SJIF IMPACT FACTOR (2015): 5.42 CRDEEP Journals
International Journal of Basic and Applied Sciences Sain & Sain Vol. 5 No. 3 ISSN: 2277-1921
International Journal of Basic and Applied Sciences. Vol. 5 No. 3. 2016. Pp. 76-82

Full Length Research Paper

Regular Solution Theory and its Application: A Preliminary Review

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Article history
Received: 10-07-2016
Revised: 15-07-2016
Accepted: 17-07-2016

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Abstract
Attempting to introduce basic concepts in different ways into a general treatment of liquid-liquid partition equilibria , the approach based on the theory of regular solutions is in many ways the simplest of those which pay special attention to the role of the two solvents. Regular solution theory then used to correlate the solubility parameter of solvent and the solubility parameter of extracted species. There are many applications have studied experimentally. The mixed extraction systems offer very interesting features and needs further investigation to elucidate the actual reason of differential behavior of the systems under conditions. Diluent effects have been analysed by the evaluation of solubility parameter of metal chelates and have been corrected with extraction parameters as much as practicable. So far other variables are concerned; we have been successful to point out the differences, although detail explanation needs through investigation.

Keywords: *Regular solution theory, solubility parameter, partition equilibria and thermodynamic parameters.*

Introduction

A regular solution is a solution that diverges from the behavior of an ideal solution only moderately. In 1920 Hildebrand[1] directed attention to the fact that the solubility of solids, plotted as a logarithm of mole fraction against reciprocal temperature, gives a family of curves in the case of solutions where no molecular changes are involved. In 1927, he designated[2] such solutions as 'regular' and in 1929 he discussed the thermodynamic significance of this regularity[3]. A regular solution is one in which the chemical effects are absent, and in which the distributions and orientations are random, just as in an ideal solution. We may conclude that the probability of X_2 [species 2] is the same in the two solutions [ideal and actual] and, therefore, that the difference in entropy is zero. We cannot expect this conclusion to hold unless the random distribution of molecules persists. We may expect further that a small correction should be applied to take care of the change in entropy accompanying changes in volume, given by $(\partial S/\partial V)_T = (\partial P/\partial T)_V$; or we may state the principle in the following form. A regular solution is one involving no entropy change when a small amount of one of its components is transferred to it from an ideal solution of the same composition, the total volume remaining unchanged. Finally, we can extrapolate our overall investigation as, the solubility parameter equations offer an useful approach to a very wide area of solutions, like a small-scale map for a very broad long-distance air view of a subcontinent. It is able to make numerical predictions about all areas; these are unlikely to prove highly accurate. When a small area is examined carefully, but they are equally unlikely to prove completely absurd. A real serious failure of basic assumptions and attracts serious attentions.

Diluents have enormous role in deciding the extraction efficiencies of liquid extraction using mixed extractants. As the same time, applicability's of regular solution theory could also be tasted from such studies, opening a new avenue in ternary adduct extraction chemistry. However such studies have been preceded by the direct evaluation of solubility parameters of metal chelates using regular solution theory.

Literature Review

The distribution of a given species A between two immiscible solvents (designated by subscripts I and II), in both of which it is soluble, will reach equilibrium when the chemical potential is the same in both phases. At this stage the ratio of its activity in the two phases achieves a constant value, independent of the total amount present. This expression of the Nernst partition law can be written in the form

$$K_D \text{ (thermodynamic constant)} = \{A\}_I/\{A\}_{II}$$
$$=([A]_I/[A]_{II}) .(f_{A,I}/ f_{A,II}) \text{----------(1)}$$

where the symbol s {A}, [A] and f refer ,respectively , to the activity, the concentration, and the activity coefficient of A. Provided the ratio of activity coefficients remains constants irrespective of the total concentration and total composition of the two phases, we can see that the ratio of concentration $s[A]_I/[A]_{II}=D$ will remain constant, even up to the point at which each phase is simultaneously saturated with the distribuends. Here, $D=[s_A]_I/[s_A]_{II}$ where $[s_A]$ now stands for the solubility of the solute species A. Any theory which makes it possible to discuss and predict the solubility of a given species in a series of different solvents solvent mixtures should thus from a possible basis for discussing distribution phenomena.

If solute dissolves in a solvent, without absorption or evolution of heat, and without any change in volume, the osmotic pressure is proportional to the concentration (at constant temperature), and the solution is said to be ideal. In many nonideal solutions there is sufficient thermal energy to overcome any tendency towards segregation due to different intermolecular force fields , and maximum randomness is achieved corresponding to the nearly ideal entropy of mixing. More precisely it can be described by Raoult's law modified with a Margules function with only one parameter α:

$P_1= x_1P^*_1f_{1,M}$(P_1 and P_2 are the osmotic pressures, P*indicates value in ideal condition)
$P_2= x_2P^*_2f_{2,M}$

Where the Margules function is

$f_{1,M} = \exp(\alpha x_2^2)$
$f_{2,M} = \exp(\alpha x_1^2)$

Notice that the Margules function always contains the opposite mole fraction. It can also be shown that if the first Margules expression holds that the other one must have the same shape using the Gibbs-Duhem relation.

The value of α can be interpreted as W/RT, where $W = 2U_{12} -U_{11} -U_{22}$ represents the difference interaction between like and unlike neighbors.

In contrast to the case of ideal solutions, regular solutions do possess an enthalpy of mixing, due to the W term. If the unlike interactions are more unfavorable than the like ones, we get competition between an entropy of mixing term that produces a minimum in the Gibbs free energy at x=0.5 and the enthalpy term that has a maximum there. At high temperatures the entropy wins and the system is fully miscible. At lower temperatures the G curve will have two minima and a maximum in between. This results in phase separation. In general there will be a temperature where the three extremes coalesce and the system becomes fully miscible and this point is known as the critical point of solubility. In contrast to ideal solutions, the volumes in the case of regular solutions are no longer strictly additive but must be calculated from the partial molar volumes that are a function of x. In such "regular solutions", where the excess entropy sE is zero, we need only know the change in free energy derived from the heat of mixing in order to calculate the solubility. The term 'regular' arose from Hildebrand's observation of the regular behavior of the plots of log x_2 against 1/T, for solubility of single solutes in different solvents.

Scatchard calculated the cohesive energy of a mole of liquid mixture by using the following assumptions:

(i) The mutual energy of two molecules depends upon the distance between them and their relative orientation, and not at all on nature of the other molecules between or around them, or on the temperature.
(ii) The distribution of molecules is completely random in position and orientation: it is independent of the temperature, and of the nature of the species present.
(iii) At constant pressure, there is no volume change on mixing.

On these premises the heat of mixing per mole of a binary mixture is given by
$\Delta E^M =(x_1v_1+ x_2v_2) (c_{11}+ c_{22} – 2c_{12}) \phi_1\phi_2$----------(2)

where x, v and ϕ are , respectively , mole fractions, molar volumes and volume fractions such that $x_1 = n_1/ (n_1 + n_2)$, $v = v/n$, and $\phi_1= n_1v_1/ (n_1v_1 + n_2v_2)$, where v is the total volume and n the number of moles.

The subscripts 1 and 2 distinguish the components of the binary mixture, and subscript 2 is customarily reserved for that species which is regarded as the solute. The cohesive energy for the pure components is given by:

$-E_1 = c_{11}v_1$ and $-E_2= c_{22}v_2$. Intermolecular attraction between unlike species are covered by Scatchard's fourth assumption, viz., (iv)

The cohesive energy for interaction between different molecules is the geometric mean of that for the pure components, so that
$c_{12} = (c_{11}c_{22})^{1/2}$ ----------(3)
For liquids at ordinary temperatures the vapor is nearly ideal , and we can identify -E with the energy of vaporization , ΔE^v , and write $c_{11} = \Delta E_1^v /v_1$, etc.

The square root of the cohesive energy density, i.e, of the energy of vaporization per unit volume, assumes a great importance in the theory of regular solutions. Hildebrand and Scott term the values solubility parameters, and designate them by the special symbolδ. Thus,

$(\Delta E^v/ v)^{1/2} = \delta$ ----------(4), It readily follows that the energy of mixing of n_1 moles of liquid 1 with n_2 moles of liquid 2 will be given by

$\Delta E^M = (n_1v_1 + n_2v_2) (\delta_1-\delta_2)^2 \phi_1\phi_2$ ----------(5)

The pure liquid is normally used as the standard state and , when dealing with the solubility of a solid , its activity is referred to the hypothetical liquid obtained by super cooling below the melting point to the temperature T . The activity of a solute (designated by subscript c) of solubility parameter δ_c in an organic solvent of solubility parameter δ_o is thus related to its molar fraction $x_{c,o}$ by the expression

$\ln a_{c,o} = \ln x_{c,o} + v_c \phi_o^2 (\delta_c - \delta_o)^2 / RT$ ----------(6), If an analogous equation can be applied to an aqueous phase, we could write

$\ln a_{c,aq} = \ln x_{c,aq} + v_c\phi_{aq}^2 (\delta_c-\delta_{aq})^2 / RT$ ----------(7)
and , if partition equilibrium is achieved between the two phases ($a_{c,o} = a_{c,aq}$), one arrives at
$\ln D_x = \ln (x_{c,o}/ x_{c,aq}) = v_c [(\delta_c - \delta_{aq})^2 – (\delta_c - \delta_o)^2] /RT$ ----------(8)

Provided the concentration of solute is so small that both ϕ_o^2 and ϕ_{aq}^2 can be equated with unity. $D_x = x_{c,o} / x_{c,aq}$ is , of course , the partition coefficient of the distributed, defined as a ratio of molar fractions.

When a binary mixture is composed of molecules whose free volumes are not the same, an expression somewhat different from Equation (5), was deduced by Hildebrand[18]. On the assumption that the free volumes are directly proportional to the molar volume, this leads to

$\ln a_1 = \ln \phi_1 + \phi_2 (1 – v_1/v_2) + v_1\phi_2^2 (\delta_1 - \delta_2)^2 /RT$ ----------(9), which differs from (6) mainly by the additional term $\phi_2(1-v_1/v_2)$. Assuming, as above, that analogous equations can be applied to both organic and aqueous phase, we arrive at

$\ln D_\Phi = \ln\Phi_{c,o}/\Phi_{c,aq} = V_c/RT [(\delta_o – \delta_{aq})^2 – (\delta_c – \delta_0)^2] + V (1/V_0- 1/V_{aq})$ -------(10)

There is, of course, no real justification for applying Equations (6) or (9) to aqueous solutions which can hardly be regarded as regular. Siekierski and Olszer[7] proposed a way out of this difficulty by selecting one organic solvent, distinguished by the subscript s, as a standard. We can write a special case of Equation (8) for the standard and obtained by subscription

$\ln D_x/D_{x,s} = V_c/RT [(\delta_c – \delta_o)^2 – (\delta_c – \delta_o)^2]$ ----------(11), in which the solubility parameter δ_{aq} no longer appears. Similarly,

$\ln D_\Phi/D_{\Phi,s} = V_c/RT [(\delta_c – \delta_s)^2 – (\delta_c – \delta_o)^2] + V_c (1/V_o – 1/V_s)$----------(12)

In effect, this procedure compares the molar fractions (or the volume fractions) of the distributed in two organic solvents o and s , under conditions where the thermodynamic activity $a_{c,o} = a_{c,s}= a_{c,aq}$. There is an implicit assumption that the composition of the aqueous phase is identical in all the distribution experiments, and that the molar volume of the distributed V_c has the same value in all solvents – including water.

Assuming no association or dissociation in the organic phase, the ratio of partition coefficients will be equal to the ratio of experimentally measured distribution ratios. Equation (11) indicates that $\ln(D_x/D_{x,s})$ should be a parabolic function of δ_o , with a maximum at $\delta_c = \delta_o$.

All the above equations are derived on the assumption that the relevant solutions are regular. Considerations of cohesive energy also appear in other treatments of liquid-liquid equilibria. For example, the relative efficiency for the extraction of indium halides by different organic solvents can be discussed[12] in terms of a general theoretical model for the partition of an ion pair[4,12]. This takes the form

$RT \ln D_m = k – \{(E_m/Є_m) – x_d[(I_{+d} – I_{+h}) n- (P_d – P_h)V_\pm] \}$----------(13)

Where the first term within the brackets refers to electrostatic energy, the second to primary salvation energy, and the third to the energy of cavity formation. Here, P_d and P_h are the internal pressures of the solvents d and h and $V_\pm$ the sum of the molar volumes of

the ionic components of the ion pair. It was found that experimental data for mixtures of hexane with twelve diluents could be satisfactorily represented by the first two terms alone, and that the correlation coefficient did not change significantly when the cavity energy term was added[12]. Since the internal pressure $P = (\delta E/\delta V)_T$ was calculated by dividing the latent heat of vaporization (corrected for external work performed by the vapor), by the molar volume it will be obvious that $P = \delta^2$, and that the third term in equation (13)is formally analogous to the corresponding term in equation (5), et seq. However, the derivation of Equation (13) does not rest primarily upon the concept of regular solutions, contrary to statements that have appeared in the literature[19,20]. It is now appropriate to review the applications of the above equations to a variety of systems that have been studied experimentally.

