Suggested Thermodynamic Standard State for Comparing Drug Molecules in Structure–Activity Studies

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Sir:

This communication presents an alternative standard state for thermodynamic studies of systems containing drug molecules. The proposed approach permits one to make *a priori* prediction of many solution properties of drug molecules. It is a logical extension of the concepts presented in a recent communication from this laboratory (1).

Theoretically, one could choose any set of conditions desired as a standard state. However, the convenience of certain conditions has led to a few choices being generally adopted (2). The state usually taken for the component designated as solvent is the pure substance at a given temperature and pressure (usually 1 atm.). The conventions used for selection of the standard state of the solute are less general. Usually when the solute and solvent are completely miscible and often when this is not the case, the pure solute at a given temperature and pressure is chosen as the standard state. For cases of limited solubility and generally for aqueous solutions, a hypothetical state in which the solute has properties of a 1 molar, 1 molal, or 1 mole fraction solution, behaving as if it were at infinite dilution, is usually chosen.

The choice of standard state becomes particularly important when attempting a comparison of "thermodynamic activities" of a series of compounds. Ferguson (3) chose the pure toxic substance as its standard state, and this convention has been generally followed since. The pure solute standard state has also been the choice for most vapor–liquid and nonelectrolyte activity coefficient studies reported to date, primarily because the pure solute standard state is physically attainable and is independent of solvent.

The use of the pure form of the drug as the standard state in applying Ferguson's principle to relate several drugs forces one to depart from thermodynamics in its usual sense. When the thermodynamic activities of several solutes (drugs) are compared, a different reference system is used for each drug (the respective pure drug). For the correlations to have any basic thermodynamic significance, the reference states must be relatable. Use of the pure material as the standard state has two basic weaknesses:

1. The usual custom of selecting the observed state of the substance at the working temperature is not very satisfactory for solid compounds, since possible polymorphic behavior complicates selection of the standard state.

Table I—Henry's Constants (torr) for Several Organic Solutes in Various Aliphatic Hydrocarbon Solvents[a]

Solvents	Solutes: Hexane	Heptane	Methyl Ethyl Ketone	Acetone
Hexane	—	—	490[e]	—
Cyclohexane	137[b]	—	—	—
Heptane	—	—	470[e]	1628[e]
2,3,4-Trimethylpentane	133[c]	38[c]	—	—
Decane	—	—	475[e]	1430[e]
Dodecane	117[b]	—	—	—
Hexadecane	109[b]	31[b]	416[e]	1342[e]
Heptadecane	120[d]	38[d]	—	—

[a] These values were calculated from activity coefficients (mole fraction concentration scale) extrapolated to infinite dilution. These activity coefficients were then multiplied by the vapor pressure of the pure solute to yield Henry's constants (*i.e.*, $H_{2,1} = \gamma_2^{\infty} \cdot P_2^0$). [b] J. S. Rowlinson, "Liquids and Liquid Mixtures," Butterworths, London, England, 1969. $T = 20°$. [c] R. E. Pescar and J. J. Martin, *Anal. Chem.*, **38**, 1661 (1966). $T = 20°$. [d] D. E. Matire and P. Riedl, *J. Phys. Chem.*, **72**, 3478 (1968). $T = 22.5°$. [e] G. J. Pierotti, C. H. Deal, and E. L. Derr, Amer. Doc. Inst., Document No. 5782, Library of Congress, 1958, pp. 1–53. $T = 25°$.

2. The most important difficulty with selection of the pure drug as the standard state applies to both solids and liquids and lies in the fact that each drug in its reference state has a substantially different environment.

If we accept the proposition that the pure drug material is neither the most suitable nor convenient reference state, what can we select, by convention, as a system which would be widely applicable and permit ready comparison? Comparison of chemical potentials and thermodynamic activities using infinitely dilute solutions as the reference state is the norm for most aqueous solutions of inorganic species. Since drug molecules operate in the intermediate environments of their receptor sites and, consequently, the drug concentration is relatively low, their chemical potentials logically should be related to their solutions rather than to their pure states.

