to expect them to form in the chromatographic stationary phase. Even though the GC studies were carried out at higher temperatures, the concentration ratio of OH donor groups to base was about 6000, that is, nearly 1000 times greater than the highest ratio of HFIPA to base used in the IR studies. The concentration of OH groups in the stationary phase is about 3 M. This is 6-fold greater than the highest concentration of HFIPA used in the IR study.

In addition to the above results, we observed a proton-transfer reaction between HFIPA (pK_a = 9.3) and triethylamine (pK_b = 3.0). This is quite rational, since both compounds are strong Bronsted acids and bases, respectively. However, it is really interesting to observe that pyridine (pK_b = 8.8) had a partial (incomplete) proton-transfer reaction with HFIPA. As shown in Figure 9, a broadened OH stretching band, with a maximum

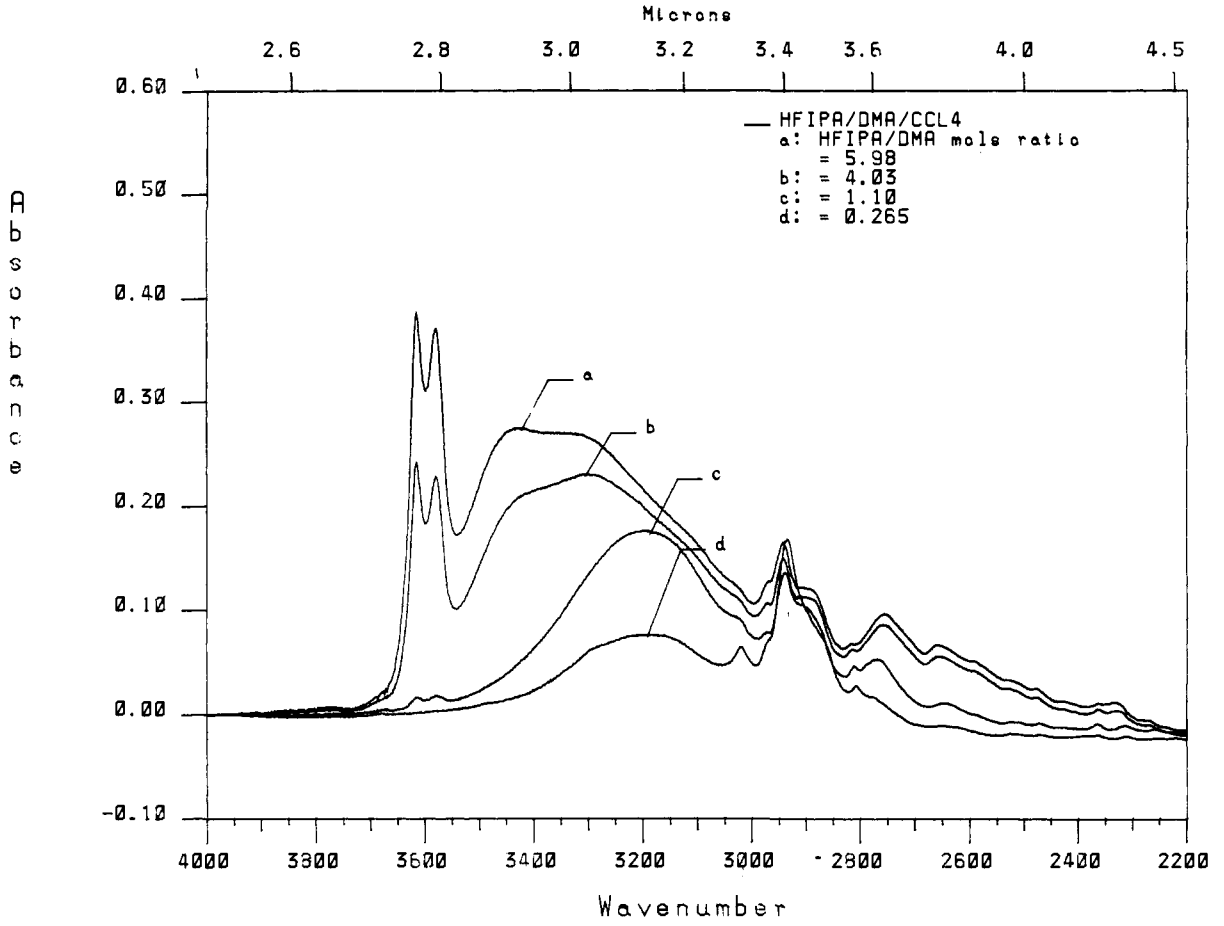

Figure 8. Plot of effect of HFIPA/DMA molar ratio on the infrared spectra of the mixture in CCl_4. The HFIPA/DMA ratio is for curve a, 5.98, for b, 4.03, for c, 1.10, and for d, 0.265.

at 3440 cm^{-1}, is due to the hydrogen bonding complex, and the other broadened band, with a maximum at 2600 cm^{-1}, is due to the ion-pair complex which resulted from the proton-transfer reaction.[33a]

Our initial goal in undertaking the IR study was to rationalize the much higher β_2^C values of certain strong acceptors (DMA, DMF, and DMSO) relative to their β_2^H values in terms of the existence of stoichiometries higher than 1:1 in the presence of excess donor. Given the near universality of stoichiometries greater than 1:1, we must now explain why in most cases, even with acceptors such as simple carbonyls, ethers, and nitriles, we find relatively good agreement between β_2^C and β_2^H. Note, however, that the β_2^C values for acyclic ethers are systematically lower than the β_2^H values. Before doing so, we must point out another fundamental difference between the chromatographic LSER approach and the classical methods of studying hydrogen bonding processes. It should be clear that, ultimately, Abraham's β_2^H scale is linearly related to the logarithm of the equilibrium constant for hydrogen bond formation.[14] In contrast, based on the ideas of Purnell[19] and Martire,[20] if we assume that our alcohol and ether phases differ only in the concentration of OH donor groups, then it is an easy matter to show that