Biological applications

There is firm experimental and theoretical justification for expecting that solution theories, in this case regular solution theory, can be applied in a semi-empirical manner to questions of biological interest. This background is outlined and one of the possible models resulting from the use of regular solution theory is applied to the analysis of erythrocyte haemolysis. Suggestive evidence arising from correlations of n-octanol- water partition coefficients with parameters appropriate to this approach tends to indicate that the regular solution theory may be applied to a wider variety of biological systems than has previously been thought.

Solubility-related phenomena are pervasive throughout the pharmaceutical and pharmacological literature. Among the areas where aspects of solution behavior arise are (a) in the design of liquid dosage forms; (b) in considerations of the influence of carrier vehicles on the biological absorption or response of a drug entity; (c) in accounting for the penetrability of molecular species into or through biological tissues and (d) in rationalizing physico-chemical influences on relative biological responses. As a more specialized component of the latter category one might also include certain factors, such as hydrophobic bonding, which relate to drug—biomacromolecule interactions. Underscoring literature accounts within each of these areas is the frequency with which simple oil-water partition coefficients are found to parallel test results obtained with biological systems. Hansch and his associates[3] have extensively exploited the ubiquitous occurrence of this correlation and have established statistical analyses that make use of N-octanol-water partition coefficients as a useful tool in the design of drug molecules or in the study of enzyme reactions. Less frequently have efforts been made to apply a theory of solution, such as regular solution theory[4], to these same types of systems. Such work as has been reported although in some instances[19] promising results have been obtained with commercial pharmaceuticals.

There are a variety of reasons why one might prefer to make use of empirical or extra thermodynamic relations involving partition coefficients rather than relations based on a solution theory in the study of pharmaceutical or pharmacological systems: (a) empirical parameters ordinarily provide better 'fits' with biological data than do theoretically-based indexes[20]; (b) partition coefficients are approximately additive—constitutive, thus enabling the estimation of values appropriate to additional compounds[21]; (c there are few theoretical constraints associated with the application of partition coefficients to interpretations of biological data as distribution processes involving an organic or lipophilic phase and an aqueous phase are linearly interrelated[22]). On the other hand, several valid reasons can also be given for desiring to take a more fundamentally based approach: (a) seemingly disparate experimental observations such as carrier vehicle influences on biological activity, isotonicity, and passive membrane transport are readily understood as involving a common physicochemical component; (b) the 'distribution system' is the biological assay object itself; thus, adjustable parameters within a theoretical framework have significance in relation to the actual test system; (c) based on a theoretical rationale it is sometimes possible to design independent types of assay for substantiation of a mechanistic hypo-thesis; (d) disagreement with theoretically-based relationships frequently are readily interpretable as providing information which is either intrinsic to the chemical nature of the compounds under consideration or is specific to biological processes; (e) in the realm of drug design, there is a potential for estimating optimum solubility characteristics without the necessity for an extensive set of test compounds and there is also afforded a possible route to the design of tissue-specific agents.

As should be evident from this brief introduction, the possible scope of application of a solution theory, in this instance regular solution theory, to biological systems is extremely broad. What we hope to do by this presentation is to report on our very preliminary findings which tend to indicate that regular solution theory might have a much more promising future in application to biological systems than has previously been thought. We do not claim our present interpretations to be immutable. Rather we anticipate .that clarifications and refinements will be made in establishing a modification of regular solution theory that is appropriate to questions of biological interest.

Historical foundations

Virtually all efforts to relate biological activity with physically-based indexes stem from observations of a relationship between narcotic potency and water solubility[23]. Later, independent investigations led Overton[24] and Meyer[25] to the finding of a correlation between narcotic potency and partition coefficient from which it was surmised that the relative effectiveness of anaesthetic compounds was due to their distribution between biological lipids and water. This observation was extended to the penetration of molecular species through membranes by Collander[26] and has reached fruition with the work of Hansch and his coworkers[3]. Meyer had a son, and it is from this Meyer's efforts that a basis for quantitative work with biological systems is derived. He showed[27] that despite the apparent trend in narcotic potency with partition coefficient, the equilibrium concentration of the drug in the organic phase of the model distribution system was effectively a constant. From this it was concluded that narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipids of cells. It was also noted that this specific concentration

depends on the nature of the animal or cell but is independent of the narcotic selected. On the distribution of phenol anaesthetics with erythrocyte membrane has verified this conclusion, but acidic compounds that are ionized and have a negative charge under the conditions of the assay are tentatively exceptions[29]. Table 1 compares the results of Meyer with those of Roth and Seeman to illustrate the basis for Meyer's hypothesis.