Water is not, however, the best common solvent for these reference states because of the complicated and highly structured nature of water. The solvent–solvent and solute–solvent interactions in water are large and complicate interpretation of thermodynamic and biological data in aqueous solution. Hansch (4) used 1-octanol as a reference solvent for partition coefficient studies. The reasons given are that pragmatically it appears to work well, giving good correlation data among a variety of compounds; it is easy to obtain as the pure material; it is insoluble in water; it is not sensitive to temperature changes; and it does not absorb strongly in the UV region, facilitating spectrophotometric measurements. Other alcohol–water systems appear to give comparable results (5). However, these alcoholic reference solvents suffer from the same disadvantages as water, being highly structured and having complex intermolecular interactions such as hydrogen bonding prevalent.

Butler (6) suggested the use of the vapor state of the substance as the reference state for compounds that may interact with the solvent. Such a choice has the advantage that there are no solute–solvent interactions to consider, so theoretical calculations and considerations

Table II—Molar Solubilities of Several Polar Substances in Nonpolar Solvents[a]

Solvent	Solute: Acetanilide	Carbazole	Picric Acid	Salicylic Acid	Phthalic Anhydride
Cyclohexane	7.5×10^{-4}	1.7×10^{-3}	4.1×10^{-4}	4.0×10^{-3}	6.4×10^{-3}
n-Hexane	—	1.3×10^{-3}	3.0×10^{-4}	3.4×10^{-3}	5.0×10^{-3}
n-Heptane	9.3×10^{-4}	1.6×10^{-3}	3.3×10^{-4}	3.3×10^{-3}	4.9×10^{-3}
Isooctane	9.3×10^{-4}	1.1×10^{-3}	2.5×10^{-4}	2.3×10^{-3}	4.22×10^{-3}
Decane	9.3×10^{-4}	1.5×10^{-3}	4.2×10^{-4}	3.2×10^{-3}	4.9×10^{-3}
Dodecane	7.8×10^{-4}	1.4×10^{-3}	3.3×10^{-4}	2.8×10^{-3}	4.8×10^{-3}
Hexadecane	8.3×10^{-4}	1.7×10^{-3}	3.9×10^{-4}	3.0×10^{-3}	4.7×10^{-3}

[a] Values are taken from H. L. Fung and T. Higuchi, *J. Pharm. Sci.*, **60**, 1782(1971).

should be somewhat easier. However, when dealing with drug molecules, one is usually interested in their behavior in dilute solutions—not in the gas phase. Thus the choice of an infinitely dilute solution appears to be a more practical reference state. Furthermore, molecules of moderate- to long-chain length may often exist in quite different conformational states in the vapor phase compared to a solution, complicating interpretation of data for such molecules.

As a universal standard state for drug molecules, we would like to suggest adoption of a hypothetical 1 molal, 1 molar, or 1 mole fraction solution, acting as if it were infinitely dilute, where the solvent is a suitable aliphatic hydrocarbon such as cyclohexane or isooctane. The reference state would then be a solution of the drug in a hydrocarbon solvent at infinite dilution, and Henry's law would be the limiting law for the system. This suggestion is similar to that followed by Deal *et al.* (7) and Christian *et al.* (8) for certain chemical systems.

Nonaromatic hydrocarbon solvents simulate the most lipoidal parts of biological systems (*e.g.*, polymethylene portions) and may reflect in the purest form the lipoidal characteristics of fatty tissues (9, 10). In addition, these solvents interact with solutes essentially only through dispersive forces and are free from specific interactions arising from hydrogen-bond formation with hydrogen donor or acceptor species or from interactions arising from dipole–dipole interactions.

A number of consequences of such a standard state demonstrates its convenience and utility in many solution studies, particularly in drug systems. Since these nonhydrogen-bonding systems with limited dipolar character form nearly ideal solutions with similar species, it is possible to convert readily from chemical potentials in one solvent (*e.g.*, cyclohexane) to other solvent systems (*e.g.*, isooctane). We thus expect that the Henry's law constant for systems of a given compound in various hydrocarbon solvents should be essentially the same, provided the solvents have similar molar volumes. Literature data illustrating the relative constancy of such values over a wide range of hydrocarbon solvents are presented in Table I.

Considering the uncertainties in the data and the differences in molar volumes of the solvents, the values are remarkably similar for solvents as different as heptane and hexadecane.

This concept also leads to the suggestion that the solubility of a given organic solid should be about the same in various nonpolar solvents corrected for differences in molar volumes (Table II). These data indicate that in the limit of very dilute solution, the solubility of a given solute is independent of the nonpolar solvent but is rather a function of the crystal and other intermolecular forces of the solute.

The concept of similar activities in nonpolar solvents can also be extended to group contributions to the distribution properties of a molecule between water and an organic phase (Table III).

The methylene group contribution is found to be relatively constant over a large range of nonpolar solvents, showing that at infinite dilution the free energy contribution of a methylene group is nearly independent of solvent and further illustrating the usefulness of the proposed standard state.

Another significant, fundamental advantage in adopting hydrocarbon solvents as media for comparison of various solutes lies in their general freedom from hydrogen-bonding tendencies. Chemical potentials of such substances as phenols, steroids, carboxylic acids, esters, amines, and organic ion-pairs are drastically affected by any hydrogen bonding with the solvent (11–13), and the apparent magnitudes of the group contributions depend directly on the hydrogen-bonding tendencies of the solvent employed. Deviations from ideality (*i.e.*, in a hydrocarbon reference solvent) of physical properties in solvents capable of hydrogen bonding or other specific intermolecular interactions yield information allowing estimation of the magnitude of these interactions (13). Work is currently in progress in this laboratory to examine these theoretically expected results.

Table III—Factorial Group Contributions of a Methylene Group to the Partition Coefficients between Water and Several Organic Solvents[a]

Solvent	log F_{CH_2}[b]
Carbon tetrachloride	0.63
Hexane	0.62
Heptane	0.62
Cyclohexane	0.62
Benzene	0.61
Isopropyl ether	0.61
Octane	0.60
Hexadecane	0.58
Dodecane	0.58
Toluene	0.58

[a] S. S. Davis, T. Higuchi, and J. H. Rytting, to be published. [b] F_{CH_2} refers to the factorial group contribution of a methylene group to the partition coefficient between water and the given solvent (1).

Many polar substances of biological interest have limited solubilities in hydrocarbon solvents which lead to experimental difficulties in measuring physicochemical properties. However, methodology has been, and is being, developed which allows one to make such measurements. The value of having data obtained in an inert solvent justifies the additional effort required. This does not imply that all work should be done in hydrocarbon solutions or that they are always the solvents of choice. In fact, often a more polar solvent is more suitable for a given experimental study. However, one would expect that data obtained in a noninteracting solvent should be more revealing in many situations than data obtained in a more polar solvent where many properties are masked by complex interactions (*e.g.*, hydrogen bonding), and this should be considered in the interpretation of data. Work is being pursued which should allow one to take into account solvent differences in the limit of infinite dilution where solute–solute interactions such as association are negligible.

(1) T. Higuchi and S. S. Davis, *J. Pharm. Sci.*, **59**, 1376(1970).
(2) I. M. Klotz, "Chemical Thermodynamics," rev. ed., W. A. Benjamin, New York, N. Y., 1964, pp. 348–358.
(3) J. Ferguson, *Proc. Roy. Soc., Ser. B*, **127**, 387(1939).
(4) C. Hansch, *Farmaco, Ed. Sci.*, **23**, 293(1968).
(5) W. Scholtan, *Arzneim.-Forsch.*, **18**, 505(1968).
(6) J. A. V. