solutes from the solvent water and the limited but important capacity of water to maintain its network of hydrogen bonds.

Hydrophobicities of solutes can readily be determined by measuring partition coefficients designated as P. Partition coefficients deal with neutral species, whereas distribution ratios incorporate concentrations of charged and/or polymeric species as well. By convention, P is defined as the ratio of concentration of the solute in octanol to its concentration in water.

$$P = [\text{conc}]_{\text{octanol}}/[\text{conc}]_{\text{aqueous}} \quad (1.41)$$

It was fortuitous that octanol was chosen as the solvent most likely to mimic the biomembrane. Extensive studies over the last 35 years (40,000 experimental P-values in 400 different solvent systems) have failed to dislodge octanol from its secure perch (107,108).

Octanol is a suitable solvent for the measurement of partition coefficients for many reasons (109, 110). It is cheap, relatively nontoxic, and chemically unreactive. The hydroxyl group has both hydrogen bond acceptor and hydrogen bond donor features capable of interacting with a large variety of polar groups. Despite its hydrophobic attributes, it is able to dissolve many more organic compounds than can alkanes, cycloalkanes, or aromatic hydrocarbons. It is UV transparent over a large range and has a vapor pressure low enough to allow for reproducible measurements. It is also elevated enough to allow for its removal under mild conditions. In addition, water saturated with octanol contains only 10^{-3} M octanol at equilibrium, whereas octanol saturated with water contains 2.3 M of water. Thus, polar groups need not be totally dehydrated in transfer from the aqueous phase to the organic phase. Likewise, hydrophobic solutes are not appreciably solvated by the 10^{-3} M octanol in the water phase unless their intrinsic log P is above 6.0. Octanol begins to absorb light below 220 nm and thus solute concentration determinations can be monitored by UV spectroscopy. More important, octanol acts as an excellent mimic for biomembranes because it shares the traits of amphiphilicity and hydrogen-bonding capability with phospholipids and proteins found in biological membranes.

The choice of the octanol/water partitioning system as a standard reference for assessing the compartmental distribution of molecules of biological interest was recently investigated by molecular dynamics simulations (111). It was determined that pure 1-octanol contains a mix of hydrogen-bonded "polymeric" species, mostly four-, five-, and six-membered ring clusters at 40°C. These small ring clusters form a central hydroxyl core from which their corresponding alkyl chains radiate outward. On the other hand, water-saturated octanol tends to form well-defined, inverted, micellar aggregates. Long hydrogen-bonded chains are absent and water molecules congregate around the octanol hydroxyls. "Hydrophilic channels" are formed by cylindrical formation of water and octanol hydroxyls with the alkyl chains extending outward. Thus, water-saturated octanol has centralized polar cores where polar solutes can localize. Hydrophobic solutes would migrate to the alkyl-rich regions. This is an elegant study that provides insight into the partitioning of benzene and phenol by analyzing the structure of the octanol/water solvation shell and delineating octanol's capability to serve as a surrogate for biomembranes.

The shake-flask method, so-called, is most commonly used to measure partition coefficients with great accuracy and precision and with a log P range that extends from -3 to $+6$ (112, 113). The procedure calls for the use of pure, distilled, deionized water, high-purity octanol, and pure solutes. At least three concentration levels of solute should be analyzed and the volumes of octanol and water should be varied according to a rough estimate of the log P value. Care should be exercised to ensure that the eventual amounts of the solute in each phase are about the same after equilibrium. Standard concentration curves using three to four known concentrations in water saturated with octanol are usually established. Generally, most methods employ a UV-based procedure, although GC and HPLC may also be used to quantitate the concentration of the solute.