A physical rationale for Meyer's hypothesis based on thermodynamic principles was subsequently put forward by Ferguson[30] and it is this rationale which provides a foundation for applying solution theories to the interpretation of biological data. Ferguson points out that under equilibrium conditions the chemical potential for a compound in the assay medium, Pa'should equal the chemical potential of the compound in the biophase, irrespective of the nature of the biophase. Necessarily, then, there is a reference chemical potential for the drug in some standard. For perfect solutions the concentration measure, and hence the concentration of a substance accumulated in a common biophase is expected to be a constant and this value should be independent of the nature of the drug. That is, drug activities assayed using a specific biological test system and measured to an equivalent endpoint in terms of molar concentrations or partial pressures should provide a constant value when these concentration measures are converted to thermodynamic activities. This has been found to be the case for a variety of biological assays where the test compounds are either in solution[30-34] or in a gaseous state[30]. Consequence discrimination between tissues would most readily be possible if the tissues involved differed greatly in their constitution. Certainly approaching the study of biological activities by the application of regular solution theory is not above severe criticism, especially if a chemically and biologically rigorous theoretical framework is desired. In attempting to apply this theory it is perhaps appropriate to take a dual perspective, the choice depending on the use that is to be made of the method. If the intention is to test the approach in terms of rigorous foundations, it would be best to consider only relatively nonpolar substances and their action on the most simple of tissues for which c values may be determined by swelling, vapor pressure, or osmotic pressure measurements. The contribution made by the Flory—Huggins[43] size correction, due to the difference in molar volumes of drug and biophase components, might also be determined.

From a drug design standpoint, however, a more flexible yet readily applied procedure is most desirable. In this case the molar volumes and solubility parameters in equations 10, 11 and 12 may be considered to be adjustable, the separate relationships providing an empirical framework within which to work. This latter view is adopted in this article. An alternative criticism might take note that Ferguson's development applies only to an equilibrium situation and hence should not be carried over into kinetic situations, e.g., membrane penetration. That this criticism is invalid is easily demonstrated from a consideration of Fick's Law for diffusion through thin membranes, which is the usual model used in biological work. If the steady-state rate of penetration is (dQ/dt) then taking the logarithm of the biological response measure corresponds to log (dQ/dt) , again equations of regular solution theory are seen to apply. Since, in taking a regular solution theory approach to analyzing biological data, attention is focused on the activity coefficient, it is appropriate to ask what the range in activity coefficients might be as it is transferred from one medium to another. What this range could be for biological tissues is as yet an open question, but extremely wide variations in the activity co-efficient have been reported by Higuchi[44] for Sarin, a nerve gas, in differing solvents (**Table 1**).

Table 1. Limiting activity coefficients of Sarin in solvents[44].

Solvent	Limiting activity-coefficient
Perfluorotributylamine	66.6
Hexadecane	15.6
Water	14
Tributylamine	10.4
Tetralin	4.3
2-Pyrrolidone	2.8
Diethylene glycol	2.4
Carbon tetrachloride	2.4
Phenyl ether	2.38
Diisooctyl adipate	1.84
Methyl salicylate	1.74
N-Methylacetamide	1.44
Dibutyl phthalate	1.42
Butyrolactone	1.31
Isoamyl alcohol	1.07
Ethyl lactate	0.535
Benzyl alcohol	0.446
m-Cresol	0.044

Application to study of erythrocyte haemolysis

A simple membrane for which an extensive literature exists and which has been the subject of a recent extrathermodynamic study[45] is the erythrocyte membrane. This system was used by Roth and Seeman[28,29] in verifying the Meyer hypothesis and as a consequence should be capable of analysis in terms of regular solution theory. We show here that (a) data correlating linearly with n-octanol: water partition coefficients sometimes show a definite parabolic trend when plotted against solubility parameters. More frequently, when such comparisons are possible, there is general agreement between the type of curve obtained by either approach, i.e., linearity in one case also is found with the other or quadratic behavior with one is also found with the other. (b) Identical conclusions are obtained taking either approach regarding the similarity in the nature of the erythrocyte membrane in differing animal species. (c) The apparent 5value for erythrocyte membrane seem to be about 8.08, which can be contrasted with an apparent ö value of around 10.5 reported[46] for nerve membrane. Solubility parameters calculated[47] for the compounds compiled by Hansch and Glave[45] when plotted with their haemolytic concentrations as the dependent variable tended to provide curves paralleling the type of equation reported from regression analysis.