$$\log k'_{alcohol}/k'_{ether} = \log (1 + K_{HB}^{1:1}[OH] + K_{HB}^{2:1}[OH]^2) \quad (13)$$

where $K_{HB}^{1:1}$ and $K_{HB}^{2:1}$ represent the equilibrium constants for 1:1 and 2:1 hydrogen bond formation and [OH] denotes the concentration of donor groups in the alcohol phase. This equation has two relevant consequences. At a fixed value of [OH], log $k'_{alcohol}/k'_{ether}$ can be linear with log $K_{HB}^{1:1}$ only when formation of the 1:1 complex is nearly complete ($K_{HB}^{1:1}[OH] \gg 1$) and when the 1:1 complex is dominant ($K_{HB}^{1:1} \gg K_{HB}^{2:1}[OH]$). These requirements are really quite restrictive and define fundamental differences between how hydrogen bonding is incorporated into the LSER formalism and how the seemingly closely related hydrogen bonding parameters are obtained from classical equilibrium studies.

We believe that agreement between β_2^C and β_2^H is as good as it is because the 2:1 complexes are generally much weaker than the 1:1 complexes unless the two sites are essentially independent and noninteracting, as in *p*-dioxane. That is, the formation of the first hydrogen bond complex shifts electron density from the base toward the acid, and, consequently, the formation constant for addition of the second donor is much smaller than that for addition of the first donor. As a consequence, its effect on retention on the GC phase is much less than is that of the stronger 1:1 complex. Other explanations are possible, such as cancellation of stoichiometric effects with higher front strain in the 2:1 complexes, but we do not have sufficient evidence to offer a more detailed explanation. It should also be borne in mind that all of the GC studies were carried out at 80 °C and all enthalpies of formation for hydrogen bonding systems are exothermic. Thus, we expect considerably smaller equilibrium constants at the higher temperatures.

