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*REVIEW ARTICLE*

# Linear Relationships between Lipophilic Character and Biological Activity of Drugs

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The classic work of Meyer (1) and Overton (2, 3) and the followup by their successors (4, 5) have provided abundant evidence that the lipophilic character of organic compounds as operationally defined by oil/water partition coefficients plays an important role in drug action. This is true at all levels of organization: enzyme, membrane, cell, and whole animal. It is now quite clear that even for *in vitro* work with enzymes or homogenates, small differences in lipophilic character can be quite important. This molecular property is only one of several which, taken together, accounts for the biological action caused by a particular drug. At present, a considerable effort is underway to separate the various physicochemical properties of drugs and, in this way, to correlate the partial contributions of hydrophobic, electronic, and steric forces to the overall properties of drugs (6–8). Even though the details of how drug action is related to physicochemical properties of drugs are not clear, it is profitable to use the phenomenological approach to separate and classify such molecular properties. This report is concerned with the use of the partition coefficient as an extrathermodynamic reference scale for characterizing one of the most important properties of small molecules acting on macromolecular systems in aqueous solutions.

The term "hydrophobic bonding" is often used to describe the free-energy changes involved in the movement of a drug from the aqueous phase to the biophase. There is considerable controversy over exactly what one means by such a term (9, 10). Of course, the free-energy change differs from system to system and depends on the type of molecule being partitioned. For example, partitioning a polar molecule such as an alcohol between heptane and water or between octanol and water would be quite different. One important driving force for partitioning is the removal of a loosely held water sheath which appears to form around organic compounds in aqueous solution (11). The removal of this sheath may be roughly the same for a given molecule in moving from water to heptane or octanol or even serum albumin. However, the polar forces that result from different functional groups make partitioning of an alcohol into heptane a different process from partitioning into octanol. The OH of the alcohol has to be pulled away from its association with water molecules in order to enter the heptane phase. This energy change can, in part, be compensated for by the association of the alcohol molecules in the heptane.

The relative effect of some polar functions on partitioning can be seen in Table I. Ethanol is about 100 times as reluctant to move from water to hexane as to move from water to octanol. Acetone shows only 5 times the reluctance, and toluene shows almost no preference for octanol or heptane. Aniline shows a preference factor of 10 for octanol over heptane, while phenol shows a preference of 300. Except for solutes

Table I—Relative Effect of Some Polar Functions on Partitioning[a]

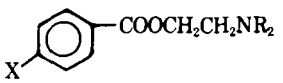
| Compound | log $P_{octanol}$ | log $P_{ether}$ | log $P_{benzene}$ | log $P_{hydrocarbon}$ |
|---|---|---|---|---|
| Ethanol | −0.2 | −0.6 | −1.5 | −2.3 hexane |
| Acetic acid | −0.2 | −0.3 | −2.0 | −2.8 hexane |
| Acetone | −0.2 | −0.2 | 0.0 | −0.9 hexane |
| Phenol | 1.5 | 1.6 | 0.4 | −1.0 hexane |
| Aniline | 0.9 | 0.9 | 1.0 | 0.0 heptane |
| Toluene | 2.7 | — | — | 2.9 heptane |
| Diethylamine | 0.5 | −0.3 | 0.0 | −0.3 cyclohexane |
| Acetanilide | 1.2 | 0.5 | 0.2 | — |

[a] Values from *Reference 12.*

like toluene, there is a large difference in log $P$ values obtained with octanol or with saturated hydrocarbons.

For many compounds, there is relatively little difference between ether and octanol partition coefficients; for some, such as acetanilide, there is a large difference.

In choosing a solvent system as a reference system for modeling hydrophobic effects in biochemical systems, one could consider two extremes. One could select a hydrocarbon solvent such as heptane in which there would be very little interaction between solute and solvent. Hence, log $P$ would be determined by the desolvation of water molecules from the solute as well as the energy required to break any hydrogen bonding or dipolar interactions between solute and water molecules. Such a reference system will no doubt correlate sets of homologous compounds such as ROH and $RCONH_2$ very well but will fail when mixed sets of congeners are used (*e.g.*, Eqs. 11, 22, 23, 32, 39, 42, 46, and 49). It will also work poorly when polyfunctional compounds such as




are considered. If there are quite wide variations in X, hydrocarbon partition coefficients alone will not go very far in structure–activity work. However, one can add additional terms to take care of special hydrogen bonding or dipolar effects. For instance, there are many examples where structure–activity relations of phenols are well correlated by log $P_{octanol}$ alone. Tables II–IV show a number of these examples as well as some where phenols were included with other more or less neutral compounds. Equation 1 (13):

$$\log P_{octanol} = 0.50 \log P_{cyclohexane} + 2.43 \quad n = 9,\ r = 0.791,\ s = 0.391 \quad \text{(Eq. 1)}$$

$$\log P_{octanol} = 1.00 \log P_{cyclohexane} + 1.20 \log K_{HB} + 2.35 \quad n = 9,\ r = 0.979,\ s = 0.140 \quad \text{(Eq. 2)}$$

shows that there is a poor correlation between octanol and hydrocarbon log $P$ values for phenols. In Eqs. 1 and 2, $n$ is the number of phenols studied, $r$ is the correlation coefficient, and $s$ is the standard deviation. While Eq. 1 is poor, if one corrects for the variations in hydrogen-bonding ability of the phenols by means of the hydrogen-bonding constant $K_{HB}$ as in Eq. 2, a good correlation is found. Moreover, the coefficient of 1 with the log $P_{cyclohexane}$ term could be interpreted to mean that desolvation effects are the same in each solvent. Of course, dipolar effects may parallel hydrogen-bonding effects, and log $K_{HB}$ may be correcting for both. Equation 2 could be used for structure–activity relation studies, but it has the great disadvantage that one would have to measure many hydrogen-bonding constants. It also has the disadvantage that log $P$ values for many polar compounds (quaternary ammonium salts, amino acids, *etc.*) would be impossible to measure using a saturated hydrocarbon. It would have the advantage of separating out the role of hydrogen bonding in drug action.

The other extreme is to use a solvent as much like the living biophases as possible. For example, one might even employ binding constants between solutes and proteins such as serum albumin, as was recently done by Kakeya *et al.* (14). These workers showed that for the correlation of sulfonamides inhibiting carbonic anhydrase, albumin binding constants gave somewhat better correlations than log $P_{octanol}$ constants. Whether the improvement is great enough to warrant the much greater difficulty in measuring such constants remains to be seen.

In selecting a reference system close to the biophase, one must keep in mind that many, if not most, drugs will be interacting with protein molecules. These large molecules contain many excellent hydrogen-bonding centers such as the amide groups. It is hard to imagine a polar drug having an OH function held in such a way that the hydrogen-bonding function could not reach a hydrogen-bonding function in the macromolecule. This would also be true of the lipid phases of cells where many ester, phosphate, and other hydrogen-bonding groups are present. The same reasoning also applies to DNA and RNA. The OH function of octanol, which can act as a hydrogen-bonding donor as well as an acceptor, would seem to be a reasonable model of macromolecules because here and there throughout the largely apolar milieu there is an OH group for hydrogen bonding. The OH function of octanol also attenuates the hydrogen-bonding effects and dipolar effects. This appears to be definitely advantageous for the correlation of nonspecific biochemical action, of which there are many examples in Tables II–IV. No doubt this also helps to simplify things when one is correlating a set of congeners containing a given pharmacophoric function in part of the molecule and a wide variety of substituent changes in another part. It may even be satisfactory for cases in which hydrogen bonding has a central role in the biochemical action if the electronic effect of molecular changes on hydrogen bonding by the drugs can be accounted for using Hammett–Taft $\sigma$ constants. When a sufficient number of good hydrogen-bonding constants are available, it may be worth attempting to factor out this effect as in Eq. 2.

The partitioning of drugs between aqueous and biophases is indeed so complex that there is very little theory one can use for guidance in the selection of the "best" reference system for hydrophobic binding. It would seem reasonable that a large amount of empirical testing of model systems should turn up a better system than octanol/water. However, it is clear from the results in Tables II–IV that octanol/water serves surprisingly well for a variety of systems.

## LINEAR FREE-ENERGY MODEL FOR STRUCTURE–ACTIVITY WORK

While Meyer (1), Overton (2, 3), and many others made structure–activity comparisons directly with oil/water partition coefficients, the authors have employed the logarithm of the partition coefficient because of the theoretical justification for the linear relationship so often observed in organic chemistry between logarithms of rate and equilibrium constants (15, 16).

The extrathermodynamic postulate upon which this present study is based is:

$$\log P_{bio} = a \log P_{octanol} + b \qquad \text{(Eq. 3)}$$

In Eq. 3, $P_{bio}$ is the partition coefficient of drug between the aqueous phase in which it is applied and the critical biophase in which it produces the observed standard biological response. The partition coefficient of the reference system (octanol/water) is designated by $P_{octanol}$, and $a$ and $b$ are constants for a given system. For many of the systems considered in this report, it is reasonable to assume essentially equilibrium conditions in the biochemical system so that Eq. 3 represents a linear free-energy relationship between two sets of equilibrium constants. The examples selected for the present review are only those linear in log $P$. Therefore, highly specific steric and electronic factors (other than nonspecific stereoelectronic factors contained in log $P$) do not appear in the form of specific parameters such as $\sigma$ or $\Delta$pKa. While only hydrophobic forces are necessary to account for activity differences between various members for a given set of congeners, significant differences between various sets appear in the intercepts.

The partition coefficient for the biochemical system can be defined as:

$$P_{bio} = C_{bio}/C_{H_2O} \qquad \text{(Eq. 4)}$$

In Eq. 4, $C_{bio}$ and $C_{H_2O}$ are defined to refer to the *molar concentration* of drug in the biophase and in the aqueous phase, respectively. For the examples to be considered, studies have been made in which the concentration of drug in the applied aqueous phase is varied until a standard response is obtained from the system in a fixed time. Under these conditions, it is assumed that concentrations of each drug in the biophase will be constant. The critical assumption is that *equivalent* biological response means *equivalent* numbers of molecules on the receptors in the biophase for each member of a congeneric set. Under these conditions, $C_{bio}$ is a constant, the value of which is set by $P_{bio}$, the level of equivalent response demanded, and the intrinsic pharmacophoric function common to members of the set. For these conditions:

$$(P_{bio})_{S.R.} = k/C_{H_2O(applied)} \qquad \text{(Eq. 5}a\text{)}$$

$$\log 1/C_{H_2O(applied)} = \log (P_{bio})_{S.R.} - \log k \qquad \text{(Eq. 5}b\text{)}$$

In Eqs. 5*a* and 5*b*, S.R. refers to standard response and $C_{H_2O(applied)}$ is the molar concentration of drug in which the protein, enzyme, or bacterium is being tested. In the case of whole animals, $C$ is usually moles/kilogram of drug injected; $(P_{bio})_{S.R.}$ is a special case of the general formulation of partitioning in the biological system. For this case, Eq. 3 becomes:

$$\log (P_{bio})_{S.R.} = a \log P_{octanol} + b \qquad \text{(Eq. 6)}$$

Substituting Eq. 6 into Eqs. 5*a* and 5*b* yields the prototype equation:

$$pC \equiv \log 1/C_{H_2O(applied)} = a \log P_{octanol} + \text{constant} \qquad \text{(Eq. 7)}$$

for systems at or near equilibrium. It is also assumed (6) to apply to systems considerably removed from equilibrium. For the nonequilibrium cases, it is assumed that the rates at which drugs reach their sites of action are linearly related to log $P$. In this situation, the linear free-energy relationship is between logarithms of rate and equilibrium constants rather than simple equilibrium constants. There is abundant evidence from simple chemical processes for this assumption (15, 16).

It is, of course, well known that the linear relationship between p$C$ and log $P$ does not extend indefinitely. In fact, considerable evidence points to a parabolic relationship between biological activity and lipophilic character (17–19). The definition of linearity for the equations considered here is that the addition of a term in $(\log P)^2$ to each of the equations in Tables II–IV does not result in a significant reduction in variance as measured by the test where $\alpha \leqq 0.10$.

The two parameters, $a$ and the intercept of Eq. 7, provide numerical indexes for classifying structure–activity relationships. The slope of Eq. 7 is a measure of the sensitivity of the system to perturbation by hydrophobic effects of the drugs.

The value of the intercept will be a function of the sensitivity of the biochemical system and the intrinsic activity of a given set of congeners. It will depend on the ratio of active sites to substrate molecules in position to react with the sites. In this discussion, a pseudo-first-order reaction is assumed, depending only on the concentration of drug applied. To obtain equations with identical intercepts, the systems under study would have to have identical concentrations of equivalent active sites, and the sets of congeners would have to have pharmacophoric functions of identical intrinsic activity. In general, one must hold the system constant; that is, a standard mouse is assumed to have always the same number of a given type of active site per kilogram of mouse. In comparing bacteria growing in various media, one assumes roughly the same concentration of bacteria. Of course, this may differ by varying amounts from laboratory to laboratory. At the present stage of quantitative structure–activity relations work, these differences are not so serious as they at first might seem. The 95% confidence intervals on the intercepts in Tables II–IV are, even in the best examples, on the order of 0.1–0.3 log unit. Thus the uncertainty in $C$ is at least one- to twofold. The surprising fact about the intercepts of similar systems in Tables II–IV is not that they are different but that they are even close. In the study of the inhibition of isolated enzymes (*e.g.*, Eq. 66, Table II), one can vary the substrate concentration at will and, in this way, affect the intercept considerably.

The intercepts allow comparisons to be made in a rough way between quite different sets of congeners

acting on quite different systems. Comparison of intercepts means comparison under isolipophilic conditions where $P = 1$ or $\log P = 0$.

For this discussion, the equations in Tables II–IV have been factored into three groups: those with slopes above 0.85, those with slopes below 0.4, and those with slopes in between. Within each group, the equations are ordered by increasing value of the intercept. Most of the equations of Tables II–IV were derived from the data in Table V. However, as indicated, some equations were previously reported. In these instances, the data are not included in Table V. The reader may consult the cited reference for values for individual data points.

## HYDROPHOBICALLY SENSITIVE LINEAR FREE-ENERGY RELATIONSHIPS

Those equations with slopes >0.85 are listed in Table II. These equations correlate the systems most sensitive to hydrophobic effects. The figure of 1.2 appears to be about the upper limit for this sensitivity coefficient. Those few examples exceeding this figure all have rather large 95% confidence limits. One might *postulate* that in almost all of these systems the biological response is mediated through membranes.

There are, of course, many examples over the years where biological response has been shown to be a function of the influence of drugs on membranes (20). While there are many ways of studying this problem, one way in which comparisons can be made is *via* linear free-energy relationships.

In a recent study (21), it was found that linear relationships between p$C$ and log $P$ are quite common in hemolysis. For 15 such linear equations obtained with different kinds of red blood cells using different sets of small molecules, a mean slope of $0.93 \pm 0.17$ was found (21). The slopes were found to be the same for positively or negatively charged sets of congeners as well as for neutral ones. However, the congeneric sets with charged molecules had much greater intercepts than the neutral sets. For seven sets of neutral drugs causing hemolysis, a mean value of $-0.09 \pm 0.23$ was found for the intercept. From these results, one can compose a synthetic equation for hemolysis by neutral molecules:

$$pC = 0.93 \pm 0.17 \log P - 0.09 \pm 0.23 \qquad \text{(Eq. 8)}$$

Hemolysis is highly dependent on hydrophobic forces as operationally defined by log $P$. The rupture of the red cell membrane by small neutral compounds appears to be largely a kind of mechanical disruption of the cell membrane. Hemolysis would seem then to be a standard of reference with which the nonspecific mechanical effects of drugs in other biochemical systems could be compared using log $P$ values as the common medium of comparison.