Correspondence for substituted benzenes tested against rabbit erythrocyte and monoglycerides tested against dove erythrocyte. In some instances, however, as for amides and carbamates tested against bovine erythrocyte, curvature in the solubility parameter plot is noted while the equation involving partition coefficients was reported to be linear. While nothing substantive can be made of this observation, the discrepancy between the two types of correlative approaches might be interpreted as indicating that a distinction between a simple partitioning model and a saturation model could be made using erythrocyte membrane data. As may have been expected, not all the data compiled by Hansch and Glave[45] led to smooth curves when 5 values were used as a measure of solubility. The reasons for this are not entirely clear, although it should be pointed out that for some sets of data there were uncertainties, while with other sets it seemed possible to group compounds into subsets based on chemical structure. Of course another possibility is that it is hoping for too much to have regular solution theory apply to all the compounds. Those sets of data which provided smooth curves of a definite quadratic nature were thus selected for regression analysis making use of an orthogonal polynomials routine for the curve fit. This may be recognized to depend on whether the compounds function in a disruptive or a protective manner towards erythrocytes. It was concluded that a distribution model for erythrocyte haemolysis is most probably invalid. The equilibrium concentration of drug in the erythrocyte membrane[28,29] is low which shows excellent agreement with the calculated values.

Indicated in any way from the results of an extra thermodynamic type of approach. Having found regular solution theory to apply to a number of studies of erythrocyte haemolysis, it is pertinent to inquire into the possible reasons for this apparent success. At first sight, the compounds would not appear suitable for study by regular solution theory, since they are either ionic or contain a functionality capable of hydrogen bonding. A plausible rationale for the findings takes note of the behavior of surface active agents at an organic medium—aqueous medium interface. Surface active agents possess a polar or charged moiety attached to an alkyl group and, at an organic—aqueous interface, the polar groups tend to be associated with the aqueous phase while the nonpolar groups tend to be in the organic phase. For erythrocyte baemolysis, the polar components of the compounds found would be associated with the aqueous assay medium while the nonpolar groups would be contained in the lipophilic interior of the membrane. Presuming the haemolytic action of the compounds to be a consequence of disruption of the interior organization of the membrane by the nonpolar substituent, it would thus be reasonable to expect regular solution theory to be applicable to erythrocyte haemolysis. The polar group no doubt also contributes to disruption of the membrane, but this functionality is maintained constant with each series of compounds and whatever contribution made by it relative to the nonpolar fragment may be considered relatively invariant in passing from one compound to another.

Conclusion

A number of biological activities, such as narcotic potency, enzymatic activities, and protein binding, have been correlated against electronic polarizability or, its magnetic equivalent, diamagnetic susceptibility[55]. It has recently been shown[39] that these electronic indexes can be used to calculate molar attraction constants, and hence in a semi-empirical manner for nonpolar and slightly polar molecules. The correlations of biological activity with electronic polarizability may thus be said to have a basis in regular solution theory. Of much more significance, however, is the attempt by Davis[56] to calculate the extra thermodynamic lipophilic parameter using solubility parameters and molar volumes. An encouraging degree of agreement was obtained between the calculated and observed values, prompting us to seek a correlation between partition coefficients and electronic polarizability. It can be stated that at least for the n-octanol—water distribution system a surprisingly good correlation between partition coefficient and electronic polarizability is found and the correlation extending over 72 compounds. Two lines are found, one for the compounds with electronegative atoms (N, 0) and the other for compounds that are ordinarily considered relatively nonpolar. The two lines suggest two types of partitioning processes which are potentially explicable in terms of molal volume differences for a compound contained in two differing phases. The latter correlation thus suggests that a large proportion of the relationships between biological activities and partition coefficients' may be profitably reinvestigated in terms appropriate to regular solution theory.

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