15 Hansen Solubility Parameters — Biological Materials

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ABSTRACT

The Hansen solubility parameters (HSP) of many biological materials can be found from correlations of how they interact with well-defined liquids. The three HSP parameters, δ_D, δ_P, and δ_H quantitatively account for the cohesion energy density arising from atomic, dispersion type interactions (D), molecular, dipolar interactions (P), and molecular, hydrogen bonding interactions (H). Examples of HSP correlations included in this chapter are DNA, cholesterol, chlorophyll, wood chemicals, polypeptides (proteins), human skin, nicotine, lard, and urea. The often-quoted "like dissolves like" has been expanded to "like seeks like" (self-association) to discuss the implications of these correlations. The ability of HSP to correlate surface phenomena has made this change mandatory.

Biological materials such as proteins and DNA have well defined structures in a given environment. DNA adopts double helices, whereas proteins consist of a combined shape of the secondary, tertiary, and in some cases quaternary structure that together determine the conformation of the protein. The ultrastructure of wood is another example of Nature's way of establishing order in complex systems. The proper function of a protein requires that certain functional groups are at precise locations within its tertiary and/or in some cases quaternary structure. The conformation of proteins and DNA can be influenced, and in many cases controlled, by solvent quality. The solvent quality in a given environment is expected to determine whether a protein is dissolved or not, and also to control the way it adsorbs onto other materials or interacts with itself. Controlled changes in solvent quality can lead to controlled changes in conformation. Solvents can change not only the ability of noncovalent interactions such as van der Waals, hydrogen bonding, and ionic bonding, but also induce chiral rotation. The key to the importance of noncovalent interaction is that such interactions can continually be broken and reformed under physiological conditions. The portion of the molecule with energy properties most similar to the surrounding liquid will be oriented toward the liquid ("like seeks like").

The term *hydrogen bonding* is generally used to describe the noncovalent interactions in DNA, proteins, and other biological molecules, implying that this is the dominating interaction. The HSP correlation based on solvent interactions with DNA resulted in $\delta_D;\delta_P;\delta_H$ values equal to 19.0;20.0;11.0. These numbers clearly show that hydrogen bonding provides by far the smallest contribution of the three types of interaction, representing only about 14% of the cohesive energy involved (using Chapter 1, Equations 1.6–1.8). The term *hydrogen bonding* must be considered as an insufficient description of the interactions that determine the structure in such molecules.

INTRODUCTION

HSP have been used to characterize many biological materials.[1–7] Most of the materials discussed in these references are also included in the present discussion, but many more can be added by experiment or calculation.

There are many simple experimental methods to determine the HSP for biological materials. These involve contacting a material of interest with a series of well-chosen liquids. The fact of solubility, differences in degree of equilibrium swelling, rapid permeation or not, significant surface adsorption or not, or other measurable quantity significantly influenced by physical affinity relations can be observed and used to find the HSP for a material being studied. These methods have been discussed in more detail in earlier chapters. The basis of the division of the cohesive energy density into three parts accounting for the atomic dispersion (D), molecular dipolar (P), and molecular hydrogen bonding (H) interactions, respectively, is given in detail in Chapter 1.

The HSP for simpler compounds can be calculated according to the methods given in Chapter 1. HSP values for nicotine, skatole, wood chemicals, etc., that are discussed in this chapter were calculated using these methods. Figure 15.1 shows a typical HSP sphere correlating experimental solubility data for lignin.[1] The good solvents are located within the sphere which is based on Chapter 1, Equation 1.9. Again, as stated in previous chapters, this equation is in agreement with the Prigogine corresponding states theory of polymer solutions as discussed in Chapter 2. The statistical thermodynamics approach presented in Chapter 3 also shows agreement with the concepts to which this book is dedicated. Furthermore, this equation has also been shown to be correct for such complex materials as asphalt and bitumen, as described in Chapter 9, and carbon dioxide solubility in solvents, as described in Chapter 10.

A HSP correlation can, of course, be used to predict the behavior of solvents not included in the experimental work. It is convenient to print the solvent database in order from best solvent to worst solvent to aid in finding alternatives. This is a quantitative application of the generally used statement "Like Dissolves Like." In the following discussion, this concept is expanded to "Like Seeks Like" (self-association). This implies that segments of molecules seek regions of similar HSP if this is possible. This may result in solutions or in selective orientation of segments of molecules in more complicated systems.

Table 15.1 contains HSP data for several biologically interesting materials. These are discussed in the following in more detail with an indication of how such data may be used. The data included in this table are the δ_D, δ_P, and δ_H parameters; the radius of interaction for the HSP correlation, Ro; if appropriate, the data fit (where a fit of 1.000 is perfect as discussed in Chapter 1). G is number of "good" solvents and the total number of solvents in a given correlation is T. The units for the solubility parameters and Ro are $MPa^{1/2}$. Plots of the kind given in Figure 15.1 for lignin are sometimes used to interpret relations among different materials. RED numbers indicate solvent quality with lower values being indicative of better solvents (see Chapter 1, Equation 1.10). The correlations reported here are a result of data processing with the SPHERE program described in Chapter 1. The output is often arranged with the best solvent (lowest RED number) at the top of the list.

A most interesting and important class of molecules are called amphipathic. These exhibit both hydrophilic and hydrophobic properties simultaneously. An example from biology is the amphipathic molecules (lipids) that form the basis of the biological membrane bilayers that surround cells. Such amphipathic molecules have a head group that is strongly hydrophilic, coupled to a hydrophobic tail – usually hydrocarbon in nature. When one attempts to dissolve these molecules in water, they form special structures. These may be monolayers on the water surface, with only the head groups immersed. Alternatively, if the mixture is vigorously stirred, micelles (spherical structures stabilized by a single layer of molecules at the water interface) or bilayer vesicles may form. Another example is amino acid side chains. These are by nature not only different in size and shape, but also in the charge they carry, their general affinity for water (hydrophilicity) and/or their general aversion to water (hydrophobicity). The native conformation of proteins is a strong

Hansen Solubility Parameters

	δ_D	δ_P	δ_H	R_O
Lignin	**21.9**	**14.1**	**16.9**	**13.7**

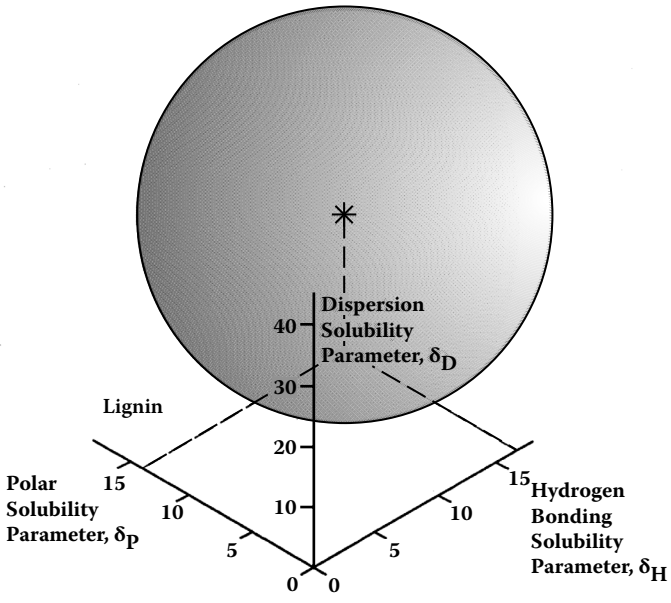

FIGURE 15.1 HSP correlation showing the solubility of lignin. Good solvents are located within the sphere. Units are $MPa^{1/2}$. (From Hansen, C.M. and Björkman, A., *Holzforschung*, 52, 339, 1998. With permission.)

function of the interactions that take place within and between polypeptide chains. This is also highly dependent on the interaction that takes place with water, as proteins exist in an aqueous environment. These general concepts of hydrophilic and hydrophobic entities can also be quantified using HSP.

HYDROPHOBIC BONDING AND HYDROPHILIC BONDING (SELF-ASSOCIATION)

The concept of "like seeks like" offers a general explanation of hydrophobic bonding. An aliphatic hydrocarbon chain on a protein, for example, is not soluble in water and ultimately finds another aliphatic hydrocarbon chain with which to associate. This same type of process leads to micelle formation when the solubility limit of surface active agents is exceeded. Hydrophobic bonding is found when the HSP for the associating segments are too low to allow solubility in the continuous phase.

When it is immersed in water a polypeptide chain will not stay in an elongated form. It will instead fold up into secondary structures according to the polarity of the side chains it contains and the rotation of peptide backbone bond angles that are largely determined by Van der Waals radii of side chains. This can be called *hydrophilic bonding*. Hydrophilic bonding is formed when the HSP for the associating segments are too high to allow solubility in the continuous phase. If the continuous phase is a hydrocarbon liquid, the associating segments may be characterized by high δ_H, for example, because of the presence of an alcohol, acid, or amide group.

TABLE 15.1
Hansen Solubility Parameter Correlations for Biologically Interesting Materials, $MPa^{1/2}$

Material	δ_D	δ_P	δ_H	Ro	FIT	G/T
DNA	19.0	20.0	11.0	11.0	1.000	6/12
Cholesterol solubility	20.4	2.8	9.4	12.6	1.000	25/41
Lard 37°C solubility	15.9	1.2	5.4	12.0	1.000	29/50
Lard 23°C solubility	17.7	2.7	4.4	8.0	1.000	21/50
Olive oil solubility	15.9	1.2	5.4	12.0	1.000	29/50
Psoriasis scales swelling	24.6	11.9	12.9	19.0	0.927	35/50
Human skin — permeation	17.6	12.5	11.0	5.0	1.000	4/13
Nicotine — calculation	18.8	7.8	6.4	—	—	—
Skatole — calculation	20.0	7.1	6.2	—	—	—
Chlorophyll — solubility	20.2	15.6	18.2	11.1	0.864	7/35
Sinapyl alcohol calculation	19.2	7.3	16.1	—	—	—
Coniferyl alcohol calculation	19.0	7.0	16.3	—	—	—
p-Coumaryl alcohol calculation	19.1	7.0	17.3	—	—	—
Lignin — solubility	21.9	14.1	16.9	13.7	0.990	16/82
Dextran C (= amorphous cellulose) See Chapter 5	24.3	19.9	22.5	17.4	0.999	5/50
Sucrose solubility	23.4	18.4	20.8	16.0	0.981	6/50
N-methyl-morpholine-N-oxide calculation	19.0	16.1	10.2			
Blood serum — swelling	25.5	10.3	22.1	17.8	0.980	4/51
Zein — solubility	22.4	9.8	19.4	11.9	0.964	4/50
Urea — solubility	22.9	14.9	21.3	16.2	0.984	14/50
Water — >1% soluble in	15.1	20.4	16.5	18.1	0.856	88/167
Water — totally miscible	18.1	17.1	16.9	13.0	0.880	47/166
Water — single molecule	15.5	16.0	42.3	—	—	—

Note: The units for the solubility parameters and Ro are $MPa^{1/2}$. G/T represents the number of good liquids (G) and the total number of liquids (T) in the correlation.

Figure 15.2 demonstrates how hydrophilic bonding between versamid polymer blocks reacted into an alkyd (polyester) polymer gives a thixotropic alkyd paint with its special nondrip properties. Agitation of the paint is enough to break the hydrophilic bonds allowing easy spreading, but they reform quickly again after application.

The most common secondary structures are alpha helices and beta sheets that are stabilized by local inter-residue interactions mediated by hydrogen bonds. An alpha helix can take the form of an amphipathic helix with a polar and a nonpolar side. This plays a crucial role in helix–helix interactions and in the interaction of small peptides that have a helical conformation with membranes, air–water interfaces, and self-assembly processes. Beta sheets are alternative secondary structure to the alpha-helix in proteins. Like alpha-helices, beta-sheet backbones are stabilized by hydrogen bonds between two beta sheets, but the bonds occur between neighboring strands. If the beta–strand contains alternating polar and non-polar residues it forms an amphipathic beta sheet. This distribution of hydrophilic and hydrophobic residues has been observed in the membrane protein porin that forms a beta-barrel structure. Here the nonpolar residues stick into the hydrophobic part of the lipid membrane and the hydrophilic residues form part of the channel interior responsible for the passage of small molecules across the membrane.

Hydrophobic bonding is a major effect that drives proper protein folding. Hydrophobic sidechains are oriented to minimize the energy lost by the intrusion of amino acids into the water solvent, which disrupts lattices of water molecules. Hydrophobic bonding forms an interior,

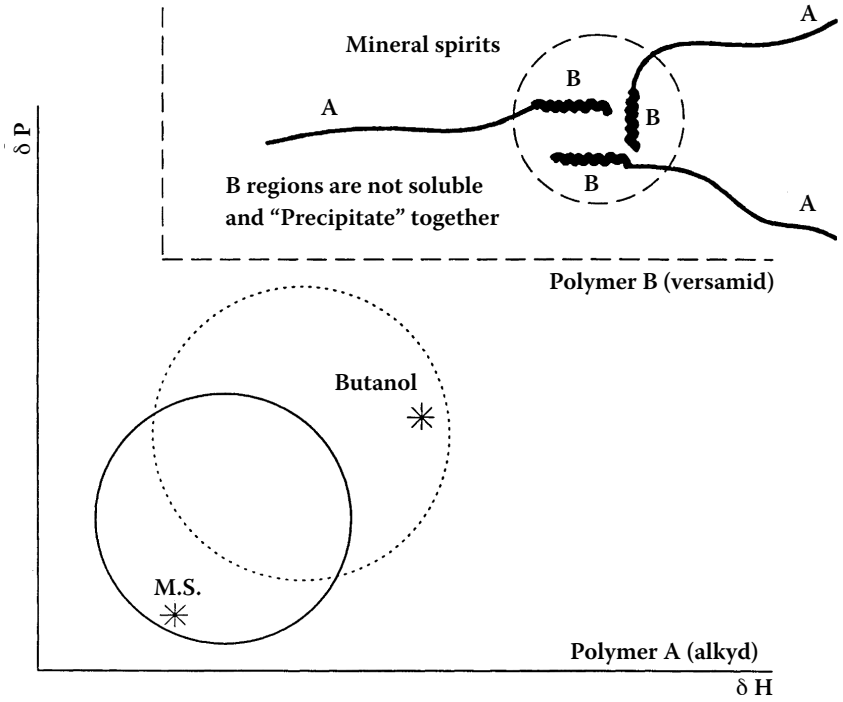

FIGURE 15.2 HSP relations for establishing thixotropy in an alkyd-type paint. The solid circle represents the solubility of the alkyd (A) and the dotted circle that of the Versamid (B). The Versamid segments associate because they are not soluble in mineral spirits. Addition of *n*-butanol destroys the thixotropic effect, since the solvent then becomes too good. Similar relations exist for the true solution of some proteins by additions of urea to water. This denatures them, by effectively dissolving them in a solvent mixture that is better than water itself.

hydrophobic protein core, where most hydrophobic sidechains can closely associate and are shielded from interactions with solvent water. Formation of "hydrogen bonds" within proteins is based on the lack of solvency in the continuous media, water, because the HSP of these segments is too high. Additions of urea, as discussed later in more detail, increase the HSP of the continuous media to such an extent that it can now dissolve the "hydrogen bonded" segments. The protein is denatured, which in fact means that these segments are dissolved in a good solvent. Additions of salts can also improve solvency for a given material or segments of materials. Additions of salts can also reduce solvency. These phenomena must also have their explanation in the "like seeks/dissolves like" phenomena, but more research is required to quantify them. Such mechanisms of controlling solvent quality can be expected to be used by Nature in many biological systems to control adsorption and/or transport of various types of materials as in self-association.

DNA

The double helix structure of DNA suggested by Watson and Crick is stabilized by hydrogen bonding between bases on opposite strands when the bases are paired in one particular way (A+T or G+C). In the Watson–Crick model the base pairs are stacked on one another with their planes nearly perpendicular to the helix axis where the hydrophilic phosphate–deoxyribose backbones are on the outside, in contact with the aqueous environment. This complementary base pairing (hybridization) is central to all processes involving nucleic acids. In cells it occurs in, e.g., DNA replication,

TABLE 15.2
Hansen Solubility Parameter Correlation for DNA

Solvent	δ_D	δ_P	δ_H	RED	V
Dimethyl sulfoxide	18.4	16.4	10.2	0.353	71.3
2,6-Dichloro-7-methyl purine	20.5	11.7	14.2	0.651	162.4
Coumarin	20.0	12.5	6.7	0.807	156.3
Purine	20.5	11.7	14.2	0.853	100.0
Caffeine	19.5	10.1	13.0	0.923	157.9
Formamide	17.2	26.2	19.0	0.977	39.8
Pyrimidine	20.5	9.4	11.3	1.002	78.8
Phenol	18.0	5.9	14.9	1.342	87.5
Urea	20.9	18.7	26.4	1.447	45.8
Cyclohexanol	17.4	4.1	13.5	1.492	106.0
Methyl riboside	17.0	12.0	32.8	2.142	117.2
Adonitol	18.0	12.0	36.0	2.393	95.1
DNA	D = 19.0 P = 20.0 H = 11.0 R_o = 11.0 FIT = 1.000 NO = 12				

Note: Units of D, P, H and Ro are $MPa^{1/2}$. V is in cc/mole. The order in the table is from expected best at the top to expected worst at the bottom.

transcription, rRNA, and tRNA structure, but it is also used in laboratories in RNA and DNA gel blots, PCR, sequencing, genotyping, microarrays, *in situ* hybridization, etc.

DNA melts (denatures) at 90-100°C in 0.1-0.2 M Na+. This may lead to deterioration of morphology. Fortunately, organic solvents reduce the thermal stability of double-stranded polynucleotides, so that hybridization can be performed at lower temperatures in the presence of formamide, for example. Formamide is often used in connection with DNA.[8] For in situ hybridization this implies that microscopic preparations must be hybridized at 65–75° for prolonged periods. The melting temperature, T_m, is found when a population of particular DNA sequences is at a midpoint between fully double-stranded and single-strand. Formamide reduces the T_m of DNA-DNA and DNA-RNA duplexes in a linear fashion by about 0.65°C for each volume percent of the solvent that is present. Other common solvents can also reduce T_m, including dimethyl sulfoxide.

An article in the older literature[9] reports aspects of the interaction of different low molecular weight materials with DNA. The summary of this article states that the order of increasing activity was found to be: adonitol, methyl riboside (both negligible) < cyclohexanol < phenol, pyrimidine, uridine < cytidine, thymidine < purine, adenosine, inosine, deoxyguanosine < caffeine, coumarin, 2,6-dichloro-7-methylpurine. Urea was ineffective with poly A and only slightly effective with DNA. At a concentration of 0.3M, purine lowered the T_m of DNA by about 9°C.

The HSP for several of these having reasonably simple structures were estimated by the methods of Chapter 1. These HSP data were divided into two arbitrary groups of "good" and "bad" with a dividing line between purine as good and pyrimidine as bad. The compounds intermediate in the above list were structurally too complicated to allow a reliable calculation. Formamide and dimethyl sulfoxide were also considered as "good" and added to the data for the correlation reported in Table 15.2.

The encouraging correlation reported in Table 15.2 ranks the given solvents in approximately the same order as that given in Reference 9. All the solvents from pyrimidine and lower were considered as being "bad" and all those above this were considered as being "good." Even urea, where performance may be affected significantly by the presence of water, seems to be placed correctly. Formamide is not at the top of the list, but is the preferred solvent of use today in many cases. The effectiveness of formamide is primarily because of its low molecular volume, but it will also be a good solvent for phosphate salts, which may also contribute some effect. Dimethyl

sulfoxide will also be a reasonably good solvent for phosphate salts. Low molecular volume is very conducive to dissolving polymers with structure or crystallinity, as the small molecules can reach the critical sites more readily than larger ones. Smaller molecules are also predicted to be thermodynamically better, all else being equal. The radius is arbitrary and depends on the criterion used for good and bad. If pyrimidine had been considered as being good, then the D, P, and H could be maintained with a slightly larger Ro, and the data fit would still be 1.000. There are many different D, P, and H, combinations possible when the data fit is 1.000, but the present correlation, in spite of the very few solvents, is still considered reasonably reliable because of the essentially correct ranking. Other supporting evidence that the correlation is reasonable can be found in the estimated HSP for adenine and thymine. These can be considered as single relevant portions of DNA. The HSP are $\delta_D;\delta_P;\delta_H$ equal to 20.0;16.0;14.9 for adenine and 19.0;20.5;13.0 for thymine. Both of these are reasonably close to HSP equal to 19.0;20.0;11.0, the estimated values for DNA based on its interaction with a number of solvents as reported in Table 15.2. All units are $MPa^{1/2}$.

The δ_H value for DNA is only 11.0 $MPa^{1/2}$ compared with δ_D equal to 19.0, and δ_P equal to 20.0. This clearly shows that the hydrogen-bonding interactions are far less important than the other two types of interaction. The cohesive energy derived from hydrogen bonding is about 14% of the total using Chapter 1, Equations 1.6 to 1.8.

CHOLESTEROL

Cholesterol has been characterized with HSP based on its solubility in a large number of solvents. δ_D, δ_P, and δ_H and Ro for cholesterol solubility were found as 20.4;2.8;9.4 and 12.6, all values having units of $MPa^{1/2}$. The test method involved placing 0.5 g of cholesterol in test tubes together with 5 ml of each of 41 different solvents. The temperature was 23°C. Total solution or not at this concentration was evaluated visually. The 25 "good" solvents dissolved the entire amount of cholesterol added. These data were analyzed by the SPHERE computer program described in Chapter 1 to find the HSP for cholesterol. This has also been reported in Reference 10. Figure 15.3 shows this HSP correlation for cholesterol. This figure also includes several solvents that are discussed in the following.

The data fit of 1.0 indicates that there are other sets of parameters for spheres which can be expected to give a perfect separation of the good solvents from the bad ones by a "spherical" HSP correlation. Continued testing with additional test solvents located in the boundary region of the sphere is possible to define it more precisely. This was not warranted under the present circumstances, but is recommended if more extensive use of these data is planned.

A general confirmation of the HSP correlation for cholesterol was done by studying mixtures of nonsolvents. Many mixtures of two nonsolvents which dissolve polymers when admixed have been reported in the literature.[1] Such synergistic mixtures can be predictably found when they are pairwise on opposite sides of an HSP sphere. The 50:50 vol mixtures of *n*-hexane with 2-nitropropane and *n*-hexane with ethanol predictably dissolved cholesterol at 0.5 g/5 ml.

During the course of this study, it also became obvious that the solubility of cholesterol in hydrocarbons was limited and quite temperature dependent, being considerably higher at slightly elevated temperatures. This behavior in hydrocarbon solvents relates to the interactions of cholesterol in the hydrocarbon (hydrophobic) portions of lipid layers. The limited solubility in hydrocarbon media and very low solubility in water favors a location at an aqueous interface with the alcohol group of the cholesterol molecule oriented toward the high energy aqueous phase, where it is more compatible, and the hydrocarbon portions oriented into the lipid layer. Changes toward lower temperature will tend to force more cholesterol out of a hydrocarbon matrix. The δ_H parameter of alcohol solvents decreases relatively more rapidly with increasing temperature than for solvents where the δ_H parameter is low (or zero), such as with the hydrocarbon solvents. This brings the HSP of the alcohol solvent closer to the HSP of the hydrocarbon solvents, and miscibility improves markedly as temperature increases.

	MATERIAL	δ_D	δ_P	δ_H	R_O
⊗	CHOLESTEROL	20.4	2.8	9.4	12.6
✳	2 – NITROPROPANE	16.2	12.1	4.1	
✳	HEXANE	14.9	0.0	0.0	
✳	ETHANOL	15.8	8.8	19.4	
●	DISSOLVING MIXTURES OF NON–SOLVENTS				

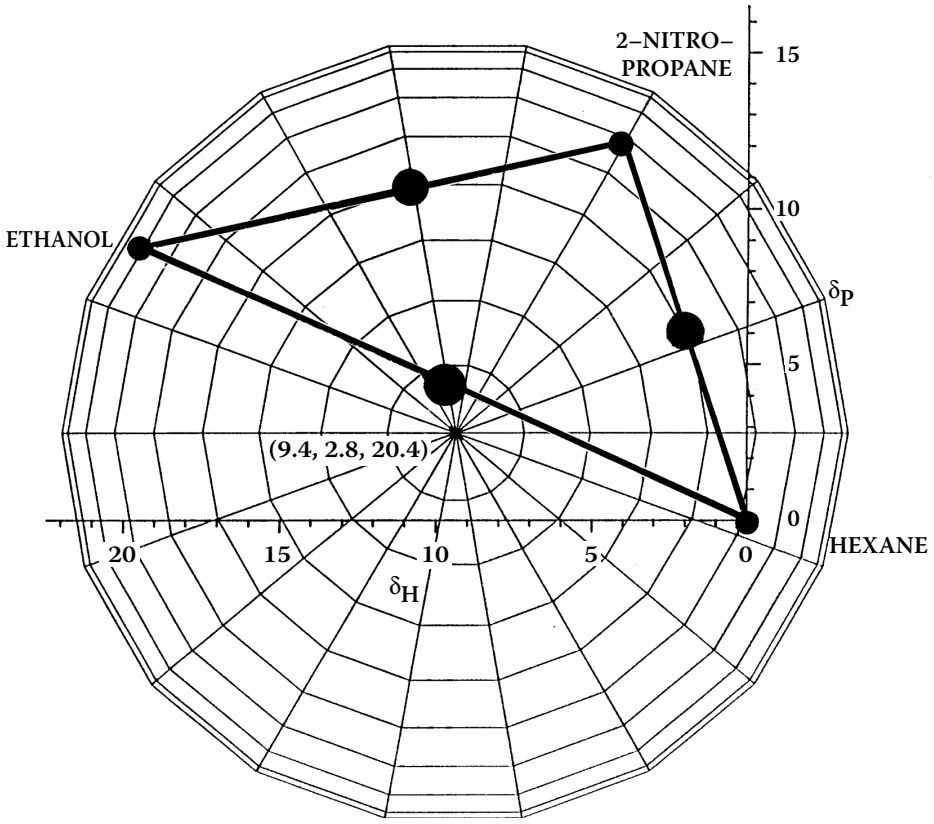

FIGURE 15.3 HSP sphere correlating the solubility of cholesterol. Nonsolvents which synergistically interact to become improved solvents when mixed are indicated. These can predictably be found by selecting pairs located on opposite sides of the HSP solubility parameter sphere. Units are $MPa^{1/2}$.

One can also surmise what might happen when ethanol or other organic solvent is present in the body. Organic solvents with HSP resembling those of the lipid layer may be found due to occupational exposure or for other reasons, such as drinking alcohol-containing beverages. The presence of ethanol or other organic solvent in the lipid layer allows greater cholesterol miscibility in its hydrocarbon portions. The reason for this is the synergistic effect of ethanol and hydrocarbon segments described earlier. The simple experiments described previously indicate that the cholesterol uptake in hydrocarbon portions of a lipid layer will be greatly enhanced when ethanol is present. This, of course, preferentially removes some of the cholesterol from the blood stream.

The solubility of cholesterol in an essentially nonsolvent such as water can be enhanced by additions of a solvent improver such as ethanol. The average HSP for these mixtures are closer to those of cholesterol itself. Therefore, those persons with alcohol in their blood can anticipate a

slightly higher solubility of cholesterol in their blood because the continuous phase has solubility parameters closer to those of cholesterol. This effect and that discussed earlier should help to reduce cholesterol levels in the blood and blood vessels of those who ingest small to moderate amounts of alcohol on a regular basis.

LARD

Experimental data and HSP correlations for the solubility of refined lard at 23°C and 37°C have been reported.[2] The criterion for a good solvent is that it totally dissolves the sample at the given temperature. The concentrations chosen were 10%. The results of the correlations are given in Table 15.1. The refined lard is a semisolid with a melting point of 42°C.

The composition of refined lard is very similar to that of human depot fat, so the conclusions drawn for the solubility of lard will also be generally valid for depot fat. Olive oil is a convenient material to use at room temperature to study the behavior of depot fat (lard), as the same solvents that dissolve it at room temperature also dissolve lard at 37°C. This is reported in Table 15.1.

The best room temperature solvents for lard include trichloroethylene, styrene, toluene, and methyl methacrylate. Octyl alcohol does not have a strong affinity for lard at room temperature with a RED number (see Chapters 1 and 2) of 0.96. The good solvents reflect the crystalline nature of the lard, as toluene, for example, is an excellent swelling solvent for partly crystalline polyethylene. Esters are among the best solvents for lard at 37°C, reflecting the presence of the ester groups in the lard, which is very nearly a liquid at this temperature.

HUMAN SKIN

A first attempt to characterize human skin with HSP was made by visually evaluating the swelling of psoriasis scales immersed for a prolonged time in different solvents.[2] Uptake could clearly be seen by dimensional changes and a marked enhancement of clarity. It was anticipated that the solubility parameter correlation for the psoriasis scales (keratin) would to some extent reflect permeation in human skin but that other factors, such as the presence of water and lipids, for example, would also be important. The data fit for this correlation (0.927) indicates that a reasonably reliable correlation for swelling of the psoriasis scales (keratin) has been found. However, the δ_D parameter is thought to be too high.