The variations in the slope of the equations used to formulate Eq. 8 are small (all things considered) as the standard deviation indicates. This implies to a first approximation that for each increment of hydrophobicity, a constant increase in membrane perturbation occurs regardless of the type of neutral function added; that is, halogen, methylene groups, aromatic rings, *etc.*, all contribute to membrane perturbation in direct proportion to their $\pi$ values ($\pi = \log P_X - \log P_H$), where $P_X$ is the partition coefficient of a derivative and $P_H$ that of the parent compound. The $\pi$ is the logarithm of the partition coefficient of a function such as Cl or $NO_2$. Compounds that do not fit Eq. 8 can be taken to have specific stereoelectronic properties for membrane disruption. Sets of ionized compounds such as ammonium salts, alkyl sulfates, or carboxylates are correlated (21) by equations having much greater intercepts than Eq. 8, indicating a specific role for the charged function.

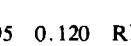
Seeman *et al.* (22) measured the partition coefficients of alcohols between red cell ghosts and water. As Eq. 9 of Table II shows, the process very closely parallels the partitioning of alcohols between octanol and water. The slope of 1 in Eq. 9 indicates the similar role of hydrophobicity in each system, while the negative intercept shows that isolipophilic molecules are more easily taken up by octanol than by red cell membranes (in fact, about 7 times more).

In recent years, interest has developed in making models of living membranes to facilitate various kinds of studies. An extremely simple but interesting model is that of silanized glass beads. Studies of alcohol disaggregation of clusters of such beads (Eqs. 10 and 13) yield a linear free-energy relationship very similar to Eq. 8 for hemolysis. The slopes are exactly the same, while the intercepts are about 0.5–0.8 lower, indicating that a 3–7 times higher alcohol concentration is needed to cause separation of the lipophilic glass beads as is necessary to rupture the lipophilic units of the red cell. The results of alcohol perturbation of synthetic black lipid membranes (BLM) (Eq. 12) are surprisingly similar to those obtained with the coated glass beads. The equation for the BLM correlates the change in permeability of potassium ion caused by alcohols on membranes prepared with lipid of sheep red cell ghosts. The permeability increase is determined from a decrease

**Table II**—Hydrophobically Sensitive Linear Free-Energy Relationships ($pC = a \log P + b$)

| Equation Number | $b$ | $a$ | $n$ | $r$ | $s$ | Compound | Reference 1[a] | Reference 2 | Type Biological Activity |
|---|---|---|---|---|---|---|---|---|---|
| 9 | $-0.883 \pm 0.39$ | $1.003 \pm 0.13$ | 5 | 0.998 | 0.082 | ROH | V-1 | 22 | Red cell ghost partition coefficient |
| 10 | $-0.801 \pm 0.17$ | $0.984 \pm 0.29$ | 4 | 0.995 | 0.077 | ROH | V-2 | 27 | Disaggregation, 0.2-mm. silanized glass beads |
| 11 | $-0.550 \pm 0.07$ | $0.891 \pm 0.12$ | 8 | 0.992 | 0.070 | Misc. | V-44 | 28 | $I_{50}$, indophenol oxidation, kidney, rabbit |
| 12 | $-0.506 \pm 0.42$ | $1.161 \pm 0.24$ | 7 | 0.985 | 0.262 | ROH | V-4 | 29 | Change in resistance, black lipid membrane |
| 13 | $-0.492 \pm 0.25$ | $0.949 \pm 0.43$ | 4 | 0.989 | 0.114 | ROH | V-5 | 27 | Disaggregation, 0.3-mm. silanized glass beads |

**Table II**—(*Continued*)

| Equation Number | *b* | *a* | *n* | *r* | *s* | Compound | Reference 1[a] | Reference 2 | Type Biological Activity |
|---|---|---|---|---|---|---|---|---|---|
| 14 | −0.445 ± 0.26 | 1.274 ± 0.35 | 4 | 0.996 | 0.082 | ROH | V-3 | 30 | Lysis, protoplasts, *M. lysodeikticus* |
| 15 | −0.430 ± 0.06 | 0.940 ± 0.04 | 12 | 0.998 | 0.067 | ROH + ketones | V-45 | 31 | MLD, *S. typhosa* |
| 16 | −0.425 ± 0.12 | 1.065 ± 0.17 | 5 | 0.996 | 0.076 | ROH | V-6 | 32 | MLD, yeast, *S. cerevisiae* |
| 17 | −0.263 ± 0.10 | 0.892 ± 0.08 | 11 | 0.993 | 0.112 | ROH + ketones | V-46 | 31 | Cytolysis, yeast cells |
| 18 | −0.242 ± 0.16 | 0.872 ± 0.19 | 5 | 0.993 | 0.100 | ROH | V-7 | 33 | −10-mv. change in rest potential, lobster axon |
| 19 | −0.108 ± 0.11 | 0.838 ± 0.14 | 5 | 0.996 | 0.070 | ROH | V-8 | 33 | −5-mv. change in rest potential, lobster axon |
| 20 | −0.056 ± 0.14 | 0.868 ± 0.07 | 6 | 0.998 | 0.046 | Phenols | V-47 | 31 | Cytolysis, yeast, *S. cerevisiae* |
| 21 | −0.026 ± 0.15 | 1.255 ± 0.06 | 9 | 0.999 | 0.115 | ROH | V-9 | 34 | Stabilization against hypotonic hemolysis, red cell |
| 22 | 0.114 ± 0.15 | 0.911 ± 0.12 | 14 | 0.977 | 0.218 | Misc. | V-48 | 35 | $I_{50}$, oxygen consumption, red cell |
| 23 | 0.130 ± 0.12 | 0.903 ± 0.08 | 33 | 0.974 | 0.195 | Misc. | 36 | 37 | $I_{100}$, frog heart |
| 24 | 0.196 ± 0.16 | 0.970 ± 0.20 | 6 | 0.990 | 0.117 | ROH | V-10 | 38 | Inhibition, yeast, *S. cerevisiae* |
| 25 | 0.214 ± 0.12 | 1.096 ± 0.07 | 8 | 0.998 | 0.103 | ROH | 36 | 39 | Inhibition, luminescence, *B. fischeri* |
| 26 | 0.258 ± 0.21 | 1.050 ± 0.10 | 8 | 0.995 | 0.142 | ROH | V-11 | 40 | MIC, sciatic nerve, frog |
| 27 | 0.280 ± 0.14 | 1.015 ± 0.14 | 6 | 0.995 | 0.094 | ROH | V-12 | 41 | Narcosis, *A. faetida* |
| 28 | 0.299 ± 0.06 | 1.048 ± 0.08 | 5 | 0.999 | 0.042 | ROH | V-13 | 42 | $I_{100}$, rabbit gut |
| 29 | 0.319 ± 0.09 | 0.895 ± 0.05 | 8 | 0.998 | 0.072 | ROH | 36 | 43 | $I_{50}$, paramecium motility |
| 30 | 0.354 ± 0.10 | 1.127 ± 0.18 | 8 | 0.987 | 0.098 | ROH | V-14 | 44 | Narcosis, goldfish, 37° |
| 31 | 0.361 ± 1.03 | 0.914 ± 0.37 | 4 | 0.991 | 0.096 | *p*-Hydroxybenzoates | V-49 | 45 | Inhibition, yeast, *S. cerevisiae* |
| 32 | 0.398 ± 0.16 | 0.863 ± 0.10 | 20 | 0.971 | 0.257 | Misc. | V-55 | 46 | Narcosis, larvae, arenicola |
| 33 | 0.516 ± 0.13 | 0.977 ± 0.19 | 10 | 0.973 | 0.134 | ROH | V-15 | 47 | $I_{50}$, tortoise heart |
| 34 | 0.532 ± 0.17 | 1.006 ± 0.31 | 6 | 0.976 | 0.138 | ROH | V-16 | 48 | $I_{30}$, paramecium motility |
| 35 | 0.540 ± 0.98 | 0.850 ± 0.32 | 9 | 0.919 | 0.213 | Carbamates | 49 | 50 | $I_{50}$, Hill reaction, chloroplasts |
| 36 | 0.564 ± 0.66 | 1.096 ± 0.39 | 4 | 0.993 | 0.241 | Misc. | V-54 | 51 | $I_{50}$, oxygen consumption, cervica ganglion, rabbit |
| 37 | 0.584 ± 0.12 | 0.976 ± 0.09 | 14 | 0.990 | 0.149 | ROH | V-17 | 52 | Narcosis, larvae, barnacle |
| 38 | 0.587 ± 0.16 | 1.223 ± 0.09 | 8 | 0.997 | 0.134 | ROH | V-18 | 53 | $I_{100}$, movement 2.5-day-old tadpoles, 18° |
| 39 | 0.600 ± 0.24 | 0.964 ± 0.14 | 22 | 0.955 | 0.390 | Misc. | 36 | 54 | Colchicinelike mitosis, allium root tip |
| 40 | 0.606 ± 0.12 | 1.155 ± 0.07 | 8 | 0.998 | 0.104 | ROH | V-19 | 53 | $I_{100}$, movement 12-day-old tadpoles, 18° |
| 41 | 0.612 ± 0.12 | 0.992 ± 0.07 | 8 | 0.997 | 0.101 | ROH | V-20 | 43 | $I_{50}$, ileum, guinea pig |
| 42 | 0.627 ± 0.19 | 0.884 ± 0.12 | 25 | 0.955 | 0.297 | Misc. | 36 | 55 | Nerve block, frog |
| 43 | 0.646 ± 0.09 | 1.120 ± 0.06 | 8 | 0.999 | 0.078 | ROH | V-21 | 53 | $I_{100}$, movement 83-day-old tadpoles, 18° |
| 44 | 0.695 ± 0.11 | 1.114 ± 0.09 | 6 | 0.998 | 0.080 | ROH | V-22 | 56 | MIC, fish |
| 45 | 0.715 ± 0.26 | 1.166 ± 0.37 | 5 | 0.986 | 0.168 | Carbamates | 36 | 39 | Inhibition, luminescence, *B. fischeri* |
| 46 | 0.757 ± 0.35 | 1.190 ± 0.25 | 14 | 0.949 | 0.379 | Misc. | V-56 | 4 | Narcosis, tadpoles |
| 47 | 0.759 ± 0.61 | 1.026 ± 0.39 | 4 | 0.992 | 0.101 | Esters | V-57 | 53 | $I_{100}$, movement 1-day-old tadpoles, 18° |
| 48 | 0.805 ± 0.48 | 1.108 ± 0.27 | 7 | 0.978 | 0.316 | Misc. | V-58 | 51 | $I_{50}$, postsynaptic pulse, cervical ganglion, rabbit |
| 49 | 0.909 ± 0.12 | 0.901 ± 0.07 | 57 | 0.962 | 0.312 | Misc. | 57 | 3 | Narcosis, tadpoles |
| 50 | 0.921 ± 0.54 | 0.910 ± 0.34 | 4 | 0.992 | 0.089 | Esters | V-59 | 53 | $I_{100}$, movement 19-day-old tadpoles, 18° |
| 51 | 0.967 ± 0.24 | 0.919 ± 0.30 | 5 | 0.985 | 0.151 | ROH | V-23 | 58 | MLD, fish, carp |
| 52 | 0.972 ± 1.1 | 1.895 ± 1.5 | 4 | 0.967 | 0.439 | Misc. | V-60 | 59 | Narcosis, tadpoles, 3° |
| 53 | 0.989 ± 0.40 | 0.881 ± 0.49 | 5 | 0.958 | 0.250 | ROH | V-24 | 58 | MLD, goldfish |
| 54 | 0.990 ± 0.15 | 0.939 ± 0.17 | 5 | 0.995 | 0.085 | Misc. | V-61 | 52 | Narcosis, larvae, barnacle |
| 55 | 1.051 ± 0.17 | 0.943 ± 0.21 | 5 | 0.993 | 0.108 | ROH | V-25 | 58 | MLD, fish, goby |
| 56 | 1.051 ± 0.17 | 0.943 ± 0.21 | 5 | 0.993 | 0.108 | ROH | V-26 | 58 | MLD, fish, roach |
| 57 | 1.159 ± 0.45 | 0.975 ± 0.19 | 7 | 0.986 | 0.233 | ROH | V-27 | 60 | $I_{50}$, pancreatic lipase, rat, $2.25 \times 10^{-4}$ *M* substrate |
| 58 | 1.290 ± 1.12 | 1.122 ± 0.58 | 7 | 0.911 | 0.184 | Barbiturates | V-62 | 61 | 50% inhibition, phosphate uptake, brain mitochondria |
| 59 | 1.368 ± 0.14 | 1.060 ± 0.18 | 8 | 0.986 | 0.134 | ROH | V-28 | 62 | $LD_{100}$, cat |
| 60 | 1.546 ± 0.25 | 1.414 ± 0.40 | 6 | 0.980 | 0.214 | Misc. | V-63 | 53 | $I_{100}$, movement 0.5-day-old tadpoles, 18° |
| 61 | 1.625 ± 0.46 | 0.953 ± 0.32 | 5 | 0.984 | 0.318 | $RNH_2 \cdot HCl$ | 21 | 63 | Hemolysis, red cell, dog, 30°, pH 7.1 |
| 62 | 1.912 ± 0.42 | 1.073 ± 0.27 | 4 | 0.997 | 0.139 | $ROSO_3^-Na^+$ | 21 | 64 | Hemolysis, red cell, human, 23–25°, pH 7.2 |
| 63 | 2.349 ± 0.43 | 0.879 ± 0.25 | 5 | 0.988 | 0.252 |  | 21 | 63 | Hemolysis, red cell, dog, 30°, pH 7.1 |
| 64 | 2.941 ± 0.40 | 0.772 ± 0.23 | 4 | 0.995 | 0.120 | $R\overset{+}{N}(CH_3)_3Br^-$ | 21 | 65 | Hemolysis, red cell, bovine, 37° |
| 65 | 2.942 ± 1.3 | 1.170 ± 0.74 | 4 | 0.979 | 0.385 | $R\overset{+}{N}(CH_3)_3Br^-$ | 21 | 65 | Hemolysis, red cell, human, 37° |
| 66 | 4.432 ± 0.53 | 1.118 ± 0.27 | 8 | 0.973 | 0.385 | $(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$ | V-65 | 66 | $I_{50}$, cholinesterase, electric eel, 0.004 *M* substrate |

[a] See *Method* section.