General Solvent Effects on Hydrogen Bond Acidity and Basicity Scales. In addition to the above specific effects, we believe that there may be more general factors that complicate the development of a general scale of hydrogen bond strength. There are fundamental differences between the present approach and that used by Abraham. First, as noted above, the hydrogen bond equilibrium constants measured by Abraham incorporate all factors that either stabilize or destabilize the product complex relative to the reactants, since he chose to base the computation of the equilibrium constant on an infinitely dilute reference state. Consequently, all differences in dispersive and dipolar interactions between either reactants or the complex with the solvent, as well as differences in cavity formation energetics, are subsumed into the equilibrium constant. In the present method, the use of a matched reference

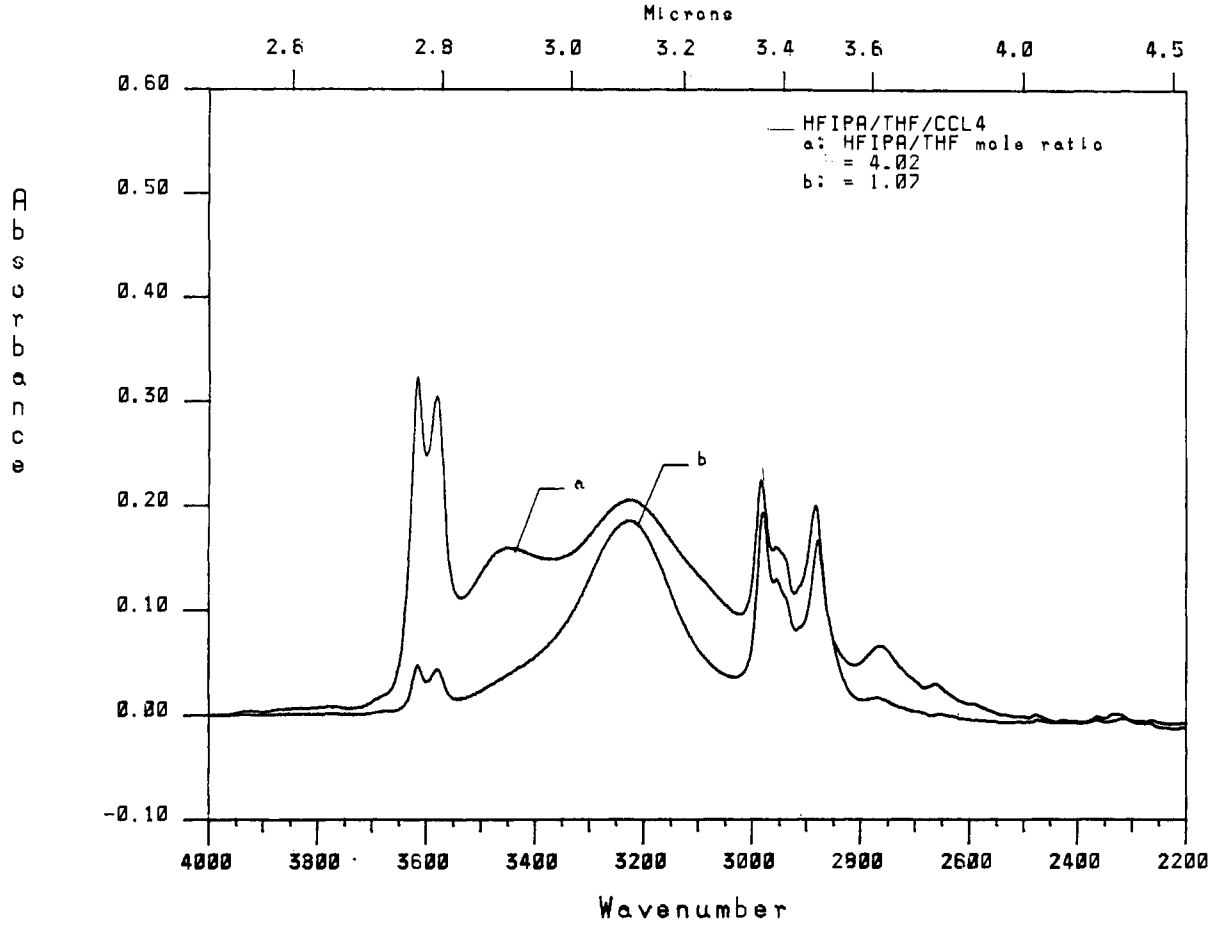

Figure 9. Plot of the effect of HFIPA/THF molar ratio on the infrared spectra of the mixture in CCl_4. The HFIPA/THF molar ratio is for curve a, 4.02 and for b, 1.07.

Table V. Infrared Study of the Apparent Stoichiometry of the Complexes[a]

base	HFIPA added (mmol)	base added (mmol)	HFIPA/base (initial)	HFIPA reacted[b]/ base
DMA	4.131	1.026	4.03	2.1
	4.097	1.005	4.08	2.0[c]
	5.162	1.005	5.14	2.0[d]
	6.007	1.005	5.96	2.2[d]
DMF	4.338	1.053	4.11	1.9
DMSO	2.708	0.673	4.02	2.3
dioxane	4.295	1.057	4.06	1.7
THF	4.697	1.169	4.02	1.5
THP	4.290	1.047	4.10	1.3
PNT	3.619	0.878	4.12	1.7
PAC	4.199	1.030	4.08	1.5
1-octyne	4.157	1.018	4.08	0.8
1-octene	4.076	1.007	4.05	0.7
octane	4.160	1.016	4.09	0.1
benzene	4.606	1.146	4.02	0.1

[a] All measurements were carried out by diluting the mixture with CCl_4 to 10 mL at 22–24 °C. [b] HFIPA reacted = HFIPA added − HFIPA remaining; HFIPA-remaining was estimated from the absorbance at 3616 cm^{-1} through an interpolation via a calibration curve. [c] This sample was made from the components without drying. [d] These sample were made for the water addition test. [e] THP; tetrahydropyran; PNT, propionitrile; PAC, propyl acetate.

phase causes considerable cancellation of these factors. That this is so is reflected in the fact that we are not able to detect by regression analysis any dependence of the ratio of capacity factors on L[16] or $\pi_2^{*,C}$.

Conclusions

Our findings raise several questions as to the development and applicability of general scales of solute hydrogen bond basicity. As noted above, the α_2^C scale of solute hydrogen bond acidity correlates rather well with the α_2^H scale based on hydrogen bond equilibrium constants, whereas the β_2^C scale does not correlate nearly so well with the β_2^H scale. We believe that this results because virtually all of the most acidic solutes tested have only a single activated proton and, in most instances, this proton is attached to an oxygen atom. In contrast, almost all of the strong hydrogen bond bases, including THF, amides, sulfoxides, and phosphorus oxides, have several lone pairs of electrons or π electrons which, in the presence of an excess of a sufficiently strong donor, can act as hydrogen bond acceptors. The sole exceptions to this broad generalization are the aliphatic amines.

Abraham and his co-workers have shown that reasonably general scales of hydrogen bond solute basicity can be established on the basis of the free energy of formation of 1:1 complexes. However, it is quite unclear whether such free energy based scales encode all the information needed to rationalize how hydrogen bond acceptor solutes interact with strong donors when the donors are present in great excess over the solute.[41] Thus, the β_2^H scale may not be equally applicable to all phenomena involving hydrogen bond formation. For example, it may not be as useful as the approach described here in explaining solvation in strong hydrogen bond donor systems, such as retention in gas chromatographic phases, solubility in water, octanol–water partition coefficients,[42] or retention in reversed-phase liquid chromatography. In contrast, the β_2^H scale should be very applicable to situations wherein the solute binds to a specific site in a protein or on a cell wall. Similarly, the β_2^H scale may be quite useful for rationalizing retention in adsorption chromatography on a polar material such as silica, where the surface silanol sites are fixed in space, or for

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retention on polymeric stationary phases. It appears that different scales may be needed, especially for complex solutes that have several hydrogen bond acceptor sites.