Permeation data generated in an extensive study allowed placement of the tested solvents into groups according to actual permeation rates through viable human skin.[4] Figure 15.4 graphically shows the HSP correlation that resulted. There are too few data to establish a reliable correlation, but a sphere with center at δ_D, δ_P, and δ_H of 17.6, 12.5, and 11.0, which has a radius of 5.0, encompasses the parameters for the four solvents with the highest permeation rates while excluding the others. The units for these parameters are $MPa^{1/2}$. n-octyl acetate has a near zero permeation rate. This correlation cannot be considered precise because of insufficient data, and there are, in fact, numerous spheres with somewhat similar but different combinations of the parameters that also can accomplish this. Nevertheless, there is a good guideline for future work, whether it be an expanded correlation or formulation of products designed for a prescribed compatibility with human skin. Calculations for skatole and nicotine predict that moderate rates of skin permeation can also be expected for these.

It might be noted that the four solvents with high permeation rates also have very high affinity for psoriasis scales according to the correlation previously noted. Likewise, the cyclic solvents propylene carbonate, gamma-butyrolactone, and sulfolane have, or are predicted to have, high affinity for psoriasis scales, but they are placed in the low permeation rate group for actual permeation through viable human skin. These all have high δ_P and low δ_H. n-butyl acetate and toluene are also in this group. This reflects the complexity of actual skin permeation and the importance of using viable skin for testing. The cyclic nature of the solvents, however, is also expected to slow the rate

SOLUBILITY PARAMETER PLOT FOR SKIN PERMEATION RATE

	δ_D	δ_P	δ_H	M_V	PERMEATION RATE
DMSO	18.4	16.4	10.2	71.3	
DMF	17.4	16.7	11.3	77.0	● HIGH
DMAC	16.8	11.5	10.2	92.5	
NMP	18.0	12.3	7.2	96.5	
MCL	18.2	6.3	6.1	63.9	○
MEK	16.0	9.0	5.1	90.1	MODERATE
ETH	15.8	8.8	19.4	58.5	
BAC	15.8	3.7	6.3	132.5	
PPC	20.0	18.0	4.1	85.0	×
TOL	18.0	1.4	2.0	106.8	LOW
BTA	19.0	16.6	7.4	76.8	
SUL	18.4	16.6	7.4	95.3	
OAC	15.8	2.9	5.1	196.0	✣ "0"

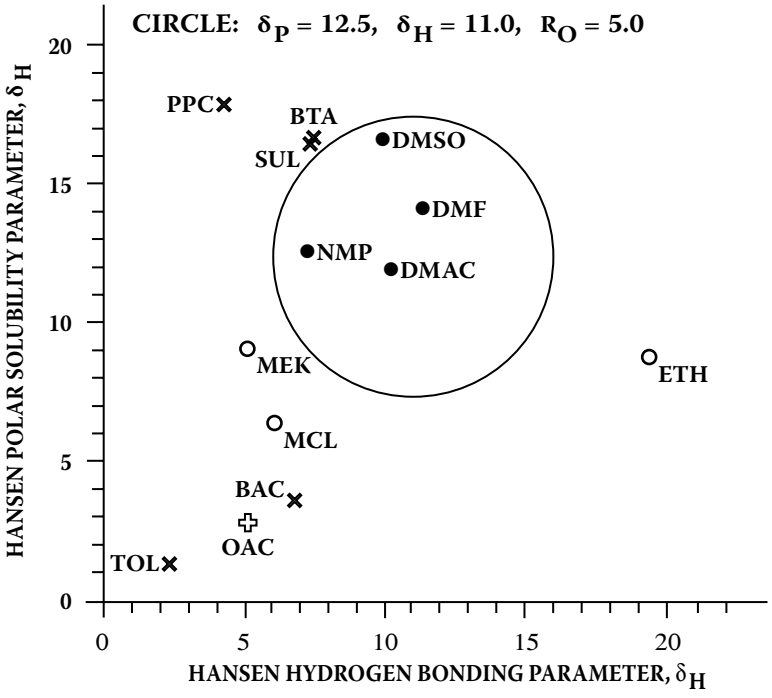

FIGURE 15.4 Permeation rates of selected solvents through viable human skin show a correlation with the HSP[4] although the data are not extensive. Units are $MPa^{1/2}$.

of permeation relative to linear solvents of comparable affinity. Factors affecting permeation have been discussed at length in Chapter 13. Of course, the presence of water and/or other skin components can also have an effect on the permeation rate. Finally, the swelling of the psoriasis scales involved equilibrium swelling of the individual systems, whereas the permeation rate studies did not have this uniformity. Concentration gradients are required for permeation to occur.

PROTEINS — BLOOD SERUM AND ZEIN

HSP correlations for the swelling of blood serum and for the solubility of zein, a protein derived from corn, are included in Table 15.1. The data used in these correlations are found in Reference 3. Solvents with the lowest RED numbers in the correlation for the solubility of zein are listed in Table 15.3. The HSP parameters for blood serum and zein are not too different. The blood serum data are based on visual observation of swelling, while the zein data are for visual observation of true solution. It is noteworthy that there are only four good solvents in the data set reported in Table 15.3, and that the HSP parameters for the proteins are much higher than for any liquid which can be used in such testing. These HSP parameters are found by a form of extrapolation, where all of the good solvents are located in the boundary region of the respective spheres. The values are very much dependent on the mathematical model which includes the coefficient "4" (see Chapter 1 and Chapter 2). The saturated solution of urea and water is also a (predictably) good solvent in that it swells blood serum and dissolves zein, but it was not included as a data point in the correlations as such. Mixtures of solvents, water, and mixtures of solvents with water have been avoided as test solvents to the extent possible because of too many interactions, which are apparently not always predictable by these simple considerations. The general prediction that additions of urea to water will improve solvency of proteins is discussed below.

CHLOROPHYLL AND LIGNIN[5]

The results of HSP correlations of solubility for lignin and chlorophyll are given in Table 15.1. More specific information on the lignin correlation is found in Table 15.4A and Table 15.4B. It can be seen that these indeed have high affinity/physical resemblance to each other, with the HSP values not being too different. A major difference is that chlorophyll is soluble in ethanol, whereas lignin is not. This indicates a higher hydrophilicity, of course, and gives a higher δ_H parameter to chlorophyll compared with lignin.

It can be presumed that the HSP for these materials are the result of natural selection by nature for optimum compatibility relations with immediate surroundings and function. A discussion of this is beyond the scope of this work, but this point has been studied in more detail for the relations among wood chemicals and wood polymers as outlined in the next section. Here, the HSP for lignin have a demonstrated clear importance with regard to compatibility relations.

WOOD CHEMICALS AND POLYMERS

The results of HSP calculations and correlations for several wood chemicals and polymers are given in Table 15.1. These results are part of a study considering the ultrastructure of wood from a solubility parameter point of view.[6] The study is based on the principle of "like seeks like" and leads to a proposed configuration of the ultrastructure. The HSP for amorphous cellulose are presumed to be similar to those of Dextran (Dextran C, British Drug Houses). The crystallinity in cellulose will require that good solvents have higher affinity/HSP than most of those dissolving Dextran, however. N-methyl-morpholine-N-oxide is an example. The HSP for Dextran are higher than those of sucrose (which values are similar to the other sugars as well). It is common for polymers to have higher HSP than the monomers from which they are made. It is also common

TABLE 15.3
Calculated Solubility Sphere for Zein

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
1,3-Benzenediol	18.0	8.4	21.0		0.761	87.5
Benzyl alcohol	18.4	6.3	13.7		0.876	103.6
Diethanolamine	17.2	10.8	21.2		0.891	95.9
Phenol	18.0	5.9	14.9		0.893	87.5
o-Methoxyphenol	18.0	8.2	13.3		0.910	109.5
Furfuryl alcohol	17.4	7.6	15.1		0.933	86.5
Hexamethylphosphoramide	18.5	8.6	11.3		0.950	175.7
3-Chloro-1-propanol	17.5	5.7	14.7		0.976	84.2
1,3-Butanediol	16.6	10.0	21.5	0*	0.991	89.9
Propylene glycol	16.8	9.4	23.3	0*	0.997	73.6
Diethylene glycol	16.6	12.0	20.7	1	0.998	94.9
Ethylenediamine	16.6	8.8	17.0		0.999	67.3
m-Cresol	18.0	5.1	12.9	1*	1.001	104.7
Aniline	19.4	5.1	10.2	0	1.004	91.5
Dipropylene glycol	16.5	10.6	17.7	0	1.004	130.9
1,1,2,2-Tetrabromoethane	22.6	5.1	8.2		1.021	116.8
Ethanolamine	17.0	15.5	21.2	0	1.037	59.8
Succinic anhydride	18.6	19.2	16.6		1.043	66.8
2-Pyrolidone	19.4	17.4	11.3		1.061	76.4
Allyl alcohol	16.2	10.8	16.8		1.068	68.4
Ethylene glycol	17.0	11.0	26.0	1*	1.068	55.8
Ethylene glycol monomethyl ether	16.2	9.2	16.4	1*	1.073	79.1
Cyclohexanol	17.4	4.1	13.5	0	1.087	106.0
Diethylenetriamine	16.7	13.3	14.3		1.090	108.0
Benzoic acid	18.2	6.9	9.8		1.099	100.0
Triethyleneglycol	16.0	12.5	18.6		1.101	114.0
1,1,2,2-Tetrachloroethane	18.8	5.1	9.4		1.108	105.2
Ethanol	15.8	8.8	19.4	0	1.112	58.5
1-Propanol	16.0	6.8	17.4		1.117	75.2
Morpholine	18.8	4.9	9.2		1.127	87.1
Ethylene glycol monoethyl ether	16.2	9.2	14.3	0	1.128	97.8
Dimethylformamide	17.4	13.7	11.3	0	1.130	77.0
Propylene glycol monophenyl ether	17.4	5.3	11.5		1.136	143.2
Quinoline	19.4	7.0	7.6		1.137	118.0
Hexylene glycol	15.7	8.4	17.8		1.140	123.0
Dimethyl sulfone	19.0	19.4	12.3		1.155	75.0
Dimethyl sulfoxide	18.4	16.4	10.2	0	1.165	71.3
Ethylene cyanohydrin	17.2	18.8	17.6		1.166	68.3
1-Butanol	16.0	5.7	15.8	0	1.169	91.5
2-Propanol	15.8	6.1	16.4		1.179	76.8
Ethylene dibromide	19.2	3.5	8.6		1.180	87.0
Tetramethylurea	16.7	8.2	11.0		1.198	120.4
Glycerol	17.4	12.1	29.3		1.198	73.3
Diethylene glycol monomethyl ether	16.2	7.8	12.6		1.200	118.0
Diethylene glycol monoethyl ether	16.1	9.2	12.2		1.221	130.9
N,N-Dimethylacetamide	16.8	11.5	10.2		1.226	92.5
Bromoform	21.4	4.1	6.1		1.228	87.5