**Table III**—Systems of Intermediate Hydrophobic Sensitivity ($pC = a \log P + b$)

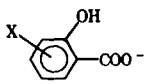
| Equation Number | $b$ | $a$ | $n$ | $r$ | $s$ | Compound | Reference 1[a] | Reference 2 | Type Biological Activity |
|---|---|---|---|---|---|---|---|---|---|
| 67 | −0.589 ± 0.12 | 0.837 ± 0.20 | 4 | 0.997 | 0.053 | ROH | V-29 | 67 | Inhibition, oxygen consumption, kidney, rabbit |
| 68 | −0.456 ± 0.18 | 0.441 ± 0.19 | 9 | 0.901 | 0.218 | ROH | V-30 | 68 | Denaturation, myoglobin, sperm whale, 18° |
| 69 | −0.360 ± 0.11 | 0.434 ± 0.12 | 10 | 0.947 | 0.146 | ROH | V-31 | 68 | Denaturation, α-chymotrypsinogen |
| 70 | −0.168 ± 0.13 | 0.792 ± 0.16 | 16 | 0.946 | 0.190 | Misc. | V-66 | 69 | Precipitation, nucleoprotein, liver, sheep, 40°, 30 min. |
| 71 | −0.143 ± 0.13 | 0.825 ± 0.16 | 16 | 0.947 | 0.194 | Misc. | V-67 | 69 | $I_{100}$, succinate oxidase, muscle, bovine, 40° |
| 72 | −0.110 ± 0.13 | 0.836 ± 0.16 | 16 | 0.947 | 0.194 | Misc. | V-68 | 69 | $I_{100}$, succinate oxidase, liver, sheep, 40° |
| 73 | −0.106 ± 0.23 | 0.785 ± 0.05 | 14 | 0.994 | 0.115 | Phenols | V-72 | 70 | MIC, *M. tuberculosis* |
| 74 | −0.102 ± 0.11 | 0.794 ± 0.19 | 4 | 0.997 | 0.051 | ROH | V-32 | 71 | Increase SH group activity, carboxyhemoglobin, human |
| 75 | −0.076 ± 0.14 | 0.774 ± 0.17 | 17 | 0.931 | 0.206 | Misc. | V-69 | 69 | Precipitation, nucleoprotein, liver, sheep, 40°, 15 min. |
| 76 | −0.003 ± 0.12 | 0.685 ± 0.14 | 15 | 0.943 | 0.158 | ROH | 72 | 73 | Denaturation, DNA, T4-phage |
| 77 | 0.026 ± 0.10 | 0.858 ± 0.11 | 13 | 0.980 | 0.130 | Misc. | V-70 | 69 | $I_{15-20}$, succinate oxidase, muscle, bovine, 40° |
| 78 | 0.061 ± 0.08 | 0.635 ± 0.12 | 9 | 0.980 | 0.085 | ROH | 74 | 75 | Inhibition, *S. aureus* |
| 79 | 0.100 ± 0.15 | 0.826 ± 0.14 | 14 | 0.963 | 0.189 | Misc. | V-71 | 69 | $I_{15-20}$, succinate oxidase, liver, sheep, 40° |
| 80 | 0.158 ± 0.14 | 0.842 ± 0.10 | 7 | 0.994 | 0.114 | ROH | V-33 | 43 | $I_{50}$, oxygen consumption, lung, guinea pig |
| 81 | 0.211 ± 0.32 | 0.844 ± 0.32 | 8 | 0.934 | 0.305 | Misc. | V-73 | 76 | Inhibition, swelling, fibrin |
| 82 | 0.284 ± 0.08 | 0.809 ± 0.04 | 53 | 0.985 | 0.174 | Misc. | V-74 | 77 | Minimum toxic dose, Madison 517 fungus |
| 83 | 0.300 ± 0.86 | 0.810 ± 0.26 | 4 | 0.994 | 0.068 | Hydrocarbons | V-75 | 78 | Narcosis, mouse, vapor |
| 84 | 0.338 ± 0.19 | 0.666 ± 0.14 | 7 | 0.984 | 0.079 | Anilines | V-76 | 79 | Cytochrome P-450 conversion to P-420, liver, rabbit |
| 85 | 0.364 ± 0.19 | 0.571 ± 0.08 | 13 | 0.979 | 0.132 | Phenols | V-77 | 79 | Cytochrome P-450 conversion to P-420, liver, rabbit |
| 86 | 0.431 ± 0.06 | 0.810 ± 0.10 | 6 | 0.996 | 0.047 | ROH | V-34 | 48 | Toxicity, paramecium |
| 87 | 0.451 ± 0.08 | 0.763 ± 0.07 | 5 | 0.999 | 0.048 | ROH | V-35 | 80 | $I_{50}$, generation time, *L. aerogenes* |
| 88 | 0.451 ± 0.06 | 0.412 ± 0.06 | 5 | 0.997 | 0.037 | Amides | 72 | 73 | Denaturation, DNA, T4-phage |
| 89 | 0.488 ± 0.41 | 0.756 ± 0.13 | 9 | 0.983 | 0.148 | Phenols | V-78 | 81 | MIC, *S. aureus* |
| 90 | 0.616 ± 0.88 | 0.690 ± 0.24 | 7 | 0.956 | 0.251 | 4-Hydroxybenzoates | 82 | 83 | MIC, *C. albicans* |
| 91 | 0.825 ± 0.43 | 0.459 ± 0.16 | 13 | 0.886 | 0.207 | Organohalides | V-79 | 77 | Minimum toxic dose, Madison 517 fungus |
| 92 | 0.873 ± 0.22 | 0.666 ± 0.08 | 4 | 0.999 | 0.020 | 4-Hydroxybenzoates | V-50 | 45 | MIC, *K. pneumoniae* |
| 93 | 0.945 ± 0.10 | 0.551 ± 0.09 | 6 | 0.993 | 0.074 | ROH | V-36 | 84 | 10% increase $Ca^{++}$ binding, red cell ghosts |
| 94 | 0.964 ± 0.40 | 0.807 ± 0.41 | 8 | 0.893 | 0.386 | Misc. | V-80 | 76 | Swelling, fibrin |
| 95 | 0.967 ± 0.28 | 0.582 ± 0.12 | 15 | 0.941 | 0.136 | Arylamines | 74[a] | 85 | MIC, *S. typhosa* |
| 96 | 1.000 ± 0.30 | 0.795 ± 0.37 | 5 | 0.970 | 0.189 | ROH | V-37 | 58 | MLD, eel |
| 97 | 1.010 ± 0.27 | 0.788 ± 0.33 | 5 | 0.975 | 0.171 | ROH | V-38 | 58 | MLD, fish, tench |
| 98 | 1.068 ± 0.17 | 0.607 ± 0.10 | 8 | 0.987 | 0.138 | ROH | 36 | 43 | Inhibition, histamine release, guinea pig |
| 99 | 1.076 ± 0.24 | 0.801 ± 0.12 | 19 | 0.960 | 0.171 | Barbiturates | 36 | 86 | $I_{50}$, cell division, egg *Arbacia* |
| 100 | 1.161 ± 0.04 | 0.674 ± 0.01 | 4 | 1.000 | 0.004 | 4-Hydroxybenzoates | V-51 | 45 | MIC, *R. nigricans* |
| 101 | 1.244 ± 0.69 | 0.643 ± 0.14 | 22 | 0.908 | 0.336 | 2-Naphthols | 74 | 87 | MIC, *S. aureus* |
| 102 | 1.342 ± 0.58 | 0.668 ± 0.14 | 10 | 0.966 | 0.262 | Phenyl methacrylates | 74 | 88 | MIC, *S. aureus* |
| 103 | 1.366 ± 0.71 | 0.527 ± 0.12 | 22 | 0.890 | 0.504 | Ethylenediamines | V-81 | 89 | MIC, *T. mentagrophytes*, 37° |
| 104 | 1.415 ± 0.69 | 0.440 ± 0.21 | 6 | 0.946 | 0.315 | $RCHBrCOO^-$ | V-86 | 90 | Bactericidal, *M. ovalis*, 37°, pH 7.5 |
| 105 | 1.451 ± 0.72 | 0.551 ± 0.22 | 6 | 0.961 | 0.331 | $RCHBrCOO^-$ | V-87 | 90 | Bactericidal, *B. diphtheriae*, 37°, pH 8.5 |
| 106 | 1.492 ± 0.08 | 0.508 ± 0.06 | 49 | 0.928 | 0.204 |  | 91[b] | 91 | Fibrinolysis, hanging clot, pH 7.4 |
| 107 | 1.512 ± 0.33 | 0.713 ± 0.13 | 17 | 0.950 | 0.160 | Misc. | 92 | 92 | 1:1 binding to hemoglobin, $3.7 \times 10^{-5}$ *M* |
| 108 | 1.530 ± 0.45 | 0.617 ± 0.11 | 10 | 0.976 | 0.204 | Phenyl methacrylates | 74 | 88 | MIC, *B. subtilis* |
| 109 | 1.547 ± 0.60 | 0.458 ± 0.11 | 20 | 0.903 | 0.395 | Ethylenediamines | V-103 | 89 | MIC, *S. aureus*, 37° |
| 110 | 1.551 ± 0.26 | 0.708 ± 0.10 | 4 | 0.999 | 0.025 | 4-Hydroxybenzoates | V-52 | 45 | MIC, *T. mentagrophytes* |
| 111 | 1.551 ± 0.26 | 0.708 ± 0.10 | 4 | 0.999 | 0.025 | 4-Hydroxybenzoates | V-53 | 45 | MIC, *T. rubrum* |
| 112 | 1.584 ± 0.46 | 0.582 ± 0.16 | 15 | 0.903 | 0.210 | Benzimidazoles | 93 | 94 | $I_{75}$, influenza B virus, 35° |
| 113 | 1.689 ± 0.24 | 0.694 ± 0.13 | 10 | 0.976 | 0.325 | $ROSO_3^-Na^+$ | 21 | 114 | MIC, *S. aureus* |
| 114 | 1.715 ± 0.69 | 0.440 ± 0.21 | 6 | 0.946 | 0.315 | $RCHBrCOO^-$ | V-88 | 90 | Bactericidal, *M. ovalis*, 37°, pH 7.5 |
| 115 | 1.753 ± 0.72 | 0.551 ± 0.22 | 6 | 0.962 | 0.329 | $RCHBrCOO^-$ | V-89 | 90 | Bactericidal, *B. diphtheriae*, 37°, pH 7.5 |
| 116 | 1.932 ± 0.28 | 0.778 ± 0.14 | 22 | 0.928 | 0.225 | $X\text{-}C_6H_4OCH_2COO^-$ | 95[c] | 95 | Inhibition, cell elongation, *Avena coleoptile*, pH 4.5 |

**Table III**—(*Continued*)

| Equation Number | *b* | *a* | *n* | *r* | *s* | Compound | Reference 1[a] | Reference 2 | Type Biological Activity |
|---|---|---|---|---|---|---|---|---|---|
| 117 | 1.953 ± 0.30 | 0.640 ± 0.14 | 16 | 0.933 | 0.110 | Misc. | 72 | 72 | 3:1 binding by bovine serum albumin, 4°, $2.5 \times 10^{-5}$ *M* |
| 118 | 2.138 ± 0.21 | 0.646 ± 0.09 | 20 | 0.959 | 0.098 | Misc. | 72 | 72 | 2:1 binding by bovine serum albumin, 4°, $2.5 \times 10^{-5}$ *M* |
| 119 | 2.179 ± 0.39 | 0.410 ± 0.20 | 12 | 0.825 | 0.146 | Barbiturates | V-91 | 96 | $LD_{50}$, mouse |
| 120 | 2.248 ± 0.57 | 0.670 ± 0.27 | 6 | 0.961 | 0.401 | $RCHOHCOO^-$ | V-94 | 97 | Bactericidal, *D. pneumoniae*, 37°, pH 8.5 |
| 121 | 2.271 ± 0.15 | 0.760 ± 0.07 | 42 | 0.958 | 0.162 | Misc. | 72 | 72 | 1:1 binding by bovine serum albumin, 4°, $2.5 \times 10^{-5}$ *M* |
| 122 | 2.301 ± 0.43 | 0.653 ± 0.23 | 14 | 0.871 | 0.152 | Barbiturates | V-95 | 98 | MED, hypnosis, rat |
| 123 | 2.382 ± 0.37 | 0.544 ± 0.22 | 10 | 0.892 | 0.138 | Barbiturates | V-93 | 99 | $ED_{50}$, hypnosis, mouse |
| 124 | 2.418 ± 0.12 | 0.546 ± 0.09 | 23 | 0.943 | 0.116 | Ureas | V-96 | 100 | MED, hypnosis, mouse |
| 125 | 2.789 ± 0.57 | 0.462 ± 0.15 | 6 | 0.974 | 0.060 | Phenyl thiocyanates | 82 | 101 | $I_{50}$, *P. cyclopium* |
| 126 | 2.863 ± 0.07 | 0.618 ± 0.13 | 5 | 0.993 | 0.048 | ROH | V-39 | 102 | $LD_{50}$, grain weevil, vapor, 25° |
| 127 | 2.906 ± 0.15 | 0.684 ± 0.26 | 4 | 0.992 | 0.051 | Ketones | V-97 | 102 | $LD_{50}$, grain weevil, vapor, 25° |
| 128 | 3.038 ± 0.09 | 0.681 ± 0.10 | 14 | 0.972 | 0.101 | ROH | V-40 | 103 | Toxicity of vapor, tomato plant |
| 129 | 3.164 ± 0.08 | 0.668 ± 0.09 | 14 | 0.978 | 0.087 | ROH | V-41 | 103 | Toxicity of vapor, red spider |
| 130 | 3.247 ± 0.16 | 0.823 ± 0.16 | 12 | 0.962 | 0.193 | Misc. | V-98 | 104 | MLD, South African toad |
| 131 | 3.283 ± 0.59 | 0.545 ± 0.17 | 13 | 0.901 | 0.147 | Benzyl isothiocyanates | 82 | 101 | $I_{50}$, *A. niger* |
| 132 | 3.406 ± 0.25 | 0.643 ± 0.09 | 7 | 0.993 | 0.089 | $R\overset{+}{N}(CH_3)_3$ | V-64 | 66 | $I_{50}$, cholinesterase, plasma, human, 0.06 *M* substrate |
| 133 | 3.645 ± 0.54 | 0.628 ± 0.26 | 6 | 0.959 | 0.138 | $RCOO^-$ | V-99 | 105 | MIC, *E. coli*, 37.5° |
| 134 | 3.694 ± 0.26 | 0.749 ± 0.15 | 19 | 0.931 | 0.322 | ROH | V-42 | 106 | $I_{25}$, esterase, liver, sheep, 0.04 *M* substrate |
| 135 | 4.082 ± 0.31 | 0.454 ± 0.09 | 7 | 0.985 | 0.094 | $R\overset{+}{N}(CH_3)_3$ | V-100 | 66 | $I_{50}$, cholinesterase, electric eel, 0.004 *M* substrate |
| 136 | 4.149 ± 0.35 | 0.497 ± 0.15 | 8 | 0.957 | 0.222 | Pyrimidines | 82 | 107 | $I_{50}$, *C. albicans* |
| 137 | 4.503 ± 0.40 | 0.607 ± 0.19 | 7 | 0.964 | 0.199 | $(CH_3)_3\overset{+}{N}(CH_2)_n\overset{+}{N}(CH_3)_3$ | V-101 | 66 | $I_{50}$, cholinesterase, plasma, human, 0.004 *M* substrate |

[a] Equation as reported in *Reference 74* contained a systematic error of 3 log units; therefore, intercepts are 3 units higher than in *Reference 74*. [b] Equation as reported in *Reference 91* was in terms of log *P* of neutral acids; log *P*'s for Eq. 106 are based on log *P* for salicylic acid measured at pH 7.20. [c] Equation as reported in *Reference 95* was in terms of $\pi$ values and was converted to log *P* by using log *P* = 1.26 for phenoxyacetic acid.

from $10^8$ to $10^6$ ohms/cm.[2] in the resistance of the synthetic lipid bilayer. No doubt, with the glass beads and the BLM, changes in the system could be made so that equations identical to Eq. 8 could be formulated; that is, changes in the size of the glass beads or the degree of disaggregation would very likely have little or no effect on the slope of the linear free-energy relationship. However, such changes would affect the sensitivity of the system and, in this way, the intercept could be manipulated. The same is true for the BLM. By changing the degree of resistance measured by organic compounds acting on the BLM or by adding impurities such as protein, one could obtain equations with considerable variation in intercept. In this fashion, one could build model systems to yield equations matching those of Table II and, possibly, Tables III and IV in slope and intercept. Thus, the perturbation of the synthetic and natural systems with ever more complex sets of congeners provides, through the common measure of octanol/water partition coefficients, a sensitive measure of the similarity of the synthetic and natural systems. This could provide very useful guidance in developing synthetic membranes.

The analogy of the disruption of glass beads with membrane disruption is not so farfetched as it at first might seem. Many kinds of membranes are made up of "elementary particles" (23) which are rather large in molecular terms.

The variation in the intercept with the demand placed on the system is well illustrated with work on the lobster axon (Eqs. 18 and 19). Here a −5-mv. change in the rest potential of the axon yields an equation with intercept identical with that for hemolysis of Eq. 8. Measuring the amount of alcohol necessary to cause a −10-mv. change results in a lower intercept, representing a one-third increase in the alcohol concentration.

Another example of variation of intercept with the demand placed upon the system is Eq. 22 correlating the 50% inhibition of oxygen consumption by red cells. The intercept of this equation is about 0.2 higher than Eq. 8 for hemolysis, although the slopes of the equations are identical. The same result is apparent in Eqs. 29 and 34 for the $I_{50}$ and $I_{30}$ equations for paramecium motility. Although the systems are somewhat different, the difference between Eq. 28 for the $I_{100}$ of rabbit gut and Eq. 41 for the $I_{50}$ of guinea pig ileum is of the expected size and direction. The difference between intercepts for the $I_{100}$ of frog heart (Eq. 23) and the $I_{50}$ of tortoise heart (Eq. 33) is about 0.4. Again this is in the right direction and of reasonable size.

Greatly different systems can be compared through the medium of log *P*. For example, comparison of the intercepts of Eqs. 16 and 59 indicates that cats are almost 100 times more easily killed by alcohols than are yeast cells. This may be a reflection of the relative stability of the membranes of yeast cells and those of the CNS of the cat. Other factors are, of course, also involved.

The intrinsic pharmacophoric function in a set of congeners plays an important role in setting the value

Table IV—Hydrophobically Insensitive Linear Free-Energy Relationships ($pC = a \log P + b$)

| Equation Number | $b$ | $a$ | $n$ | $r$ | $s$ | Compound | Reference 1[a] | Reference 2 | Type Biological Activity |
|---|---|---|---|---|---|---|---|---|---|
| 138 | −0.729 ± 0.14 | 0.224 ± 0.15 | 7 | 0.865 | 0.129 | ROH | V-43 | 68 | Denaturation, Cytochrome C VI, horse heart |
| 139 | 1.568 ● 0.25 | 0.328 ± 0.12 | 5 | 0.980 | 0.054 | RCHO | V-102 | 77 | Minimum toxic dose, Madison 517 fungus |
| 140 | 1.742 ± 0.57 | 0.342 ± 0.10 | 19 | 0.862 | 0.399 | Ethylenediamines | V-82 | 89 | MIC, *C. albicans*, 37° |
| 141 | 1.919 ± 0.52 | 0.288 ± 0.10 | 17 | 0.852 | 0.323 | Ethylenediamines | V-83 | 89 | MIC, *S. sonnei*, 37° |
| 142 | 2.232 ± 0.43 | 0.208 ± 0.08 | 16 | 0.845 | 0.314 | Ethylenediamines | V-85 | 89 | MIC, *E. coli*, 37° |
| 143 | 2.290 ± 0.14 | 0.316 ± 0.09 | 10 | 0.947 | 0.053 | Barbiturates | V-92 | 99 | $LD_{50}$, mouse |
| 144 | 2.415 ± 0.69 | 0.370 ± 0.21 | 6 | 0.926 | 0.316 | $RCHBrCO_2^-$ | V-90 | 90 | Bactericidal, *M. ovalis*, 37°, pH 6.0 |
| 145 | 2.428 ± 0.58 | 0.388 ± 0.11 | 17 | 0.894 | 0.429 | Ethylenediamines | V-84 | 89 | MIC, *V. metchnikovi*, 37° |
| 146 | 2.552 ± 0.23 | 0.332 ± 0.08 | 17 | 0.918 | 0.144 | Imidazolin-2-ones | 108 | 109 | $I_{50}$, motor activity, mouse |
| 147 | 2.721 ± 0.33 | 0.161 ± 0.08 | 10 | 0.849 | 0.148 | Phenyl methacrylates | 74 | 88 | Inhibition, *S. lutea* |

[a] See *Method* section.

of the intercept. The examples at the beginning of Table II are for neutral compounds, mostly alcohols. Also at the beginning are the synthetic systems, as well as those natural systems upon which rather drastic demands have been placed. The equations on the charged molecules toward the end of Table II have intercepts several orders of magnitude higher, indicating the specific role played by charge. An in between example is that of inhibition of bacterial luminescence. Equation 25 of intercept 0.21 correlates the effect of alcohols on this process, and Eq. 45 of intercept 0.71 correlates the effect of carbamates on luminescence. The carbamates are 3 times as potent.

The rather drastic biological response of protoplast lysis (Eq. 14) and the killing of yeast cells (Eq. 16) give correlations with low intercepts (−0.4). These equations are strikingly similar to the linear free-energy equations correlating the synthetic BLM and glass bead systems.

A great deal of work has been done with tadpoles. Part of this work was done in an effort to see if narcotic response is a function of age (Eqs. 38, 40, 43, 47, 50, and 60). Except for Eq. 60, the intercepts fall in the range of 0.6–1.0. However, for the 0.5-day-old tadpoles (Eq. 60), the intercept of 1.5 indicates that these very young organisms are more sensitive to narcosis.

The mean slope for the seven equations correlating tadpole narcosis (omitting the poor low temperature correlation of Eq. 52) is 1.12. The slope of Eq. 12 for the BLM is 1.16. Thus, in this sense, the BLM is a good model for the membranes of a living system, assuming that it is membrane perturbation in tadpoles which causes the narcosis. However, the difference in intercepts indicates that the BLM is 20–30 times as resistant to perturbation (as defined by the $10^8$–$10^6$ ohms/cm.$^2$ change in resistance) as the tadpoles.

Equation 39 correlates a diverse set of molecules which cause an abnormal kind of mitosis resembling that caused by colchicine. The role of hydrophobic forces in causing this kind of abnormal mitotic activity is closely related to that inhibiting tortoise heart, guinea pig ileum, tadpoles, *etc.*

The mean value and standard deviation for the slopes in Table II are 1.01 ± 0.13. These values are for 57 examples; the unusual result at the low temperature (Eq. 52) was excluded. With the exception of Eq. 66 involving enzymes and Eqs. 10 and 13 for glass beads, one might postulate that in all of these examples the ultimate biological response is the result of membrane perturbation. The mean slope is close to that of Eq. 8.

## SYSTEMS OF INTERMEDIATE HYDROPHOBIC SENSITIVITY

The equations of Table III have slopes in the range of 0.40–0.85. For the 71 examples, a mean value with standard deviation of 0.66 ± 0.12 is found. While this slope is significantly different from the mean of 1.01 found for the examples in Table II, there are borderline examples which could be placed in Table II. For example, Eqs. 67, 71, 72, 77, 81, 86, 94, and 130 involve processes quite similar to those of Table II, and many of these slopes are close to 0.85. Small differences in slopes cannot be taken seriously. One must also not overlook the 95% confidence intervals associated with these figures.

Table III contains a much more heterogeneous group of systems and a wider variety of drugs. One obvious difference between the systems of Tables II and III is that only one correlation with bacteria (Eq. 15) or fungi is found in Table II while a good many are found in Table III, even though it seems likely that many of the examples of inhibition of bacteria may be caused by nonspecific membrane perturbation. There are two important differences between the membranes of red cells and nerves in Table II and the bacteria of Table III. The red cells and nerves have membranes with much higher lipid content and are less rigid than the bacterial cell wall. Simple lipid content alone does not seem to account for the difference. For example, all equations on yeast (*S. cerevisiae*) fall in Table II. Although the structure of this yeast cell wall is not well understood, the lipid content seems to fall between 8 and 13% (24). This is about midway between that found for Gram-positive and Gram-negative cells, equations for which fall in Table III. Thus, these yeast cells resemble red cells or nerve cells rather than fungi or bacteria in their sensitivity to lipophilic compounds. The very close agreement between Eqs. 16 and 17 for rupture of yeast cells and Eq. 8 for hemolysis of red cells is striking. The equation for inhibition of yeast cells (Eq. 24) is close to Eq. 22 for the $I_{50}$ of oxygen consumption by red cells.

**Table V**—Data for Tables II–IV

| Alcohol | log *P* | V-1 pC Obs. | V-2 pC Obs. | V-3 pC Obs. | V-4 pC Obs. | V-5 pC Obs. | V-6 pC Obs. | V-7 pC Obs. | V-8 pC Obs. | V-9 pC Obs. | V-10 pC Obs. | V-11 pC Obs. | V-12 pC Obs. | V-13 pC Obs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Methyl | −0.66 | — | −1.39 | — | — | −1.03 | −1.05 | −0.75 | −0.60 | — | −0.38 | — | −0.30 | −0.40 |
| Ethyl* | −0.16 | — | −1.03 | −0.60 | −0.48 | −0.75 | −0.68 | −0.37 | −0.26 | — | −0.11 | — | 0.00 | 0.10 |
| Propyl | 0.34 | — | −0.50 | −0.07 | −0.15 | −0.22 | −0.11 | −0.08 | 0.09 | 0.52 | 0.57 | 0.66 | — | 0.70 |
| Isopropyl* | 0.14 | — | — | — | — | — | — | — | — | 0.15 | — | 0.45 | — | — |
| Butyl | 0.88 | — | 0.11 | 0.62 | 0.52 | 0.41 | — | 0.50 | 0.62 | 1.10 | 0.96 | 1.17 | 1.22 | 1.25 |
| Pentyl | 1.40 | 0.53 | — | — | 1.00 | — | — | 1.06 | 1.12 | 1.82 | 1.55 | 1.68 | 1.70 | 1.73 |
| Hexyl | 2.03 | — | — | — | 1.55 | — | — | — | — | — | — | — | — | — |
| Heptyl* | 2.53 | 1.59 | — | — | 2.27 | — | — | — | — | 3.00 | — | — | — | — |
| Octyl* | 3.03 | 2.18 | — | — | 3.42 | — | — | — | — | 3.70 | — | — | — | — |
| Isobutyl | 0.65 | — | — | — | — | — | 0.28 | — | — | — | 0.96 | — | — | — |
| *sec*-Butyl | 0.61 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| *tert*-Butyl | 0.37 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Isopentyl | 1.16 | — | — | — | — | — | 0.85 | — | — | — | — | — | 1.52 | — |
| *tert*-Pentyl | 0.89 | — | — | — | — | — | — | — | — | 0.95 | — | 1.09 | 1.10 | — |
| Decyl* | 4.03 | 3.09 | — | — | — | — | — | — | — | 5.18 | — | — | — | — |
| Undecyl* | 4.53 | — | — | — | — | — | — | — | — | 5.65 | — | — | — | — |
| Menthol* | 3.03 | — | — | — | — | — | — | — | — | — | — | 3.29 | — | — |
| Thymol | 3.30 | — | — | — | — | — | — | — | — | — | — | 3.66 | — | — |
| 2-Naphthol | 2.84 | — | — | — | — | — | — | — | — | — | — | 3.52 | — | — |
| Benzyl | 1.10 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Ethylene glycol | −1.93 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Propylene glycol* | −1.43 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 3-Pentyl* | 1.16 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| *sec*-Pentyl* | 1.16 | — | — | 1.10 | — | — | — | — | — | — | — | — | — | — |
| 2-Methylbutyl* | 1.16 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Nonyl* | 3.53 | 2.76 | — | — | — | — | — | — | — | — | — | — | — | — |
| 1,2-Dimethyl-propyl* | 0.91 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1-Methyl-3-phenylpropyl* | 2.18 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1-Phenylethyl | 1.36 | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 1-Phenylpropyl | 1.88 | — | — | — | — | — | — | — | — | — | — | — | — | — |

| Alcohol | V-14 pC Obs. | V-15 pC Obs. | V-16 pC Obs. | V-17 pC Obs. | V-18 pC Obs. | V-19 pC Obs. | V-20 pC Obs. | V-21 pC Obs. | V-22 pC Obs. | V-23 pC Obs. | V-24 pC Obs. | V-25 pC Obs. | V-26 pC Obs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Methyl | −0.30 | −0.03 | −0.09 | −0.14 | −0.20 | −0.14 | 0.09 | −0.04 | 0.00 | 0.49 | 0.65 | 0.52 | 0.52 |
| Ethyl* | 0.00 | 0.28 | 0.24 | 0.28 | 0.21 | 0.28 | 0.32 | 0.39 | 0.46 | 0.65 | 0.53 | 0.77 | 0.77 |
| Propyl | 0.78 | 0.72 | 0.92 | 0.79 | 0.98 | 0.98 | 0.83 | 0.97 | 1.03 | 1.33 | 1.33 | 1.34 | 1.34 |
| Isopropyl* | 0.60 | 0.63 | 0.68 | 0.92 | — | — | — | — | — | — | — | — | — |
| Butyl | 1.40 | 1.39 | 1.27 | 1.46 | 1.72 | 1.67 | 1.57 | 1.63 | 1.66 | 1.67 | 1.67 | 1.97 | 1.97 |
| Pentyl | — | — | — | 1.84 | — | — | 2.05 | — | 2.38 | 2.35 | 2.35 | 2.35 | 2.35 |
| Hexyl | — | — | — | 2.41 | 3.17 | 2.99 | 2.60 | 2.99 | — | — | — | — | — |
| Heptyl* | — | — | — | 3.02 | 3.70 | 3.57 | 3.15 | 3.55 | 3.46 | — | — | — | — |
| Octyl* | — | — | — | 3.62 | 4.12 | 3.97 | 3.60 | 3.93 | — | — | — | — | — |
| Isobutyl | 1.10 | 1.32 | 1.37 | 1.54 | — | — | — | — | — | — | — | — | — |
| *sec*-Butyl | 1.00 | 1.21 | — | 1.16 | — | — | — | — | — | — | — | — | — |
| *tert*-Butyl | 0.70 | 0.84 | — | 0.98 | — | — | — | — | — | — | — | — | — |
| Isopentyl | — | 1.77 | — | 1.86 | 2.18 | 2.09 | — | 2.00 | — | — | — | — | — |
| *tert*-Pentyl | — | 1.15 | — | 1.34 | — | — | — | — | — | — | — | — | — |
| Benzyl | 2.12[a] | — | — | 2.15[b] | — | — | — | — | — | — | — | — | — |

| Alcohol | V-27 pC Obs. | V-28 pC Obs. | V-29 pC Obs. | V-30 pC Obs. | V-31 pC Obs. | V-32 pC Obs. | V-33 pC Obs. | V-34 pC Obs. | V-35 pC Obs. | V-36 pC Obs. | V-37 pC Obs. | V-38 pC Obs. | V-39 pC Obs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Methyl | — | 0.84 | −1.10 | −1.09 | −0.86 | −0.66 | −0.40 | −0.08 | −0.01 | 0.59 | 0.65 | 0.65 | 2.50 |
| Ethyl* | — | 1.07 | −0.77 | −0.72 | −0.58 | −0.20 | −0.12 | 0.24 | 0.26 | 0.89 | 0.61 | 0.65 | 2.73 |
| Propyl | 1.45 | 1.57 | −0.33 | −0.30 | −0.20 | 0.21 | 0.53 | 0.70 | 0.72 | 1.02 | 1.33 | 1.33 | 3.08 |
| Isopropyl* | — | 1.48 | — | −0.53 | −0.42 | — | — | 0.57 | — | — | — | — | 2.90 |
| Butyl | 1.83 | 2.48 | 0.18 | 0.10 | 0.15 | 0.56 | 0.92 | 1.11 | 1.14 | 1.52 | 1.67 | 1.67 | 3.44 |
| Pentyl | 2.57 | 2.85 | — | — | — | — | 1.46 | — | — | 1.70 | 2.17 | 2.17 | — |
| Hexyl | 3.13 | — | — | — | — | — | 1.92 | — | 2.00 | 2.06 | — | — | — |
| Heptyl* | 3.88 | — | — | — | — | — | 2.15 | — | — | — | — | — | — |
| Octyl* | 4.37 | — | — | — | — | — | — | — | — | — | — | — | — |
| Isobutyl | — | 2.01 | — | 0.10 | 0.10 | — | — | 1.01 | — | — | — | — | — |
| *sec*-Butyl | — | — | — | — | −0.04 | — | — | — | — | — | — | — | — |
| *tert*-Butyl | — | — | — | −0.38 | −0.30 | — | — | — | — | — | — | — | — |
| Isopentyl | — | 2.62 | — | — | — | — | — | — | — | — | — | — | — |
| *tert*-Pentyl | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Decyl* | 4.77 | — | — | — | — | — | — | — | — | — | — | — | — |
| Benzyl | — | 2.24[c] | — | — | — | — | — | — | — | — | — | — | — |
| Ethylene glycol | — | — | — | −1.15 | −1.04 | — | — | — | — | — | — | — | — |
| Propylene glycol* | — | — | — | −0.93 | −0.93 | — | — | — | — | — | — | — | — |