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Nearest-Neighbor Recognition in Phospholipid Membranes: A Molecular-Level Approach to the Study of Membrane Suprastructure[1]

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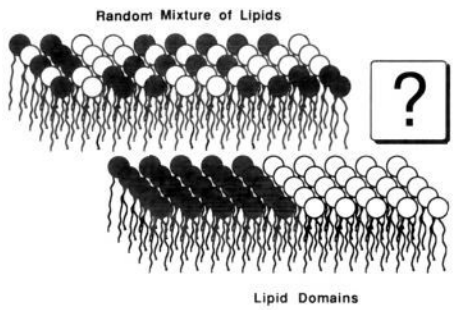
Abstract: A molecular-level approach has been devised for probing the lateral organization of phospholipid bilayers. This method is based on the equilibration of disulfide-based phospholipid dimers via thiolate–disulfide interchange reactions. Analysis of resulting product mixtures defines the tendency of one phospholipid monomer to become a covalently attached nearest neighbor of another. Investigation of equilibrium mixtures derived from *dimeric* analogs of 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC) and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) has yielded conclusive evidence that the lipid monomers are randomly distributed throughout the membrane in the fluid phase and also in the gel–fluid coexistence region. Additional support for random organization in the gel–fluid region has been obtained by use of differential scanning calorimetry (DSC). When the difference in alkyl chain length between the equilibrating monomers is increased from two to four methylene groups (i.e., dimeric analogs of 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) are used instead of DPPC), the membrane suprastructure remains random in the fluid phase. In the gel–fluid coexistence region, however, a significant deviation from randomness is observed. This deviation implies the presence of lipid domains and is consistent with the appearance of phase separation, as indicated by DSC analysis. Examination of the temperature dependence of this nearest-neighbor recognition supports the hypothesis that the packing forces that govern such recognition can be very similar to those that govern domain formation. Previous conclusions that have been drawn from quick-freeze DSC experiments with DMPC/DPPC bilayers are critically examined in light of these findings.

Introduction

One of the most significant challenges that lies at the interface of chemistry and biology is to define the suprastructure of biological membranes. In particular, the specific time-averaged, lateral distribution of the lipids and proteins that make up these biological enclosures remains to be established.[3-5] Do lipids organize themselves into nonrandom clusters, i.e., domains? If domains exist, do they have any functional importance? Are they intimately involved, for example, in basic membrane processes such as fusion, transport, recognition, and catalysis? Do changes in lateral organization accompany the formation of a diseased state, e.g., the malignant transformation of cells? Can such changes alter the presentation of receptors at the cell surface or the activities of membrane-bound enzymes? Are lipid domains in cancer cells unique, and can they serve as specific targets for chemotherapy? These questions are not only of considerable theoretical interest but they also have important practical implications. A firm understanding of the suprastructure of biological membranes has the potential for bringing exploitable targets into clear focus, which could assist the rational design of novel classes of membrane-disrupting drugs.[6]

Despite the considerable amount of effort that has been spent in investigating the lateral organization of lipid membranes, definitive proof of suprastructure in even the simplest of systems has remained elusive. In nearly all studies to date, a combination of thermal, spectroscopic, electron microscopic, and chemical methods has been used to infer the presence or absence of lipid domains.[7-12] While strong evidence has been obtained which supports the existence of domains in certain binary mixtures of phospholipids at temperatures in which the gel and fluid phase coexist (i.e., the gel–fluid coexistence region), the precise organization of lipid bilayers in the physiologically relevant fluid phase remains ill-defined. The major difficulty has been the absence of experimental techniques that can be applied directly to the fluid phase.



In this article we describe a fundamentally new approach to the study of the lateral organization of lipid bilayers. Our

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