TABLE 15.3 (CONTINUED)
Calculated Solubility Sphere for Zein

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
2-Butanol	15.8	5.7	14.5		1.232	92.0
1-Octanol	17.0	3.3	11.9		1.233	157.7
Ethyl lactate	16.0	7.6	12.5		1.236	115.0
Methyl salicylate	16.0	8.0	12.3		1.239	129.0
Zein	D = 22.4	P = 9.8	H = 19.4	RAD. = 11.9	FIT = 0.964	NO = 50

Note: Units are $MPa^{1/2}$. This table contains the first entries in a much larger database to show which solvents are most likely to affect proteins. The SOLUB column indicates good solvents with a 1, bad solvents with a 0, and untested solvents with a blank. The "*" points out those solvents that do not conform exactly with the correlation.

that the solubility of crystalline polymers requires good solvents to have higher HSP than otherwise expected and that smaller molecular volume is an advantage.

The relatively high HSP for cellulose, which also includes a large number of –OH groups, provides a proper energetic environment for the backbones of hemicelluloses, as well as those of their side groups which contain –OH groups. The hemicellulose side groups with acetyl and ether linkages can be expected to orient toward the lower HSP lignin. Neither lignin nor hemicelluloses are compatible with cellulose in the usual sense, but the hemicelluloses can form oriented configurations in connection with cellulose and with lignin. The monomers for lignin, sinapyl alcohol, coniferyl alcohol, and *p*-coumaryl alcohol all have HSP which are on the boundary of the solubility sphere for solubility of Dextran (amorphous cellulose), so their affinities indicate they will seek the lower HSP domain of the lignin. Hemicelluloses act like surfactants, with some side groups favoring the cellulose environment and others favoring the lignin environment. If one considers the HSP for higher ketones, esters, and ethers in Table 15.4, it can be seen that none of these simple liquids will dissolve lignin. This indicates that the acetyl- and ether-containing side groups on the hemicelluloses may not penetrate lignin as such but prefer to remain on its surface, probably finding a local (interface) site with closest possible HSP. A sketch of these predicted relations is found in Figure 15.5. This is a clear example of self-association in nature.

In addition to those previously mentioned, one can deduce which chemicals are most prone to penetrate directly through wood. These will dissolve lignin. Included are chlorinated phenols and other wood impregnation materials. It is known that pentachlorophenol, for example, readily diffuses into and through wood specimens. Still another question is how wood transports its own chemicals at various stages of the life of a tree. The same principles are valid. A preferred pathway is where HSP are similar. This can be made possible by molecular rotation and orientation. This can perhaps change with time and local environment.

Other types of predictions are possible from comparisons of the HSP correlations in Table 15.1. For example, it can be determined that all the solvents dissolving lignin are also predicted to swell psoriasis scales. This generality then suggests special care is in order when handling wood-impregnating chemicals. The protective clothing chosen should have HSP quite different from the HSP of the chemical involved, as discussed in Chapter 13.

An important effect that may have been overlooked in the solubility of wood and wood components is that there are acid groups present in hemicelluloses, for example, and these can be neutralized by bases. This gives an organic salt with high HSP.[11] (See also Chapter 18.) Such a salt is hydrophilic and will collect water. This may lead to phase separation, and some destruction of ultrastructure is possible. This is an effect which is known to have caused blistering in coatings.

TABLE 15.4A
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
Acetic acid	14.5	8.0	13.5	0	1.195	57.1
Acetic anhydride	16.0	11.7	10.2	0	1.006	94.5
Acetone	15.5	10.4	7.0	0	1.212	74.0
Acetonitrile	15.3	18.0	6.1	0	1.277	52.6
Acetophenone	19.6	8.6	3.7	0	1.096	117.4
Aniline	19.4	5.1	10.2	0	0.897	91.5
Benzaldehyde	19.4	7.4	5.3	0	1.044	101.5
Benzene	18.4	0.0	2.0	0	1.582	89.4
1-Bromonaphthalene	20.3	3.1	4.1	0	1.254	140.0
1,3-Butanediol	16.6	10.0	21.5	1	0.895	89.9
1-Butanol	16.0	5.7	15.8	0	1.060	91.5
Butyl acetate	15.8	3.7	6.3	0	1.403	132.5
Butyl lactate	15.8	6.5	10.2	0	1.158	149.0
Butyric acid	14.9	4.1	10.6	0	1.337	110.0
gamma-Butyrolactone	19.0	16.6	7.4	1	0.833	76.8
Butyronitrile	15.3	12.4	5.1	0	1.298	87.3
Carbon disulfide	20.5	0.0	0.6	0	1.586	60.0
Carbon tetrachloride	17.8	0.0	0.6	0	1.683	97.1
Chlorobenzene	19.0	4.3	2.0	0	1.369	102.1
1-Chlorobutane	16.2	5.5	2.0	0	1.506	104.5
Chloroform	17.8	3.1	5.7	0	1.293	80.7
m-Cresol	18.0	5.1	12.9	1	0.917	104.7
Cyclohexane	16.8	0.0	0.2	0	1.761	108.7
Cyclohexanol	17.4	4.1	13.5	0	1.013	106.0
Cyclohexanone	17.8	6.3	5.1	0	1.193	104.0
Cyclohexylchloride	17.3	5.5	2.0	0	1.424	118.6
Diacetone alcohol	15.8	8.2	10.8	0	1.085	124.2
o-Dichlorobenzene	19.2	6.3	3.3	0	1.210	112.8
2,2-Dichlorodiethyl ether	18.8	9.0	5.7	0	1.006	117.2
Diethylamine	14.9	2.3	6.1	0	1.552	103.2
Diethylene glycol	16.6	12.0	20.7	1	0.836	94.9
Diethylene glycol monobutyl ether	16.0	7.0	10.6	0	1.105	170.6
Diethylene glycol monomethyl ether	16.2	7.8	12.6	1*	1.001	118.0
Diethyl ether	14.5	2.9	5.1	0	1.605	104.8
Diethyl sulfide	16.8	3.1	2.0	0	1.543	107.4
Di(isobutyl) ketone	16.0	3.7	4.1	0	1.480	177.1
Dimethylformamide	17.4	13.7	11.3	1	0.774	77.0
Dimethyl sulfoxide	18.4	16.4	10.2	1	0.727	71.3
1,4-Dioxane	19.0	1.8	7.4	0	1.211	85.7
Dipropylamine	15.3	1.4	4.1	0	1.631	136.9
Dipropylene glycol	16.5	10.6	17.7	1	0.831	130.9
Ethanol	15.8	8.8	19.4	1	0.988	58.5
Ethanolamine	17.0	15.5	21.2	1	0.788	59.8
Ethyl acetate	15.8	5.3	7.2	0	1.306	98.5
Ethylbenzene	17.8	0.6	1.4	0	1.615	123.1
2-Ethyl-1-butanol	15.8	4.3	13.5	0	1.169	123.2
Ethylene glycol	17.0	11.0	26.0	1*	1.002	55.8
Ethylene glycol monobutyl ether	16.0	5.1	12.3	0	1.134	131.6
Ethylene glycol monoethyl ether	16.2	9.2	14.3	1	0.925	97.8
Ethylene glycol monoethyl ether acetate	15.9	4.7	10.6	0	1.204	136.1

TABLE 15.4A (CONTINUED)
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
Ethylene glycol monomethyl ether	16.2	9.2	16.4	1	0.906	79.1
Furan	17.8	1.8	5.3	0	1.372	72.5
Glycerol	17.4	12.1	29.3	0	1.128	73.3
Hexane	14.9	0.0	0.0	0	1.904	131.6
Isoamyl acetate	15.3	3.1	7.0	0	1.447	148.8
Isobutyl isobutyrate	15.1	2.9	5.9	0	1.516	163.0
Isooctyl alcohol	14.4	7.3	12.9	0	1.237	156.6
Isophorone	16.6	8.2	7.4	0	1.125	150.5
Mesityl oxide	16.4	6.1	6.1	0	1.268	115.6
Methanol	15.1	12.3	22.3	0	1.076	40.7
Methylal	15.0	1.8	8.6	0	1.479	169.4
Methyl ethyl ketone	16.0	9.0	5.1	0	1.274	90.1
Methyl isoamyl ketone	16.0	5.7	4.1	0	1.411	142.8
Methyl isobutyl carbinol	15.4	3.3	12.3	0	1.279	127.2
Methyl isobutyl ketone	15.3	6.1	4.1	0	1.464	125.8
Morpholine	18.8	4.9	9.2	1	0.986	87.1
Nitrobenzene	20.0	8.6	4.1	0	1.054	102.7
Nitroethane	16.0	15.5	4.5	0	1.254	71.5
Nitromethane	15.8	18.8	5.1	0	1.286	54.3
2-Nitropropane	16.2	12.1	4.1	0	1.260	86.9
1-Pentanol	15.9	4.5	13.9	0	1.143	108.6
1-Propanol	16.0	6.8	17.4	0	1.117	75.2
Propylene carbonate	20.0	18.0	4.1	0	1.513	85.0
Propylene glycol	16.8	9.4	23.3	0*	0.944	73.6
Pyridine	19.0	8.8	5.9	1	0.987	80.9
Styrene	18.6	1.0	4.1	0	1.421	115.6
Tetrahydrofuran	16.8	5.7	8.0	0	1.163	81.7
Tetrahydronaphthalene	19.6	2.0	2.9	0	1.392	136.0
Toluene	18.0	1.4	2.0	0	1.538	106.8
1,1,1-Trichloroethane	16.8	4.3	2.0	0	1.500	99.3
Trichloroethylene	18.0	3.1	5.3	0	1.298	90.2
Xylene	17.6	1.0	3.1	0	1.524	123.3
Lignin	D = 21.9	P = 14.1	H = 16.9	R_o = 13.7	FIT = 0.990	NO = 82

UREA

Data for the HSP correlation for urea solubility in organic solvents are given in Table 15.1. All of the parameters are rather high, which is characteristic of a low molecular weight solid. The data fit is very good. Perhaps the most interesting thing about this correlation is that it clearly shows that additions of urea to water will improve solubility for a variety of materials including proteins. This is the reason for the improved solubility discussed previously in connection with the destruction of hydrophilic bonding in proteins. The saturated solution of urea and water is also the best physically acting solvent for whole, dried blood that the author could locate in a previous (unpublished) study.