(*Continued*)

**Table V—(*Continued*)**

| Alcohol | V-40 pC Obs. | V-41 pC Obs. | V-42 pC Obs. | V-43 pC Obs. |
|---|---|---|---|---|
| Methyl | 2.60 | 2.80 | 3.36 | −1.09 |
| Ethyl* | 2.76 | 3.00 | 3.85 | −0.87 |
| Propyl | 3.33 | 3.32 | 4.28 | −0.60 |
| *sec*-Propyl* | 3.18 | 3.26 | — | −0.66 |
| Butyl | 3.69 | 3.77 | 4.43 | — |
| Pentyl | 4.05 | 4.09 | 5.05 | — |
| Hexyl | — | — | 5.31 | — |
| Heptyl* | — | — | 5.74 | — |
| Octyl* | — | — | 6.05 | — |
| Isobutyl | 3.57 | 3.72 | — | — |
| *sec*-Butyl | 3.46 | 3.62 | 3.64 | — |
| *tert*-Butyl | 3.41 | 3.28 | — | −0.56 |
| Isopentyl | 3.95 | 4.09 | 4.77 | — |
| *tert*-Pentyl | 3.51 | 3.75 | 3.50 | — |
| Ethylene glycol | — | — | — | −1.14 |
| Propylene glycol* | — | — | — | −0.93 |
| 3-Pentyl* | 3.69 | 3.81 | 4.26 | — |
| *sec*-Pentyl* | 3.77 | 3.90 | 4.40 | — |
| 2-Methylbutyl* | 3.77 | 3.96 | 4.70 | — |
| Nonyl* | — | — | 6.30 | — |
| 1,2-Dimethylpropyl* | — | — | 4.08 | — |
| 1-Methyl-3-phenylpropyl* | — | — | 5.55 | — |
| 1-Phenylethyl | — | — | 4.97 | — |
| 1-Phenylpropyl | — | — | 5.35 | — |

| V-44 | | | V-45 | | | V-46 | | |
|---|---|---|---|---|---|---|---|---|
| | log *P* | pC Obs. | | log *P* | pC Obs. | | log *P* | pC Obs. |
| Acetone | −0.24 | −0.71 | Methyl alcohol | −0.66 | −1.03 | Methyl alcohol | −0.66 | −0.89 |
| 2-Butanone | 0.29 | −0.30 | Ethyl alcohol* | −0.16 | −0.69 | Ethyl alcohol* | −0.16 | −0.60 |
| 2-Pentanone* | 0.79 | 0.20 | Propyl alcohol | 0.34 | −0.18 | Propyl alcohol | 0.34 | 0.00 |
| 3-Pentanone* | 0.79 | 0.24 | Butyl alcohol | 0.88 | 0.35 | Butyl alcohol | 0.88 | 0.46 |
| Methyl alcohol | −0.66 | −1.10 | Pentyl alcohol | 1.40 | 0.89 | Pentyl alcohol | 1.40 | 0.94 |
| Ethyl alcohol* | −0.16 | −0.77 | Hexyl alcohol | 2.03 | 1.41 | Hexyl alcohol | 2.03 | 1.52 |
| Propyl alcohol | 0.34 | −0.33 | Heptyl alcohol* | 2.53 | 1.92 | Heptyl alcohol* | 2.53 | 1.95 |
| Butyl alcohol | 0.88 | 0.18 | Octyl alcohol* | 3.03 | 2.47 | Cyclohexyl alcohol | 1.23 | 0.92 |
| | | | Cyclohexyl alcohol | 1.23 | 0.75 | Acetone | −0.24 | −0.37 |
| | | | Acetone | −0.24 | −0.59 | 2-Butanone | 0.29 | 0.15 |
| | | | 2-Butanone | 0.29 | −0.10 | 2-Pentanone* | 0.79 | 0.59 |
| | | | 2-Pentanone* | 0.79 | 0.41 | | | |

| V-47 | | | V-48 | | | | V-49 | V-50 | V-51 | V-52 | V-53 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | log *P* | pC Obs. | | log *P* | pC Obs. | | log *P* | pC Obs. | pC Obs. | pC Obs. | pC Obs. | pC Obs. |
| Resorcinol | 0.80 | 0.67 | Methyl alcohol | −0.66 | −0.70 | Methyl *p*-hydroxybenzoate | 1.96 | 2.18 | 2.18 | 2.48 | 2.92 | 2.92 |
| Phenol | 1.46 | 1.25 | Ethyl alcohol* | −0.16 | −0.20 | Ethyl *p*-hydroxybenzoate* | 2.46 | 2.52 | 2.52 | 2.82 | 3.32 | 3.32 |
| 2-Methylphenol | 1.95 | 1.60 | Propyl alcohol | 0.34 | 0.10 | Propyl *p*-hydroxybenzoate* | 2.96 | 3.16 | 2.82 | 3.16 | 3.65 | 3.65 |
| 3-Methylphenol | 1.96 | 1.60 | Butyl alcohol | 0.88 | 0.82 | Butyl *p*-hydroxybenzoate* | 3.46 | 3.49 | 3.19 | 3.49 | 3.99 | 3.99 |
| 4-Methylphenol | 1.94 | 1.60 | Pentyl alcohol | 1.40 | 1.35 | | | | | | | |
| Thymol | 3.30 | 2.85 | Methylal* | −0.16 | 0.22 | | | | | | | |
| | | | Acetal* | 1.14 | 0.85 | | | | | | | |
| | | | Acetone | −0.24 | 0.05 | | | | | | | |
| | | | 2-Pentanone* | 0.79 | 0.77 | | | | | | | |
| | | | Acetophenone | 1.58 | 1.85 | | | | | | | |
| | | | Acetonitrile | −0.34 | 0.07 | | | | | | | |
| | | | Propionitrile* | 0.16 | 0.44 | | | | | | | |
| | | | Valeronitrile* | 1.16 | 1.22 | | | | | | | |
| | | | Thymol | 3.30 | 3.15 | | | | | | | |

| V-54 | | | V-55 | | | V-56 | | |
|---|---|---|---|---|---|---|---|---|
| | log *P* | pC Obs. | | log *P* | pC Obs. | | log *P* | pC Obs. |
| Ethyl alcohol* | −0.16 | 0.15 | Methyl alcohol | −0.66 | −0.40 | Ethyl alcohol* | −0.16 | 0.48 |
| Pentyl alcohol | 1.40 | 2.27 | Ethyl alcohol* | −0.16 | −0.01 | Propyl alcohol | 0.34 | 0.95 |
| Octyl alcohol* | 3.03 | 3.80 | Propyl alcohol | 0.34 | 0.47 | Butyl alcohol | 0.88 | 1.52 |
| Ethyl carbamate | −0.15 | 0.55 | Isopropyl alcohol | 0.14 | 0.41 | Valeramide* | 0.29 | 1.15 |
| | | | Butyl alcohol | 0.88 | 1.06 | Ethyl ether | 0.77 | 1.62 |
| | | | Pentyl alcohol | 1.40 | 1.64 | Benzamide | 0.64 | 1.88 |
| | | | Octyl alcohol* | 3.03 | 3.00 | Salicylamide | 1.28 | 2.48 |
| | | | Ethyl acetate | 0.73 | 0.89 | *o*-Nitroaniline | 1.83 | 2.60 |
| | | | Ethyl propionate* | 1.23 | 1.41 | Chloroform | 1.97 | 4.09 |
| | | | Ethyl butyrate* | 1.73 | 1.89 | Thymol | 3.30 | 4.33 |
| | | | Ethyl nitrate* | 1.15 | 1.29 | Antipyrine | 0.23 | 1.15 |
| | | | Ethyl valerate* | 2.23 | 3.00 | Aminopyrine | 0.80 | 1.52 |

Table V—(*Continued*)

| V-54 | | | V-55 | | | V-56 | | |
|---|---|---|---|---|---|---|---|---|
| | log *P* | p*C* Obs. | | log *P* | p*C* Obs. | | log *P* | p*C* Obs. |
| | | | Ethyl carbamate | −0.15 | 0.47 | Phenobarbital | 1.42 | 2.09 |
| | | | Methyl carbamate* | −0.65 | 0.18 | Carbon disulfide[d] | 2.00 | 3.30 |
| | | | Benzene | 2.13 | 2.28 | | | |
| | | | Toluene | 2.69 | 2.29 | | | |
| | | | Nitromethane | −0.33 | 0.36 | | | |
| | | | Acetonitrile | −0.34 | 0.02 | | | |
| | | | Carbon tetrachloride[d] | 2.64 | 2.59 | | | |
| | | | Acetanilide | 1.16 | 1.68 | | | |

| V-57 | | | V-58 | | | V-59 | | | V-60 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | log *P* | p*C* Obs. | | log *P* | p*C* Obs. | | log *P* | p*C* Obs. | | log *P* | p*C* Obs. |
| Ethyl acetate | 0.73 | 1.43 | Chloroform | 1.97 | 3.23 | Ethyl acetate | 0.73 | 1.52 | Salicylamide | 1.28 | 3.11 |
| Ethyl propionate* | 1.23 | 2.12 | Chloretone | 2.03 | 2.89 | Ethyl propionate* | 1.23 | 2.11 | Benzamide | 0.64 | 2.70 |
| Ethyl butyrate* | 1.73 | 2.57 | Ethyl ether | 0.77 | 1.85 | Ethyl butyrate* | 1.73 | 2.55 | Ethyl alcohol* | −0.16 | 0.48 |
| Ethyl valerate* | 2.23 | 2.99 | Amobarbital | 2.07 | 3.34 | Ethyl valerate* | 2.23 | 2.89 | Acetone | −0.24 | 0.48 |
| | | | Ethyl carbamate | −0.15 | 0.85 | | | | | | |
| | | | Ethyl alcohol* | −0.16 | 0.18 | | | | | | |
| | | | Octyl alcohol* | 3.03 | 3.89 | | | | | | |

| V-61 | | | V-62 | | | | | V-63 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | log *P* | p*C* Obs. | R | R′ | R″ | log *P* | p*C* Obs. | | log *P* | p*C* Obs. |
| Acetone | −0.24 | 0.68 | H | Ethyl | 2-Pentyl | 2.07 | 3.67 | Nitromethane | −0.33 | 0.85 |
| 2-Butanone | 0.29 | 1.26 | H | Allyl | 2-Pentyl | 2.15 | 3.88 | Methyl carbamate* | −0.65 | 0.59 |
| 3-Pentanone* | 0.79 | 1.71 | H | Ethyl | Isopentyl* | 2.07 | 3.38 | Ethyl carbamate | −0.15 | 1.46 |
| 2-Heptanone* | 1.79 | 2.66 | H | Ethyl | 1,3-Dimethylbutyl* | 2.25 | 3.93 | Propyl carbamate* | 0.35 | 8.33 |
| Propionitrile* | 0.16 | 1.26 | Methyl | Methyl | Cyclohex-1-ene | 1.47 | 3.02 | Isobutyl carbamate* | 0.65 | 2.49 |
| | | | H | Ethyl | Butyl | 1.89 | 3.17 | Isopentyl carbamate* | 1.15 | 3.00 |
| | | | H | Ethyl | Phenyl | 1.42 | 2.93 | | | |

| V-64 | | | V-65 | | |
|---|---|---|---|---|---|
| $R-\overset{+}{N}(CH_3)_3$ R | log *P* | p*C* Obs. | $(CH_3)_3\overset{+}{N}-(CH_2)_n-\overset{+}{N}(CH_3)_3$ *n* | log *P* | p*C* Obs. |
| Ethyl* | −4.22 | 0.75 | 4* | −3.34 | 1.05 |
| Propyl* | −3.72 | 0.95 | 5* | −2.84 | 1.25 |
| Butyl* | −3.22 | 1.25 | 6* | −2.34 | 1.75 |
| Pentyl* | −2.72 | 1.75 | 7* | −1.84 | 1.95 |
| Hexyl* | −2.22 | 1.95 | 8* | −1.34 | 2.55 |
| Heptyl* | −1.72 | 2.40 | 9* | −0.84 | 3.50 |
| Octyl* | −1.22 | 2.55 | 10 | −0.34 | 4.70 |
| | | | 12* | 0.66 | 5.05 |

| | log *P* | V-66 p*C* Obs. | V-67 p*C* Obs. | V-68 p*C* Obs. | V-69 p*C* Obs. | V-70 p*C* Obs. | V-71 p*C* Obs. | V-72 | log *P* | p*C* Obs. |
|---|---|---|---|---|---|---|---|---|---|---|
| Methyl alcohol | −0.66 | −0.80 | −0.78 | −0.76 | −0.76 | −0.57 | −0.50 | Phenol | 1.46 | 0.95 |
| Ethyl alcohol* | −0.16 | −0.52 | −0.50 | −0.47 | −0.38 | −0.09 | −0.20 | 4-Bromophenol | 2.59 | 1.94 |
| Propyl alcohol | 0.34 | −0.16 | −0.08 | −0.04 | −0.05 | 0.12 | 0.17 | 4-Bromo-2-methylphenol* | 3.09 | 2.35 |
| Isobutyl alcohol | 0.65 | 0.34 | 0.36 | 0.39 | 0.35 | 0.60 | 0.62 | 4-Bromo-2-ethylphenol* | 3.59 | 2.70 |
| Isopentyl alcohol | 1.16 | 0.62 | 0.72 | 0.74 | 0.68 | 0.85 | 0.89 | 4-Bromo-2-propylphenol* | 4.09 | 3.18 |
| Allyl alcohol | 0.17 | −0.17 | −0.21 | −0.13 | −0.13 | 0.05 | 0.17 | 4-Bromo-2-butylphenol* | 4.59 | 3.76 |
| Acetone | −0.24 | −0.43 | −0.40 | −0.38 | −0.21 | −0.10 | −0.05 | 4-Bromo-2-pentylphenol* | 5.09 | 3.99 |
| 2-Butanone | 0.29 | 0.03 | 0.03 | 0.09 | 0.15 | 0.33 | 0.42 | 4-Bromo-2-*sec*-pentylphenol* | 4.89 | 3.54 |
| 2-Pentanone* | 0.79 | 0.41 | 0.42 | 0.47 | 0.44 | 0.74 | 0.89 | 4-Bromo-2-hexylphenol* | 5.59 | 4.26 |
| Aniline | 0.90 | 0.68 | 0.72 | 0.77 | 0.96 | 1.05 | 1.15 | 4-Bromo-2-cyclohexylphenol* | 5.10 | 3.75 |
| Pyridine | 0.65 | 0.35 | 0.39 | 0.40 | 0.36 | 0.62 | 0.85 | 2-Bromophenol | 2.35 | 1.78 |
| Phenol | 1.46 | 1.10 | 1.15 | 1.22 | 1.10 | 1.40 | 1.52 | 2-Bromo-4-*tert*-pentylphenol* | 4.53 | 3.39 |
| 2-Cresol | 1.95 | 1.26 | 1.39 | 1.43 | 1.40 | 1.60 | 1.72 | 2-Bromo-4-hexylphenol* | 5.35 | 4.11 |
| Propyl carbamate* | 0.35 | 0.32 | 0.37 | 0.41 | 0.43 | — | — | 2-Bromo-4-propyl-3,5-dimethylphenol* | 4.85 | 3.69 |
| Ethyl carbamate | −0.15 | −0.03 | 0.04 | 0.02 | 0.08 | — | — | | | |
| Antipyrine | 0.23 | 0.43 | 0.47 | 0.54 | 0.51 | — | — | | | |
| Ethyl ether | 0.77 | — | — | — | 0.36 | — | — | | | |
| Chloroform | 1.97 | — | — | — | — | — | 1.40 | | | |

(*Continued*)

**Table V—(*Continued*)**

**V-73**

| | log *P* | pC Obs. |
|---|---|---|
| Chloroform | 1.97 | 2.18 |
| Methyl alcohol | −0.66 | 0.00 |
| Ethyl alcohol* | −0.16 | 0.30 |
| Propyl alcohol | 0.34 | 0.48 |
| Butyl alcohol | 0.88 | 0.60 |
| Pentyl alcohol | 1.40 | 1.41 |
| Ethyl ether | 0.77 | 0.72 |
| Ethyl carbamate | −0.15 | −0.30 |

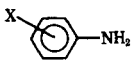
**V-74**

| | log *P* | pC Obs. | | log *P* | pC Obs. |
|---|---|---|---|---|---|
| Methyl alcohol | −0.66 | −0.24 | Methyl acetate* | 0.23 | 0.59 |
| Ethyl alcohol* | −0.16 | −0.04 | Ethyl acetate | 0.73 | 0.80 |
| Propyl alcohol | 0.34 | 0.44 | Propyl acetate* | 1.23 | 1.23 |
| Butyl alcohol | 0.88 | 0.87 | Butyl acetate* | 1.73 | 1.69 |
| Pentyl alcohol | 1.40 | 1.38 | Pentyl acetate* | 2.23 | 2.15 |
| Hexyl alcohol | 2.03 | 1.83 | Heptyl acetate* | 3.23 | 2.60 |
| Heptyl alcohol | 2.53 | 2.32 | Ethyl propionate* | 1.23 | 1.20 |
| Octyl alcohol* | 3.03 | 2.86 | Ethyl butyrate* | 1.73 | 1.63 |
| Nonyl alcohol* | 3.53 | 3.18 | Ethyl caproate* | 2.73 | 2.59 |
| Decyl alcohol* | 4.03 | 3.57 | Ethyl caprylate* | 3.73 | 3.39 |
| Allyl alcohol[e] | 0.17 | 2.04 | Pentyl butyrate* | 3.23 | 2.85 |
| Isopropyl alcohol* | 0.14 | 0.24 | 2-Ethylbutyl acetate* | 2.53 | 2.36 |
| *sec*-Butyl alcohol | 0.61 | 0.60 | Ethyl lactate* | 0.38 | 0.79 |
| *tert*-Butyl alcohol | 0.37 | 0.46 | Pentyl lactate* | 1.88 | 1.79 |
| *sec*-Pentyl alcohol* | 1.16 | 1.08 | 1-Methylisopentyl acetate* | 2.33 | 2.14 |
| 2-Methylbutyl alcohol* | 1.16 | 1.19 | Pentyl-*tert*-pentyl acetate* | 3.36 | 3.60 |
| 3-Methylbutyl alcohol* | 1.16 | 1.25 | Isobutyl alcohol | 0.65 | 0.77 |
| 3-Pentyl alcohol* | 1.16 | 1.01 | 2-Heptanone* | 1.76 | 1.94 |
| *tert*-Pentyl alcohol | 0.89 | 0.81 | 1,3-Butylene glycol* | −0.93 | −0.04 |
| 1,3-Dimethylbutyl alcohol* | 1.46 | 1.44 | 2,3-Butylene glycol* | −0.93 | −0.12 |
| 2-Ethylbutyl alcohol* | 1.68 | 1.73 | 2-Methyl-2,4-pentanediol* | −0.13 | 0.32 |
| 1-Methylheptyl alcohol* | 2.83 | 2.49 | 2-Ethyl-1,3-hexanediol* | 0.87 | 1.13 |
| 2-Ethylhexyl alcohol* | 2.83 | 2.55 | Ethyl acetoacetate[f] | 1.23 | 1.21 |
| Diphenylmethyl alcohol | 2.67 | 2.57 | | | |
| Phenethyl alcohol | 1.36 | 1.57 | | | |
| 3-Phenylpropyl alcohol | 1.88 | 2.00 | | | |
| Ethyl ether | 0.77 | 0.55 | | | |
| Propyl ether* | 1.77 | 1.55 | | | |
| Isopropyl ether* | 1.37 | 1.13 | | | |
| Butyl ether* | 2.77 | 2.54 | | | |
| Acetone | −0.24 | 0.15 | | | |

**V-75**

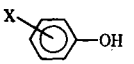
| | log *P* | pC Obs. |
|---|---|---|
| Pentane* | 2.50 | 2.28 |
| Hexane* | 3.00 | 2.77 |
| Heptane* | 3.50 | 3.19 |
| Octane* | 4.00 | 3.49 |

**V-76**



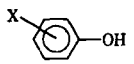
| X | log *P* | pC Obs. |
|---|---|---|
| H | 0.90 | 0.87 |
| 3-Hydroxy | 0.17 | 0.46 |
| 4-Fluoro | 1.15 | 1.12 |
| 4-Methyl | 1.39 | 1.30 |
| 3-Methyl | 1.40 | 1.31 |
| 2-Chloro | 1.90 | 1.48 |
| 3-Chloro | 1.88 | 1.68 |

**V-77**



| X | log *P* | pC Obs. |
|---|---|---|
| H | 1.46 | 1.07 |
| 3-Hydroxy | 0.80 | 0.81 |
| 3-Amino | 0.17 | 0.46 |
| 4-Methyl | 1.94 | 1.48 |
| 4-Carboxy | 1.50 | 1.15 |
| 3-Methyl | 2.01 | 1.50 |
| 2-Chloro | 2.15 | 1.60 |
| 3-Ethyl | 2.40 | 1.82 |
| 4-Bromo | 2.59 | 2.04 |
| 2-Iodo | 2.65 | 2.09 |
| 2,4-Dichloro* | 3.08 | 2.11 |
| 2,4,6-Trichloro | 3.06 | 2.21 |
| 2,3,4,6-Tetrachloro* | 4.10 | 2.65 |
| Pentachloro | 5.01 | 2.90 |

**V-78**



| X | log *P* | pC Obs. |
|---|---|---|
| H | 1.46 | 1.63 |
| 4-Methyl | 1.94 | 1.92 |
| 4-Ethyl* | 2.46 | 2.28 |
| 4-Propyl* | 2.96 | 2.54 |
| 4-Butyl* | 3.46 | 3.25 |
| 4-Pentyl* | 3.96 | 3.63 |
| 4-Hexyl* | 4.46 | 3.63 |
| 4-*sec*-Butyl* | 3.26 | 3.03 |
| 4-*tert*-Pentyl* | 3.81 | 3.47 |

**V-79**

| | log *P* | pC Obs. |
|---|---|---|
| Butyl bromide* | 2.60 | 2.00 |
| Pentyl bromide* | 3.10 | 2.48 |
| Hexyl bromide* | 3.60 | 2.82 |
| Heptyl bromide* | 4.10 | 2.41 |
| Butyl chloride | 2.39 | 1.60 |
| Pentyl chloride* | 2.89 | 2.16 |
| Hexyl chloride* | 3.39 | 2.43 |
| Chloroform | 1.97 | 1.69 |

**V-80**

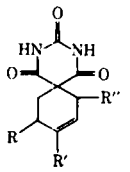
| | log *P* | pC Obs. |
|---|---|---|
| Chloroform | 1.97 | 2.80 |
| Methyl alcohol | −0.66 | 0.90 |
| Ethyl alcohol* | −0.16 | 0.90 |
| Propyl alcohol | 0.34 | 0.60 |
| Butyl alcohol | 0.88 | 1.51 |
| Pentyl alcohol | 1.40 | 2.02 |
| Ethyl ether | 0.77 | 1.92 |
| Ethyl carbamate | −0.15 | 0.60 |

**Table V**—(*Continued*)

| | V-79 | | V-80 | |
|---|---|---|---|---|
| | log *P* | p*C* Obs. | log *P* | p*C* Obs. |
| Carbon tetrachloride[d] | 2.64 | 1.85 | | |
| β,β-Dichloroethyl ether* | 1.55 | 1.57 | | |
| 3-Chloropropyl acetate* | 1.62 | 1.49 | | |
| 2,3-Dibromopropyl alcohol* | 1.54 | 1.57 | | |
| Chloretone | 2.03 | 2.00 | | |

| $R_1R_2N(CH_2)_2N(CH_3)_2$ | | | V-81 | V-82 | V-83 | V-84 | V-85 | V-103 |
|---|---|---|---|---|---|---|---|---|
| $R_1$ | $R_2$ | log *P* | p*C* Obs. | p*C* Obs. | p*C* Obs. | p*C* Obs. | p*C* Obs. | p*C* Obs. |
| Phenyl | Methyl* | 1.93 | 2.73 | 2.73 | 2.75 | 3.35 | 2.44 | 3.05 |
| Cyclohexyl | Methyl* | 2.31 | 2.27 | 2.27 | — | — | — | — |
| Octyl | Butyl* | 5.30 | — | 3.36 | 3.20 | 4.11 | — | — |
| Octyl | Isopropyl* | 4.60 | 2.86 | — | 2.88 | — | 2.88 | 3.18 |
| Nonyl | Methyl* | 4.30 | 3.31 | 2.84 | 3.45 | 4.06 | — | 3.45 |
| Heptyl | Propyl* | 4.30 | 3.73 | 2.84 | 2.80 | 3.40 | — | 2.80 |
| Octyl | Propyl* | 4.80 | 3.82 | 2.86 | 3.18 | — | 2.88 | 3.18 |
| Heptyl | Butyl* | 4.80 | — | — | 3.18 | 4.09 | — | 3.58 |
| Dodecyl | Methyl* | 5.80 | 4.35 | 4.35 | — | 4.74 | 3.86 | 4.35 |
| Heptyl | Isopropyl* | 4.10 | 2.84 | — | — | — | — | 2.84 |
| Tetradecyl | Methyl* | 6.80 | 5.45 | — | — | 5.45 | — | 5.13 |
| Cyclopentyl | Methyl* | 1.94 | — | 2.71 | 2.73 | — | — | 2.73 |
| 1-Naphthyl | Methyl* | 3.17 | 3.46 | — | — | 4.36 | 3.46 | — |
| Octyl | Hexyl* | 6.30 | 4.45 | 3.41 | 3.85 | 4.76 | 3.85 | 4.45 |
| 1-Naphthyl | Butyl* | 4.67 | 3.53 | — | 2.93 | 3.83 | 2.63 | 3.83 |
| 1-Naphthyl | Octyl* | 6.67 | 5.12 | 4.21 | 4.21 | 5.74 | 3.61 | 4.51 |
| Phenyl | Octyl* | 5.43 | 4.14 | 3.84 | 3.84 | — | 3.54 | 4.14 |
| Phenyl | Butyl* | 3.43 | 3.77 | 2.82 | 2.84 | 3.14 | 2.84 | 3.14 |
| 4-Methoxyphenyl | Heptyl* | 4.89 | 4.77 | 2.96 | 2.96 | 4.47 | 3.26 | — |
| 1-Naphthyl | Decyl* | 7.67 | 5.15 | — | 4.25 | — | 3.95 | 5.15 |
| 1-Naphthyl | Nonyl* | 7.17 | 5.42 | 4.53 | 4.53 | — | 3.93 | 5.13 |
| Tridecyl | Methyl* | 6.30 | 3.81 | 4.15 | — | — | — | 5.06 |
| Octadecyl | Methyl* | 8.80 | 6.44 | 4.47 | — | 5.55 | 3.76 | 5.25 |
| Heptadecyl | Methyl* | 8.30 | 5.42 | 4.45 | 3.93 | 5.63 | 3.93 | — |
| 4-Chlorophenyl | Heptyl* | 5.86 | — | 3.90 | — | — | — | 4.39 |
| Methyl | Methyl | 0.30 | — | — | — | 2.68 | 2.38 | — |
| 1-Naphthyl | Hexyl* | 5.67 | 5.08 | 4.47 | — | 5.08 | — | — |

| $RCHBrCO_2^-$ | | V-86 | V-87 | V-88 | V-89 | V-90 | V-91 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| R | log *P* | p*C* Obs. | p*C* Obs. | p*C* Obs. | p*C* Obs. | p*C* Obs. | R | R′ | log *P* | p*C* Obs. |
| Octyl* | 0.32 | 1.60 | 1.60 | 1.90 | 1.90 | 2.50 | $CH_3$ | $C_2H_3CH{=}C(CH_3)-$* | 1.15 | 2.62 |
| Decyl* | 1.32 | 1.90 | 2.20 | 2.20 | 2.50 | 2.81 | $C_2H_5$ | $C_2H_5CH{=}C(CH_3)-$* | 1.65 | 3.09 |
| Dodecyl* | 2.32 | 2.20 | 2.50 | 2.50 | 2.81 | 3.11 | $C_3H_7$ | $C_2H_5CH{=}C(CH_3)-$* | 2.15 | 2.95 |
| Tetradecyl* | 3.32 | 3.11 | 3.41 | 3.41 | 3.71 | 4.01 | $CH_3$ | $CH_3CH{=}C(C_2H_5)-$* | 1.15 | 2.56 |
| Hexadecyl* | 4.32 | 3.71 | 4.31 | 4.01 | 4.61 | 4.31 | $C_2H_5$ | $CH_3CH{=}C(C_2H_5)-$* | 1.65 | 2.90 |
| Octadecyl* | 5.32 | 3.41 | 4.01 | 3.71 | 4.31 | 4.01 | $C_3H_7$ | $CH_3CH{=}C(C_2H_5)-$* | 2.15 | 2.95 |
| | | | | | | | iso-$C_3H_7$ | $CH_3CH{=}C(C_2H_5)-$* | 1.95 | 3.19 |
| | | | | | | | $CH_3$ | $C_3H_7CH{=}C(CH_3)-$* | 1.65 | 2.78 |
| | | | | | | | $C_2H_5$ | $C_3H_7CH{=}C(CH_3)-$* | 2.15 | 3.17 |
| | | | | | | | $CH_3$ | $C_4H_9CH{=}C(CH_3)-$* | 2.15 | 2.82 |
| | | | | | | | $C_2H_5$ | $C_4H_9CH{=}C(CH_3)-$* | 2.65 | 3.29 |
| | | | | | | | $C_2H_5$ | $C_2H_5CH{=}C(C_3H_7)-$* | 2.65 | 3.29 |