The fact of high HSP for urea/water mixtures has led to its use in many varied types of products.[7] The saturated solution of urea in water has found particular successes in the following examples.

TABLE 15.4B
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
2-Pyrolidone	19.4	17.4	11.3		0.599	76.4
Succinic anhydride	18.6	19.2	16.6		0.609	66.8
Dimethyl sulfone	19.0	19.4	12.3		0.665	75.0
Dimethyl sulfoxide	18.4	16.4	10.2	1	0.727	71.3
Hexamethylphosphoramide	18.5	8.6	11.3		0.758	175.7
o-Methoxyphenol	18.0	8.2	13.3		0.761	109.5
1,3-Butanediol	18.0	8.4	21.0		0.766	87.5
Ethylene cyanohydrin	17.2	18.8	17.6		0.769	68.3
Dimethyl formamide	17.4	13.7	11.3	1	0.774	77.0
Diethylenetriamine	16.7	13.3	14.3		0.785	108.0
Ethanolamine	17.0	15.5	21.2	1	0.788	59.8
Diethanolamine	17.2	10.8	21.2		0.792	95.9
Benzyl alcohol	18.4	6.3	13.7		0.800	103.6
Furfuryl alcohol	17.4	7.6	15.1		0.821	86.5
Dipropylene glycol	16.5	10.6	17.7	1	0.831	130.9
gamma-Butyrolactone	19.0	16.6	7.4	1	0.833	76.8
Diethylene glycol	16.6	12.0	20.7	1	0.836	94.9
Phenol	18.0	5.9	14.9		0.839	87.5
Ethylenediamine	16.6	8.8	17.0		0.865	67.3
Allyl alcohol	16.2	10.8	16.8		0.866	68.4
Triethyleneglycol	16.0	12.5	18.6		0.878	114.0
1,3-Butanediol	16.6	10.0	21.5	1	0.895	89.9
Aniline	19.4	5.1	10.2	1	0.897	91.5
3-Chloro-1-propanol	17.5	5.7	14.7		0.902	84.2
Ethylene glycol monomethyl ether	16.2	9.2	16.4	1	0.906	79.1
N,N-Dimethyl acetamide	16.8	11.5	10.2		0.911	92.5
Trimethylphosphate	16.7	15.9	10.2		0.913	115.8
Benzoic acid	18.2	6.9	9.8		0.915	100.0
m-Cresol	18.0	5.1	12.9	1	0.917	104.7
Methyl-2-pyrrolidone	18.0	12.3	7.2		0.918	96.5
1,1,2,2-Tetrabromoethane	22.6	5.1	8.2		0.919	116.8
Ethylene glycol monoethyl ether	16.2	9.2	14.3	1	0.925	97.8
Quinoline	19.4	7.0	7.6		0.929	118.0
Propylene glycol	16.8	9.4	23.3	0*	0.944	73.6
Triethylphosphate	16.7	11.4	9.2		0.965	171.0
1,1,2,2-Tetrachloroethane	18.8	5.1	9.4		0.968	105.2
Tetramethylurea	16.7	8.2	11.0		0.973	120.4
Diethylene glycol monoethyl ether	16.1	9.2	12.2		0.981	130.9
Morpholine	18.8	4.9	9.2	1	0.986	87.1
Pyridine	19.0	8.8	5.9	1	0.987	80.9
Ethanol	15.8	8.8	19.4	1	0.988	58.5
Furfural	18.6	14.9	5.1		0.989	83.2
Hexylene glycol	15.7	8.4	17.8		0.998	123.0
Propylene glycol monophenyl ether	17.4	5.3	11.5		1.000	143.2
Diethylene glycol monomethyl ether	16.2	7.8	12.6	1*	1.001	118.0
Ethylene glycol	17.0	11.0	26.0	1	1.002	55.8
2,2-Dichlorodiethyl ether	18.8	9.0	5.7	0	1.006	117.2
Acetic anhydride	16.0	11.7	10.2	0	1.006	94.5
Tricresyl phosphate	19.0	12.3	4.5		1.008	316.0
Cyclohexanol	17.4	4.1	13.5	0	1.013	106.0

TABLE 15.4B (CONTINUED)
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
1-Propanol	16.0	6.8	17.4	0	1.013	75.2
Propylene carbonate	20.0	18.0	4.1	0	1.015	85.0
Triethyanolamine	17.3	22.4	23.3		1.018	133.2
Nonyl phenoxy ethanol	16.7	10.2	8.4		1.021	275.0
Methyl salicylate	16.0	8.0	12.3		1.026	129.0
Dimethyl phthalate	18.6	10.8	4.9		1.028	163.0
Ethyl lactate	16.0	7.6	12.5		1.034	115.0
Benzaldehyde	19.4	7.4	5.3	0	1.044	101.5
Trifluoroacetic acid	15.6	9.9	11.6		1.044	74.2
Di-(2-Chloro-isopropyl) ether	19.0	8.2	5.1		1.052	146.0
Nitrobenzene	20.0	8.6	4.1	0	1.054	102.7
Ethylene dibromide	19.2	3.5	8.6		1.059	87.0
1-Butanol	16.0	5.7	15.8	0	1.060	91.5
2-Propanol	15.8	6.1	16.4		1.066	76.8
Methanol	15.1	12.3	22.3	0	1.076	40.7
Bromoform	21.4	4.1	6.1		1.077	87.5
Diacetone alcohol	15.8	8.2	10.8	0	1.085	124.2
Ethylene carbonate	19.4	21.7	5.1		1.088	66.0
Epichlorohydrin	19.0	10.2	3.7		1.090	79.9
2-Butanol	15.8	5.7	14.5		1.095	92.0
Acetophenone	19.6	8.6	3.7	0	1.096	117.4
Diethylene glycol monobutyl ether	16.0	7.0	10.6	0	1.105	170.6
Methylene dichloride	18.2	6.3	6.1		1.112	63.9
Benzyl butyl phthalate	19.0	11.2	3.1		1.113	306.0
Acrylonitrile	16.4	17.4	6.8		1.116	67.1
Formic acid	14.3	11.9	16.6		1.121	37.8
Isophorone	16.6	8.2	7.4	0	1.125	150.5
1-Octanol	17.0	3.3	11.9		1.125	157.7
Glycerol	17.4	12.1	29.3	0	1.128	73.3
Formamide	17.2	26.2	19.0		1.129	39.8
Ethylene glycol monobutyl ether	16.0	5.1	12.3	0	1.134	131.6
Ethylene dichloride	19.0	7.4	4.1		1.136	79.4
1-Pentanol	15.9	4.5	13.9	0	1.143	108.6
1-Nitropropane	16.6	12.3	5.5		1.144	88.4
Bromobenzene	20.5	5.5	4.1		1.144	105.3
Ethylene glycol monomethyl ether acetate	15.9	5.5	11.6		1.145	121.6
Ethyl cinnamate	18.4	8.2	4.1		1.149	166.8
Propylene glycol monomethyl ether	15.6	6.3	11.6		1.149	93.8
Diethyl phthalate	17.6	9.6	4.5		1.149	198.0
Diethyl sulfate	15.7	14.7	7.1		1.154	131.5
Butyl lactate	15.8	6.5	10.2	0	1.158	149.0
Diethylene glycol hexyl ether	16.0	6.0	10.0		1.160	204.3
Propylene glycol monoethyl ether	15.7	6.5	10.5		1.160	115.6
Propylamine	16.9	4.9	8.6		1.162	83.0
Tetrahydrofuran	16.8	5.7	8.0	0	1.163	81.7
2-Octanol	16.1	4.9	11.0		1.163	159.1
2-Ethyl-1-butanol	15.8	4.3	13.5	0	1.169	123.2
Isobutyl alcohol	15.1	5.7	15.9		1.169	92.8
2-Methyl-1-propanol	15.1	5.7	15.9		1.169	92.8
1-Decanol	17.5	2.6	10.0		1.171	191.8