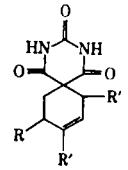


| R | R′ | R″ | log *P* | V-92 p*C* Obs. | V-93 p*C* Obs. |
|---|---|---|---|---|---|
| Unsaturated | | | | | |
| H | H | $CH_3$* | 0.75 | 2.56 | 2.69 |
| H | H | $C_2H_5$* | 1.25 | 2.62 | 2.96 |
| H | H | $C_3H_7$* | 1.75 | 2.78 | 3.27 |
| H | H | iso-$C_3H_7$* | 1.55 | 2.76 | 3.28 |
| $CH_3$ | $CH_3$ | $CH_3$* | 1.55 | 2.71 | 3.13 |

| V-94 | | | V-95 | | | |
|---|---|---|---|---|---|---|
| $RCHOHCO_2^-$ R | log *P* | p*C* Obs. | R | R′ | log *P* | p*C* Obs. |
| Octyl* | −1.22 | 1.30 | Ethyl | Ethyl | 0.65 | 2.79 |
| Decyl* | −0.22 | 1.90 | Ethyl | Phenyl | 1.42 | 3.12 |
| Dodecyl* | 0.78 | 3.11 | Ethyl | Isopentyl* | 2.07 | 3.50 |
| Tetradecyl* | 1.78 | 3.41 | Ethyl | 2-Methylbutyl* | 2.07 | 3.45 |
| Hexadecyl* | 2.78 | 4.61 | Ethyl | 1-Ethylpropyl* | 2.07 | 3.81 |
| Octadecyl* | 3.78 | 4.31 | Ethyl | 1,2-Dimethylpropyl* | 1.87 | 3.45 |

(*Continued*)

**Table V**—(*Continued*)

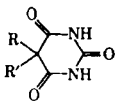


| R | R′ | R″ | V-92 log *P* | V-92 p*C* Obs. | V-93 p*C* Obs. |
|---|---|---|---|---|---|
| Saturated | | | | | |
| H | H | $CH_3$* | 1.05 | 2.67 | 3.06 |
| H | H | $C_2H_5$* | 1.55 | 2.81 | 3.33 |
| H | H | $C_3H_7$* | 2.05 | 2.94 | 3.65 |
| H | H | iso-$C_3H_7$* | 1.85 | 2.94 | 3.55 |
| H | H | $C_4H_9$* | 2.35 | 3.06 | 3.45 |

**V-94** $RCHOHCO_2^-$

| R | log *P* | p*C* Obs. |
|---|---|---|

**V-95**



| R | R′ | log *P* | p*C* Obs. |
|---|---|---|---|
| Ethyl | *sec*-Pentyl | 2.07 | 3.81 |
| Ethyl | Cyclopentyl* | 1.79 | 3.45 |
| Ethyl | Butyl | 1.89 | 3.33 |
| Ethyl | Isobutyl | 1.69 | 3.28 |
| Ethyl | *sec*-Butyl | 1.69 | 3.63 |
| Allyl | 2-Pentyl* | 2.15 | 3.83 |
| Allyl | 3-Pentyl* | 2.15 | 3.77 |
| Allyl | Cyclopentyl* | 1.99 | 3.67 |

**V-96** $R(R')NC(=O)-NH_2$

| R | R′ | log *P* | p*C* Obs. |
|---|---|---|---|
| Methyl | Phenyl* | 0.42 | 2.46 |
| Ethyl | Phenyl* | 0.92 | 2.80 |
| Propyl | Phenyl* | 1.42 | 3.20 |
| Butyl | Phenyl* | 1.92 | 3.42 |
| Methyl | 2-Tolyl* | 0.92 | 2.82 |
| Ethyl | 2-Tolyl* | 1.42 | 3.25 |
| Propyl | 2-Tolyl* | 1.92 | 3.51 |
| Butyl | 2-Tolyl* | 2.42 | 3.89 |
| Methyl | 3-Tolyl* | 0.92 | 3.00 |
| Ethyl | 3-Tolyl* | 1.42 | 3.20 |
| Propyl | 3-Tolyl* | 1.92 | 3.51 |
| Methyl | 3-Anisyl* | 0.42 | 2.84 |
| Ethyl | 3-Anisyl* | 0.92 | 3.16 |
| Methyl | 3-Phenethyl* | 0.92 | 3.05 |
| Ethyl | 3-Phenethyl* | 1.42 | 3.25 |
| Methyl | 4-Tolyl* | 0.92 | 2.90 |
| Ethyl | 4-Tolyl* | 1.42 | 3.20 |
| Propyl | 4-Tolyl* | 1.92 | 3.42 |
| Butyl | 4-Tolyl* | 2.42 | 3.60 |
| Methyl | 4-Anisyl* | 0.42 | 2.62 |
| Ethyl | 4-Anisyl* | 0.92 | 2.86 |
| Methyl | 4-Phenethyl* | 0.92 | 2.84 |
| Ethyl | 4-Phenethyl* | 1.42 | 3.00 |

**V-97**

| | log *P* | p*C* Obs. |
|---|---|---|
| Acetone | −0.24 | 2.72 |
| 2-Butanone | 0.29 | 3.15 |
| 3-Pentanone* | 0.79 | 3.40 |
| 2-Pentanone* | 0.79 | 3.47 |

**V-98**

| | log *P* | p*C* Obs. |
|---|---|---|
| Methyl alcohol | −0.66 | 2.63 |
| Ethyl alcohol* | −0.16 | 3.00 |
| Isopropyl alcohol* | 0.14 | 3.35 |
| *sec*-Butyl alcohol | 0.61 | 3.66 |
| *tert*-Butyl alcohol | 0.37 | 3.69 |
| 2-Ethylpropyl alcohol* | 1.16 | 4.20 |
| 2-Methylbutyl alcohol* | 1.16 | 4.25 |
| Isopentyl alcohol | 1.16 | 4.46 |
| Pentyl alcohol | 1.40 | 4.54 |
| Hexyl alcohol | 2.03 | 4.79 |
| Ethyl ether | 0.77 | 3.47 |
| Acetone | −0.24 | 3.28 |
| Benzyl alcohol[g] | 1.10 | 4.63 |
| Allyl alcohol[g] | 0.17 | 5.38 |

**V-99**

| $RCOO^-$ R | log *P* | p*C* Obs. |
|---|---|---|
| $C_6H_5$—* | −2.23 | 2.00 |
| $C_6H_5CH_2$—* | −2.80 | 1.95 |
| $C_6H_5CH(CH_3)$—* | −2.50 | 2.17 |
| $C_6H_5CH(C_2H_5)$—* | −2.00 | 2.42 |
| $C_6H_5CH(C_3H_7)$—* | −1.50 | 2.74 |
| $C_6H_5CH(C_4H_9)$—* | −1.00 | 3.04 |

**V-100** $R-\overset{+}{N}(CH_3)_3$

| R | log *P* | p*C* Obs. |
|---|---|---|
| Methyl* | −4.72 | 1.85 |
| Ethyl* | −4.22 | 2.15 |
| Propyl* | −3.72 | 2.50 |
| Butyl* | −3.22 | 2.70 |
| Pentyl* | −2.72 | 2.80 |
| Hexyl* | −2.22 | 3.15 |
| Heptyl* | −1.72 | 3.20 |

**V-101** $(CH_3)_3-\overset{+}{N}(CH_2)_n-\overset{+}{N}(CH_3)_3$

| *n* | log *P* | p*C* Obs. |
|---|---|---|
| 4* | −3.34 | 2.75 |
| 5* | −2.84 | 2.55 |
| 6* | −2.34 | 3.00 |
| 7* | −1.84 | 3.45 |
| 8* | −1.34 | 3.50 |
| 9* | −0.84 | 4.00 |
| 10 | −0.34 | 4.45 |

**V-102**

| Aldehydes | log *P* | p*C* Obs. |
|---|---|---|
| Butyraldehyde[h] | 1.18 | 1.93 |
| Pentaldehyde* | 1.68 | 2.09 |
| Isopentaldehyde* | 1.48 | 2.07 |
| Hexaldehyde* | 2.18 | 2.36 |
| 2-Ethylhexaldehyde* | 2.98 | 2.51 |

* Calculated log *P*. [a] Not included in the derivation of Eq. 30. [b] Not included in the derivation of Eq. 37. [c] Not included in the derivation of Eq. 59. [d] Log *P* calculated using Eq. 148. [e] Not included in the derivation of Eq. 88. [f] Log *P* calculated using Eq. 149. [g] Not included in the derivation of Eq. 130. [h] Log *P* calculated using Eq. 150.

As in Table II, the more drastic kinds of perturbation with nonspecific compounds yield equations with low intercepts. Most of the equations with negative intercepts involve extensive protein denaturation.

The kind of perturbation studies on a given organism will determine the form of the linear free-energy relationship. For example, Eq. 25 of Table II correlates the inhibition of luminescence of bacteria. The slope and intercept of this equation are higher than Eq. 78 of Table III for inhibition by ROH of *Staphylococcus aureus*. Equation 25 is more closely related to Eq. 22; this would indicate that the membranes involved with the enzymes controlling luminescence are different from those involved with the control of growth. Another example is Eq. 93, correlating the increase in $Ca^{+2}$ binding of red cell ghosts. The slope and intercept of this equation are quite different from others associated with red cells (Eqs. 21, 22, and 61–65). The higher intercept indicates that this process is much more sensitive to alcohols than hemolysis (Eq. 8) or oxygen consumption (Eq. 22).

It is significant that low concentrations of lipophilic

compounds may stabilize protein or strengthen membranes while the same compounds at higher concentrations destabilize. Equation 21 of Table II shows that, under certain conditions, alcohols can stabilize red cells against hypotonic hemolysis. In Eq. 81 of Table III, it is seen that low concentrations of lipophilic compounds inhibit the swelling of fibrin. There is a serious need for more studies of this kind since so little of this type of work has been done. The concentration differences between stabilization and destabilization are surprisingly small.

Whether drugs are given in aqueous solution or in the form of vapor has an important effect on activity if activity is compared in moles per liter of molecules in the vapor phase or moles per liter of solution. Equations 126–129 have intercepts of about 3. These equations are for simple alcohols and ketones, of which there are many examples in Tables II–IV with intercepts near 0. These compounds appear to be about 1000 times more toxic on a molar basis in the vapor form. It would appear that in these examples the molecules must move more or less directly from the vapor onto the sites involved in the pharmacophoric action. Equations correlating toxicity to organisms as different as tomato plants, red spiders, and grain weevils yield equations almost identical in slope and intercept.

The result in Eq. 130 on the South African toad is unusual. This is the only example found having such a high intercept for the action of miscellaneous neutral compounds acting on a whole animal. Whether this indicates an extremely sensitive animal or the unusual administration (injection into the tongue) is not clear.

In all of the examples in Tables II–IV where the molecules are largely ionized under the experimental conditions, the log $P$ values for the ionized form have been utilized in deriving the linear free-energy relationships. The partition coefficients are really for the ion pairs; that is, the sodium salts in the case of the acids and the hydrochlorides or hydrobromides for the ammonium compounds. The intercepts of the equations correlating ionized sets of congeners are all rather high, indicating the high intrinsic activity of ions by this kind of isolipophilic comparison. Whether this high activity is to be ascribed primarily to the ionic portion of the molecule or whether it is due to the large apolar portion of the drug necessary to counterbalance the ionic head and thus yield a molecule of log $P = 0$ is not clear. (Comparing intercepts means making comparisons between cases under the condition of $P = 1$ or log $P = 0$.) In fact, the biochemical result is caused by the combined action of the two parts of the molecule. In any event, intercepts do constitute one way of categorizing relative intrinsic pharmacophoric activity, even though they do not always allow a complete and clean separation of the role of, say, an alkyl chain and a cationic head.

One can use the equations of Tables II–IV to show similarity as well as difference in effect of different functional groups. The slopes and intercepts of Eqs. 84 and 85 correlating the conversion of Cytochrome P-450 to P-420 are essentially identical. This indicates no specific role for the OH or $NH_2$ functions. Since there is a variety of changes in the substituents on the rings in these examples, they serve to illustrate the advantage of the octanol/water system in minimizing hydrogen bonding and dipolar effects in the partitioning of the anilines and phenols onto the Cytochrome P-450. The rather low intercepts characterize the conversion of P-450 to P-420 as a very nonspecific process.

## HYDROPHOBICALLY INSENSITIVE LINEAR FREE-ENERGY RELATIONSHIPS

In Table IV, there are a few examples of equations with very low slopes (<0.4). While only a few are known involving the single variable log $P$, many examples are in hand where the coefficient with the log $P$ term is <0.4, but these are for more complex systems and other variables (such as $\sigma$ or $E_s$) must be included in the equations to obtain good correlations. Since these more complex equations cannot be discussed at the present time, there are no generalizations to make about systems that are sensitive to hydrophobic effects but where large increases in lipophilic character are needed to produce significant changes in biochemical response.

## GENERAL CONSIDERATIONS

Up to this point, the authors have considered only the possibility that the slope of the equations of Tables II–IV is determined by the nature of the lipophilic phase (membrane or macromolecule). The nature of the aqueous phase must not be overlooked. In fact, this phase provides the driving force for the phase transfer of the small molecules. The more ordered the water molecules are about the apolar portions of the small molecules, the greater is the entropy change in the phase transfer. Other solutes in the aqueous phase (amino acids or peptides, for example) might, to a certain extent, hinder the formation of the envelope of water molecules about the apolar parts of the compounds undergoing the phase transfer. This would lower the entropy change in desolvation and, thereby, diminish the apparent hydrophobic character of the apolar portion of the drugs. The result would be a lower value for the slope in the correlation equations.

Another very important factor which must be remembered in comparing values of slopes is that the general relationship for a large range in log $P$ values between p$C$ and log $P$ is not linear but parabolic. Meaningful linear relationships between p$C$ and log $P$ will only occur when one is working with a set of congeners having a good spread in log $P$ values, the majority of which are considerably below log $P_0$. With a rather narrow set of log $P$ values, all sorts of slopes might arise, depending on which part of the parabola relating p$C$ and log $P$ the set of congeners happens to fall.

The many good correlations of Tables II–IV provide some support for the hypothesis used in formulating Eq. 7 that equivalent amounts of hydrophobic material in the form of small molecules on the active sites of macromolecules or membranes produce equivalent biological responses. This assumes that either no special pharmacophoric function is necessary for a given set of congeners producing a specific response or else all members of the set have essentially the same pharmacophoric function. This being so, one might ex-

pect that the molar volume of the narcotic is critical, as indeed Mullins (25) suggested. This single parameter serves well to correlate structure with activity in a homologous series or for a set of very apolar molecules. However, for a set of neutral molecules of mixed functionality, it gives poor correlations. This is because it is the "effective" molar volume which is important; that is, the molar volume of material which actually penetrates into the biophase under the conditions of the experiment. Such functions as OH, OR, and COOH which have a strong affinity for the aqueous phase lower the "effective" molar volume. Mullins (25) attempted to handle the different activities of functional groups by means of the Hildebrand solubility parameter, $\delta$. This parameter was developed for apolar liquids and has not received enough subsequent attention so that it can be utilized at present.

Ever since the work of Meyer (1) and Overton (2, 3) in the early part of this century, efforts have been made to explain exactly how small lipophilic molecules bring about anesthesia and narcosis. The results in Tables II–IV indicate that the introduction of lipophilic molecules into living organisms causes minor or major disturbances (depending on log $P$ and the amount employed) in most of the macromolecular systems with which they come in contact. The greater the degree of narcosis produced, the greater the number of biochemical systems inhibited. Unfortunately, at the present time, there are not enough equations on the various enzyme systems and organelles to tell to what extent these are inhibited individually, let alone the effect on their cooperativeness, to understand all that is involved in the narcosis of a complex organism such as a cat. For example, the intercept of Eq. 48 correlating the $I_{50}$ of the postsynaptic pulse of the rabbit cervical ganglion is considerably below Eq. 59 correlating the $LD_{100}$ for cats. No doubt, an equation something below $I_{50}$ ($I_{20}$, $I_{10}$, *etc.*) could be found with the same intercept as the $LD_{100}$ equation for cats. In this way, one could find the degree of postsynaptic pulse depression that occurs in the killing of mammals by alcohols. Equation 57 on the $I_{50}$ of pancreatic lipase of rats has an intercept of about the same value as that for the $LD_{100}$ of cats. This enzyme system is badly disrupted (as, no doubt, many others are) at drug concentrations necessary to kill cats. These examples show in a crude way how extrathermodynamic equations can be used to make rough judgments from isolated systems about more complex systems.

Although there is good variation in the various kinds of biological systems in Tables II–IV, there is not as much variation in the classes of molecules studied as one would like. Simple aliphatic alcohols are by far the most popular drugs studied. No doubt this is because of their ready availability and their reasonable solubility in aqueous solutions. Considering just aliphatic alcohols, there is about a 2.0 log unit range in the intercepts of these equations. The sensitivity of the different systems varies by 100-fold according to this standard. Most of these equations have intercepts within a 1 log unit range. Except for the single outstanding example of $I_{25}$ for sheep liver esterase (Eq. 134), the nonspecific binding by serum albumin, and cases where drugs were given in the vapor phase, one does not find equations correlating simple neutral compounds with intercepts above 2. As mentioned previously, in studying enzymes out of their natural environment, one can vary the value of the intercept greatly by the selection of the substrate concentration for the inhibition study. Even so, sheep liver esterase seems remarkably sensitive to alcohols. It may be that the alcohol of the natural substrate formed on hydrolysis, glycerol, is very readily desorbed from the enzyme so that poisoning of the enzyme does not occur. The much more lipophilic aliphatic alcohols must be much more strongly held by the active site.

Most of the high intercepts in Tables II–IV are for equations involving ionic species. The few exceptions are for special types of compounds. There are not enough of these examples in hand to warrant an attempt at classification.

The data sets on which Eqs. 30, 37, 59, 82, and 130 are based contain benzyl and allyl alcohols, respectively. These molecules were not used in deriving the equations since we previously noted that allylic hydrogens seem to be invariably more toxic than one would expect from lipophilic character alone (26). While they are more toxic in living systems than log $P$ would predict, normal well-predicted results are obtained in nonliving systems (Eqs. 70–72, 75, 77, and 79). This suggests that it is not simply a different physical property of the benzylic hydrogens or the OH function which is involved but that a chemical property is involved.

In summary, one can say that there is a strong central tendency for slopes of about 1 and about 0.7. There is another group for which more examples are needed with slopes in the range of 0.2–0.4. The intercepts constitute more of a continuum. It is hoped that the phenomenological organization of structure and activity of Tables II–IV will serve as a useful basis set with which new results can be compared. It is the authors' belief that such correlations will provide new insight into the role of hydrophobic forces in biochemical processes.

## METHOD

Table V contains the biological data and partition coefficients used to derive the equations found in Tables II–IV. The equations of Table II are those with slopes of 0.85 or greater; Table III contains those with slopes in the range of 0.85–0.40; Table IV is a tabulation of the equations with slopes less than 0.40. In each case, the equations are arranged in order of ascending intercepts. In Tables II–IV, the slope with its 95% confidence interval is noted by $a$, $b$ is the $Y$ intercept with its 95% confidence interval, $r$ is the correlation coefficient, and $s$ the standard deviation for the regression. The column denoted by *Reference 1* refers to the position in Table V where the data are presented. If the data were previously correlated and published, this reference is given in the *Reference 1* column. The *Reference 2* column of Table II refers to the original literature reference from which the biological data were obtained.

The biological data in Table V are given as the logarithm of the reciprocal of the molar concentration

of the compound required to give a standard biological response, *i.e.*, $ED_{50}$, $I_{50}$, $LD_{100}$, *etc.* The data for each series of compounds must be given in the same units in order for comparisons to be made regarding the intercepts. The partition coefficients are from the octanol/water system and were either determined experimentally or calculated from additivity principles (110). The calculated values are noted in Table V by a single asterisk.

The data sets that contain alcohols exclusively are given in Table V-1–43. Using additivity principles (110), the calculated values of the log of the partition coefficient (log *P*) for straight-chain alcohols were obtained using the experimental log *P* for the nearest homolog below it as a base and adding 0.50 $\pi$ unit for each methylene group. For example, the log *P* for ethanol was calculated from the value of −0.66 of methanol as follows: log $P_{ethanol}$ = −0.66 + 0.50. The value for nonanol was obtained using hexanol as the base: log $P_{nonanol}$ = 2.03 + 1.50 = 3.53. The log *P* for menthol was calculated using the experimental value of 1.23 for cyclohexane as the base and the additivity principle that a branched chain reduces log *P* by 0.20 $\pi$ unit for each branch: log $P_{menthol}$ = log $P_{cyclohexanol}$ + $4(\pi CH_3)$ − $\pi_{branching}$ = 1.23 + 2.00 − 0.20 = 3.03. The branched isomers of pentanol, 3-pentyl, 1-methylbutyl, 1,2-dimethylpropyl, *etc.*, were assigned the experimental value for isopentanol of 1.16.

In the same way the value for 2-pentanone was obtained using 2-butanone as base: log $P_{2\text{-pentanone}}$ = 0.29 + 0.50 = 0.79. The log *P*'s for the homologs of methyl *p*-hydroxybenzoate were calculated using the value of 1.96 for methyl *p*-hydroxybenzoate.

The log *P*'s for methylal and acetal in Table V-48 were calculated from the experimental value of 0.84 for diethoxymethane in the following manner: log $P_{methylal}$ = 0.84 − $2(\pi CH_3)$ = −0.16, and log $P_{acetal}$ = 0.84 + $\pi_{branched}$ + $\pi CH_3$ = 1.14. The straight-chain nitriles were calculated using acetonitrile as the base. The homologous esters were calculated from the experimental value of 0.73 for ethyl acetate. The log *P* for ethyl nitrate in Table V-55 was calculated from the determined value of 2.15 for butyl nitrate by subtracting $\pi$ for two methylene groups to give a value of 1.15; methyl carbamate was calculated from ethyl carbamate by subtracting $\pi$ for one methylene group.

The log *P* in octanol for carbon disulfide found in Table V-56 was calculated using Eq. 148:

$$\log P_{oils} = 1.12 \log P_{octanol} - 0.32 \quad \begin{matrix} n & r & s \\ 14 & 0.988 & 0.233 \end{matrix} \quad \text{(Eq. 148)}$$

and the average of the values from oils of 2.08 and 1.70; the former value was reported by Macy (111) and the latter by Meyer and Hemmi (4). This gives a value of 2.00 for carbon disulfide. The octanol partition coefficient for carbon tetrachloride was calculated from Eq. 148 which relates the log *P* determined in oils to that in octanol (13). The log $P_{oils}$ of 2.66 reported by Macy (111) was used in Eq. 148 to calculate log *P* of $CCl_4$ = 2.64.

By using butyramide as the base, valeramide was calculated as follows: log $P_{valeramide}$ = log $P_{butyramide}$ + $\pi CH_3$ = −0.21 + 0.50 = 0.29.

The log *P* assigned to 5-ethyl-5-isopentyl barbiturate is that determined for its isomer, 5-ethyl-5-(2-pentyl) barbiturate, while that for 5-ethyl-5-(1,3-dimethylbutyl) barbiturate was calculated from the log *P* = 0.65 for the 5,5-diethyl barbiturate as follows: log $P_{5\text{-ethyl-5-(1,3-dimethylbutyl) barbiturate}}$ = 0.65 + $4(\pi CH_3)$ − $2(\pi_{branching})$ = 0.65 + 2.00 − 0.40 = 2.25. The experimentally determined value for decyltrimethylammonium bromide of −0.22 was used to calculate the partition coefficients of the homologs in Table V-64 and 100.

The log *P*'s calculated for the diquaternary ammonium salts in Table V-65 and 101 were calculated from the experimental value of −0.34 for decamethonium ($n$ = 10) by adding or subtracting 0.50 $\pi$ unit for each methylene group. In calculating the log *P*'s given in Table V-72 for the phenols, the base compounds used were 4- and 2-bromophenol with log *P* = 2.59 and 2.35, respectively. The additivity principles for methylene groups and for branching were used as in previous calculations. The $\pi$ value for the 4-cyclohexyl group was taken from the phenoxyacetic acid series (110).

By using Eq. 149:

$$\log P_{oils} = 1.10 \log P_{octanol} - 1.31 \quad \begin{matrix} n & r & s \\ 65 & 0.981 & 0.271 \end{matrix} \quad \text{(Eq. 149)}$$

which relates the log of the partition coefficient in oils (13) to the log *P* in octanol for solutes capable of hydrogen-bond donation, the log *P* in octanol for ethyl acetoacetate was calculated to be 1.23. The log *P* in oils for ethyl acetate is reported by Macy (111) to be 0.04. To calculate the values for ethyl lactate and pentyl lactate, the log *P* = −0.62 for lactic acid reported by Collander (112) was used as the base; to this was added 0.50 $\pi$ for each methylene group required to give the desired ester.

In Table V-77, the log of the partition coefficient calculated for 2,4-dichlorophenol was based on 2-chlorophenol and $\pi_{4\text{-Cl}}$ = 0.93 from the phenol system (110). Using $\pi_{3\text{-Cl}}$ = 1.04 from the same system and log *P* = 3.06 for 2,4,6-trichlorophenol, a value of 4.10 was calculated for 2,3,4,6-tetrachlorophenol. The log of the partition coefficient calculated in Table V-78 for 4-*tert*-pentylphenol was based on the value of 3.31 for 4-*tert*-butylphenol; 0.50 $\pi$ was added for the methylene group.

The log *P* for $\beta,\beta$-dichloroethyl ether in Table V-79 was calculated from $\pi$ for the chloro group in the aliphatic series and ethyl ether as base as follows: log *P* = log $P_{ether}$ + $2\pi_{Cl}$ = 0.77 + 0.78 = 1.55. By using propyl alcohol as base and $\pi_{Br}$ = 0.60 from the aliphatic series, a value of log *P* = 1.54 was calculated for 2,3-dibromopropyl alcohol. The method used to calculate the log *P*'s for the ethylenediamines of Table V-81, 85, and 103 is published (82). The method for calculating the partition coefficients for the $\alpha$-bromo acids of Table V-86 and 90 are published (21). An explanation for calculating the partition coefficients for the barbiturates of Table V-91, 93, and 95 has been published (36).

The partition coefficients calculated in Table V-94 for the $\alpha$-hydroxy acids are for the ionized form. It has been found that $\pi$ for converting an acid to its anionic form reduces log *P* by 4.10$\pi$ (21). By using this value

and lactic acid as base, the log $P$ for $\alpha$-hydroxydecanoic acid anion in Table V-94 was calculated as follows: $\log P = \log P_{\text{lactic acid}} + \pi_{\text{ionization}} + 7\pi CH_3 = -0.62 - 4.10 + 3.50 = -1.22$.

The partition coefficients for the ureas of Table V-96 were based on the experimental value of log $P$ = 0.42 for 1-methyl-1-phenylurea. By using $\pi_{\text{ionization}} = -4.10$ for carboxylic acids, the log $P$'s for the ionized acids in Table V-99 were calculated as previously discussed.

The value of the partition coefficient for butyraldehyde, on which calculations for the compounds in Table V-102 were based, was calculated from the log $P$ in isobutanol = 1.20 reported by Collander (113) using Eq. 150 (13):

$$\log P_{\text{isobutanol}} = 0.70 \log P_{\text{octanol}} + \underset{0.38}{\overset{n}{57}} \quad \underset{0.993}{\overset{r}{}} \quad \underset{0.123}{\overset{s}{}} \quad \text{(Eq. 150)}$$

From this equation, a value of log $P$ = 1.18 is obtained for butyraldehyde.

Additional compounds have been added, as more partition coefficients have become available, to several sets of data referred to in this report and published previously. These data sets are those used to derive Eqs. 23, 39, and 49.

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## *RESEARCH ARTICLES*

# Toxicity Profile of Chloroacetaldehyde

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**Abstract** □ Chloroacetaldehyde, a probable metabolite of 2-chloroethanol (ethylene chlorohydrin), was studied in a number of *in vivo* animal systems, in *in vitro* hemolysis tests, and in tissue cultures to obtain a toxicity profile of the compound. Acute toxicity tests were conducted in mice, rats, guinea pigs, and rabbits by one or more routes of administration. Tissue culture tests utilized both the agar-overlay and protein assay methods. Irritant activity was evaluated by intramuscular implantation, intradermal injection, and dermal and ophthalmic applications in the rabbit. Acute cardiovascular effects in rabbits were also determined. Sleeping-time tests in mice were conducted to assess the effect of chloroacetaldehyde pretreatment (inhalation and intraperitoneal) upon drug-metabolizing enzymes. The compound was tested in guinea pigs for its sensitizing potential. Cumulative (30 daily injections) and subacute (three injections per week for 12 weeks) toxicity studies were conducted to evaluate subtle toxic effects (*e.g.*, weight gain, hematology, and histopathology) as well as lethality. Chloroacetaldehyde is a very toxic and irritating compound in acute tests; in tests of longer duration, most of the parameters measured appeared to be normal in animals that survived its lethal activity. The acute toxic effects of chloroacetaldehyde are compared with those of 2-chloroethanol. The former is inherently more toxic and irritating, while the latter exhibits greater ease of quantitative penetration through the GI tract and the intact skin.

**Keyphrases** □ Chloroacetaldehyde—toxicity, compared to ethylene chlorohydrin □ Toxicity—chloroacetaldehyde, compared to ethylene chlorohydrin

Chloroacetaldehyde ($ClCH_2CHO$) is a liquid at room temperature. As the anhydrous material, it polymerizes on standing (1) and, in aqueous solutions in excess of 50%, forms a half-hydrate which precipitates as white crystals (2). It is intensely irritating to human eyes, skin, mucous membranes, and the respiratory tract (1), and its highly toxic nature is suggested by its "threshold limit value" (TLV) of 1 p.p.m., which should not be allowed to fluctuate above this amount even for short periods of time (3). The uses of chloroacetaldehyde as well as its physical and chemical properties were presented previously (1, 2).

Ethylene oxide sterilization of plastics, spices, and foods, in the presence of chlorides, produces 2-chloroethanol as a reaction product. Johnson (4), in studies conducted on rats, indicated that 2-chloroethanol was