TABLE 15.4B (CONTINUED)
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
Propylene glycol monopropyl ether	15.8	7.0	9.2		1.174	130.3
Dibutyl phthalate	17.8	8.6	4.1		1.180	266.0
Dipropylene glycol methyl ether	15.5	5.7	11.2		1.192	157.4
Cyclohexanone	17.8	6.3	5.1	0	1.193	104.0
Acetic acid	14.5	8.0	13.5	0	1.195	57.1
Ethyl formate	15.5	8.4	8.4		1.196	80.2
Trichlorobiphenyl	19.2	5.3	4.1		1.200	187.0
Anisole	17.8	4.1	6.7		1.202	119.1
Ethylene glycol monoethyl ether acetate	15.9	4.7	10.6	0	1.204	136.1
o-Dichlorobenzene	19.2	6.3	3.3	0	1.210	112.8
1,4-Dioxane	19.0	1.8	7.4	0	1.211	85.7
Acetone	15.5	10.4	7.0	0	1.212	74.0
Nonyl phenol	16.5	4.1	9.2		1.212	231.0
Acetaldehyde	14.7	8.0	11.3		1.212	57.1
1,1-Dimethyl hydrazine	15.3	5.9	11.0		1.213	76.0
bis-(m-Phenoxyphenyl) ether	19.6	3.1	5.1		1.224	373.0
2,4-Pentanedione	17.1	9.0	4.1		1.226	103.1
Ethyl chloroformate	15.5	10.0	6.7		1.232	95.6
Dibenzyl ether	17.3	3.7	7.3		1.232	192.7
2-Ethyl hexanol	15.9	3.3	11.8		1.236	156.6
Isooctyl alcohol	14.4	7.3	12.9	0	1.237	156.6
Tetrachloroethylene	19.0	6.5	2.9		1.237	101.1
2-(Diethylamino) ethanol	14.9	5.8	12.0		1.241	133.2
Benzyl chloride	18.8	7.1	2.6		1.247	115.0
Benzonitrile	17.4	9.0	3.3		1.247	102.6
Ethyl bromide	16.5	8.0	5.1		1.250	76.9
Nitroethane	16.0	15.5	4.5	0	1.254	71.5
1-Bromonaphthalene	20.3	3.1	4.1	0	1.254	140.0
Naphthalene	19.2	2.0	5.9		1.257	111.5
2-Nitropropane	16.2	12.1	4.1	0	1.260	86.9
Methyl acetate	15.5	7.2	7.6		1.260	79.7
2,2,4-Trimethyl 1,3-pentanediol monoisobutyrate	15.1	6.1	9.8		1.263	227.4
Methylene diiodide	17.8	3.9	5.5		1.267	80.5
Butylamine	16.2	4.5	8.0		1.267	99.0
Mesityl oxide	16.4	6.1	6.1	0	1.268	115.6
1,1-Dichloroethylene	17.0	6.8	4.5		1.271	79.0
Propionitrile	15.3	14.3	5.5		1.273	70.9
Methyl ethyl ketone	16.0	9.0	5.1	0	1.274	90.1
Acetonitrile	15.3	18.0	6.1	0	1.277	52.6
Methyl isobutyl carbinol	15.4	3.3	12.3	0	1.279	127.2
Ethanethiol	15.7	6.5	7.1		1.280	74.3
Methyl methacrylate	17.5	5.5	4.3		1.286	106.5
Nitromethane	15.8	18.8	5.1	0	1.286	54.3
Chloroform	17.8	3.1	5.7	0	1.293	80.7
Diethylene glycol butyl ether acetate	16.0	4.1	8.2		1.295	208.2
Butyronitrile	15.3	12.4	5.1	0	1.298	87.3
Trichloroethylene	18.0	3.1	5.3	0	1.298	90.2
Cyclohexylamine	17.2	3.1	6.5		1.301	113.8
Methyl acrylate	15.3	9.3	5.9		1.302	113.8
Ethyl acetate	15.8	5.3	7.2	0	1.306	98.5

TABLE 15.4B (CONTINUED)
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
Propylene glycol monoisobutyl ether	15.1	4.7	9.8		1.313	132.2
Propylene glycol monobutyl ether	15.3	4.5	9.2		1.317	132.0
Di(2-Methoxyethyl) ether	15.7	6.1	6.5		1.318	142.0
Ethylene glycol butyl ether acetate	15.3	4.5	8.8		1.330	171.2
1-Methyl naphthalene	20.6	0.8	4.7		1.331	138.8
Bromochloromethane	17.3	5.7	3.5		1.336	65.0
Butyric acid	14.9	4.1	10.6	0	1.337	110.0
Diethyl ketone	15.8	7.6	4.7		1.346	106.4
Ethyl acrylate	15.5	7.1	5.5		1.351	108.8
Tributyl phosphate	16.3	6.3	4.3		1.356	345.0
Diethyl carbonate	16.6	3.1	6.1		1.366	121.0
Chlorobenzene	19.0	4.3	2.0	0	1.369	102.1
Furan	17.8	1.8	5.3	0	1.372	72.5
Dioctyl phthalate	16.6	7.0	3.1		1.372	377.0
Di-iso-butyl carbinol	14.9	3.1	10.8		1.374	177.8
Methacrylonitrile	15.3	10.8	3.6		1.389	83.9
Tetrahydronaphthalene	19.6	2.0	2.9	0	1.392	136.0
Butyl acrylate	15.6	6.2	4.9		1.395	143.8
Butyl acetate	15.8	3.7	6.3	0	1.403	132.5
Stearic acid	16.3	3.3	5.5		1.408	326.0
Methyl isoamyl ketone	16.0	5.7	4.1	0	1.411	142.8
Ethyl butyl ketone	16.2	5.0	4.1		1.417	139.0
Octanoic acid	15.1	3.3	8.2		1.418	159.0
Styrene	18.6	1.0	4.1	0	1.421	115.6
Cyclohexylchloride	17.3	5.5	2.0	0	1.424	118.6
Amyl acetate	15.8	3.3	6.1		1.427	148.0
Butyraldehyde	14.7	5.3	7.0		1.428	88.5
sec-Butyl acetate	15.0	3.7	7.6		1.432	133.6
Ethyl amyl ketone	16.2	4.5	4.1		1.434	156.0
Isoamyl acetate	15.3	3.1	7.0	0	1.447	148.8
Biphenyl	21.4	1.0	2.0		1.450	154.1
Dichloromonoflouromethane	15.8	3.1	5.7		1.451	75.4
Propyl chloride	16.0	7.8	2.0		1.462	88.1
Methyl butyl ketone	15.3	6.1	4.1		1.464	123.6
Methyl isobutyl ketone	15.3	6.1	4.1	0	1.464	125.8
Methyl amyl acetate	15.2	3.1	6.8		1.465	167.4
Isobutyl acetate	15.1	3.7	6.3		1.470	133.5
Methyl chloride	15.3	6.1	3.9		1.473	55.4
Methylal	15.0	1.8	8.6	0	1.479	169.4
Di(isobutyl) ketone	16.0	3.7	4.1	0	1.480	177.1
Ethyl chloride	15.7	6.1	2.9		1.485	70.0
Tridecyl alcohol	14.3	3.1	9.0		1.486	242.0
1,1,1-Trichloroethane	16.8	4.3	2.0	0	1.500	99.3
1,1-Dichlorethane	16.5	8.2	0.4		1.502	84.8
1-Chlorobutane	16.2	5.5	2.0	0	1.506	104.5
o-Xylene	17.8	1.0	3.1		1.512	121.2
Isobutyl isobutyrate	15.1	2.9	5.9	0	1.516	163.0
Xylene	17.6	1.0	3.1	0	1.524	123.3
Oleyl alcohol	14.3	2.6	8.0		1.535	316.0
Toluene	18.0	1.4	2.0	0	1.538	106.8

TABLE 15.4B (CONTINUED)
Calculated Solubility Sphere for Lignin Solubility

Solvent	δ_D	δ_P	δ_H	SOLUB	RED	V
Diethyl sulfide	16.8	3.1	2.0	0	1.543	107.4
Diethyl amine	14.9	2.3	6.1	0	1.552	103.2
Benzene	18.4	0.0	2.0	0	1.582	89.4
Naphtha.high-flash	17.9	0.7	1.8		1.585	181.8
Carbon disulfide	20.5	0.0	0.6	0	1.586	60.0
Oleic acid	14.3	3.1	5.5		1.603	320.0
Diethyl ether	14.5	2.9	5.1	0	1.605	104.8
Triethylene glycol monooleyl ether	13.3	3.1	8.4		1.614	418.5
Ethylbenzene	17.8	0.6	1.4	0	1.615	123.1
Methyl oleate	14.5	3.9	3.7		1.628	340.0
Dipropylamine	5.3	1.4	4.1	0	1.631	136.9
Dibutyl stearate	14.5	3.7	3.5		1.643	382.0
Triethylamine	17.8	0.4	1.0		1.645	138.6
Trimethylbenzene	17.8	0.4	1.0		1.645	133.6
Isopropyl palmitate	14.3	3.9	3.7		1.647	330.0
Dibutyl sebacate	13.9	4.5	4.1		1.652	339.0
cis-Decahydronaphthalene	18.8	0.0	0.0		1.669	156.9
para-Diethyl benzene	18.0	0.0	0.6		1.673	156.9
Mesitylene	18.0	0.0	0.6		1.673	139.8
Carbon tetrachloride	17.8	0.0	0.6	0	1.683	97.1
trans-Decahydronaphthalene	18.0	0.0	0.0		1.704	156.9
Chlorodiflouromethane	12.3	6.3	5.7		1.719	72.9
Cyclohexane	16.8	0.0	0.2	0	1.761	108.7
Methyl cyclohexane	16.0	0.0	1.0		1.774	128.3
Eicosane	16.5	0.0	0.0		1.790	359.8
Trichlorofluoromethane	15.3	2.0	0.0		1.797	92.8
Hexadecane	16.3	0.0	0.0		1.803	294.1
Dodecane	16.0	0.0	0.0		1.823	228.6
Mineral spirits	15.8	0.1	0.2		1.823	125.0
Decane	15.7	0.0	0.0		1.844	195.9
Nonane	15.7	0.0	0.0		1.844	179.7
Octane	15.5	0.0	0.0		1.858	163.5
1,1,2-Trichlorotrifluoroethane	14.7	1.6	0.0		1.860	119.2
Heptane	15.3	0.0	0.0		1.873	147.4
Hexane	14.9	0.0	0.0	0	1.904	131.6
Pentane	14.5	0.0	0.0		1.936	116.2
Tetraethylorthosilicate	13.9	0.4	0.6		1.944	224.0
Butane	14.1	0.0	0.0		1.969	101.4
2,2,2,4-Trimethylpentane	14.1	0.0	0.0		1.969	166.1
Isopentane	13.7	0.0	0.0		2.003	117.4
1,2-Dichlorotetrafluoroethane	12.6	1.8	0.0		2.042	117.6
Dichlorodifluoromethane	12.3	2.0	0.0		2.065	92.3
Water	15.5	16.0	42.3		2.081	18.0
Perfluoro(dimethylcyclohexane)	12.4	0.0	0.0		2.122	217.4
Perfluoromethylcyclohexane	12.4	0.0	0.0		2.122	196.0
Perfluoroheptane	12.0	0.0	0.0		2.161	227.3
Bromotrifluoromethane	9.6	2.4	0.0		2.340	97.0
Lignin	D = 21.9	P = 14.1	H = 16.9	RAD. = 13.7	FIT = 0.990	NO = 82

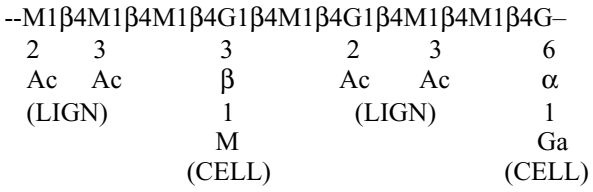

FIGURE 15.5 Expected generalized sketch of the configuration of cellulose, hemicelluloses, and lignin in wood cell walls. See text or Reference 6 for further details. The sketch is for glucomannan. M is mannose monomer; G is glucose monomer; Ga is galactose monomer; Ac is an acetyl group; (LIGN) is a region similar in HSP to lignin (or acetal etc.); (CELL) is a region similar in HSP to cellulose, being any of cellulose, hemicellulose backbone, or hemicellulose side chain with an alcohol group (M, Ga).

1. Lithographic stones were previously conditioned to make them more receptive to ink by application of this liquid to change wetting behavior.
2. The saturated solution of urea and water, which swells and softens wood, has been used to give wood flexibility so that it can easily be formed.
3. It has been used by Eskimos to soften seal skins by swelling and softening them. A similar application in Mexico involves curing leather. This application probably originated in prehistoric times.
4. It has been used to improve the flow of house paints on cold days or when no other source of liquid has been available (such as on a scaffold), as it is a good solvent miscible in many paints.
5. It is reported to have been used to set hair, as it also softens and swells it.
6. It was used in the early manufacture of gunpowder as a dispersion medium during grinding because of improved wetting for the powder.
7. Amazonian Indians used this liquid to coagulate latex prior to sale and shipment. This was practiced particularly during World War II.

Other unspecified and undocumented uses include those possible because the liquid has the ability to soften human skin, thus allowing easier transport of medicinal chemicals into the body. Urea itself has HSP very close to those of sugar and proteins. As all of these are biocompatible materials, it is clear that the incorporation of significant numbers of urea groups in, for example, polyurethane polymers or other products, can greatly enhance biocompatibility.

WATER

Water has been discussed in detail in Chapter 1. Briefly stated, one can use the HSP for water or a correlation for water solubility to get a general explanation for observed phenomena. Accurate calculation of the HSP for solvent–water mixtures cannot be expected because of the irregularities of water associating with itself, the solvent, and a potential solute. Lindenfors[12] described the association of two molecules of water with one molecule of dimethyl sulfoxide, a solvent frequently mentioned in connection with biological systems. A simplistic approach based on the ratio of δ_H for water as a single molecule vs. that in the correlation(s) for water solubility suggests that $(42.3/16.5)^2$ or about six water molecules are linked by hydrogen bonding into some type of entity. Various structures for assemblies of water molecules have been discussed in the literature. The clusters with six water molecules are among the more probable ones.[13] The data on water solubility used in the HSP correlations are reported by Wallström and Svenningsen.[14]

SURFACE MOBILITY

Surface mobility allows given segments of molecules to orient at surfaces in a direction where their HSP match more closely. The surfaces of hydrophobic polymers (peat moss) can become hydrophilic when contacted with water. One can speculate as to why this occurs. One possibility is that this phenomenon conserves water within the structure. Whenever water is present on an otherwise hydrophobic surface, it can become hydrophilic if the surface molecules can rotate or move hydrophilic entities toward the water. This allows the water to spontaneously spread and potentially enter the structure if there are suitable passages. When this is accomplished, and contact with water ceases, the surface dries and becomes hydrophobic once more. The molecules rotate with a lower energy moiety toward the air. This hydrophobic surface helps prevent evaporation of water, as water is not particularly soluble in it, and the hydrophilic segments oriented toward the interior of the structure will help bind the water where it is. The basis of the orientation effects described earlier for hemicelluloses is another example of orientation toward regions where HSP matches better. These phenomena are also discussed in Chapter 18. It is also appropriate to repeat that solvent quality has a great deal to do with pigment dispersion stability, in that the adsorbed stabilizing polymer should remain on the pigment surface. A solvent which is too good can remove it. This is discussed in detail in Chapter 5.

The implication of these examples is that solvent quality is very important for the orientation of molecules at interfaces. A change in solvent quality can easily lead to a change in the configuration of molecules at surfaces. It is not surprising that Nature has used this to advantage in various ways.

CHIRAL ROTATION, HYDROGEN BONDING, AND NANOENGINEERING

It has been found that anthracene units appended to a single screw-sense helical polyguanidine changed orientation when the temperature was increased beyond 38.5°C.[15] The configuration found above 38.5°C was the same as that found in tetrahydrofurane. At temperatures lower than this, the orientation of the appended anthracene was that found in toluene. A mixture of tetrahydrofurane/toluene equal to 90/10 vol% approximated the conditions at the critical temperature. For those who have diligently read this handbook, it would appear obvious that it is the cohesive energy density just above or just below the critical temperature that controls the structure. More specifically it is the set of HSP values that do this, as these reflect the mix of sources of the cohesive energy density according to Equation 1.6 to Equation 1.8. There is also massive evidence showing that the interactions can be interpreted as the difference in HSP using Equation 1.9. It is well known that solubility limits can be passed by lowering the temperature in some cases and by increasing it in other cases. When the cohesive energy density of the solvent is higher than that of the polymer, solvency increases with increased temperature. When the cohesive energy density of the solvent is lower than that of the polymer, solvency decreases with increases in temperature. This is discussed in Chapter 2 and has been thoroughly treated by Patterson.[16,17] In the present case the HSP of toluene are comparable to those of anthracene whereas tetrahydrofuran has much higher values. δ_D, δ_P, and δ_H equal to 18.7, 4.1, and 3.3 for anthracene have been reported by a multiple regression technique based on its solubility in a large number of solvents.[18] The corresponding values are 18.0, 1.4, and 2.0 for toluene and 16.8, 5.7, and 8.0 for tetrahydrofurane. Thus increasing the temperature will increase the solvency in tetrahydrofurane to the point where it becomes able to cause the appended anthracene to adopt the same orientation as it has in toluene. As toluene has lower HSP than anthracene, the solvency will decrease with increases in temperature.

Extending this way of thinking to the problem of moving very large biological molecules — while they are being assembled, for example — is presumably one of controlling the local solubility. When the molecule is locally able to reside in the surrounding fluid, it can move much more readily

than when it is not. An insoluble molecule or molecular segment will adsorb at a location where the energies (HSP) match, and where the geometry is also accommodating. This is most often called *hydrogen bonding*, but it must be all three (or more) types of cohesive energy that are collectively active. The molecule or molecular segment can be removed again when it and the surrounding liquid have a favorable energy relation.

CONCLUSION

Many materials of biological significance have been assigned HSP based on their interaction with a large number of solvents whose HSP are known. A correlation for solvent effects on DNA has ranked the extent of these effects for different solvents in essentially the same order as that reported in an older study.[9] This correlation for DNA can presumably be improved by additional data, but still reflects the magnitudes of the types of energies that are involved in forming/destroying the double helices. The $\delta_D;\delta_P;\delta_H$ found for DNA are 19.0;20.0;11.0, all in $MPa^{1/2}$. This clearly shows that hydrogen bonding is by far the smallest of the energies involved in the noncovalent interactions that determine the DNA structure.

A HSP correlation has been used to find predictably synergistic solvent mixtures where two nonsolvents dissolve cholesterol when mixed. The ethanol/aliphatic hydrocarbon synergistic mixture is discussed as being of particular interest to the fate of cholesterol in lipid layers. The HSP of chlorophyll and lignin are quite similar, indicating they will be compatible with very much the same kind of surroundings. The physical interrelationships for wood chemicals and wood polymers (lignin, hemicelluloses, and cellulose) are discussed. The side chains on hemicelluloses which contain alcohol groups and the hemicellulose backbone will be most compatible with cellulose and will orient toward this. The hemicellulose side chains without alcohol groups (acetal, acid) are closer in HSP to lignin and will orient in this direction. The acetal side chains actually have lower HSP than will dissolve lignin, for which reason they are expected to lie on the surface of the lignin or perhaps penetrate slightly into the lignin at very special local points where the HSP match is better than the average values seen over the lignin molecule as a whole.

Molecular design of molecules or structures that change conformation with slight changes in the cohesive energy characteristics of given continuous media seems possible using HSP concepts. The changes are caused by preferred orientation of segments of one conformation toward the continuous phase, where its HSP match better, thus reducing the free energy of the system. If the cohesive energy characteristics of the continuous media change in a direction that no longer favors this orientation, the molecule will change configuration to one where the free energy is lower. The attraction of the segments not oriented toward the continuous phase to neighboring molecules is commonly called *hydrogen bonding in proteins and similar materials.* This attraction is caused collectively by all the types of energy involved through the prevailing difference in HSP and is a result of insolubility (rejection by) the continuous media. Geometrical considerations are clearly also a major factor in addition to the cohesive energy density focused upon here.

HSP analyses of relative affinities can be applied to a large number of other biological materials and may provide insights into relationships which are not readily obvious or cannot be studied otherwise. The best situation is where the materials in question can be tested directly, otherwise the calculation procedures described in Chapter 1 can be used with some loss of reliability in the predictions.

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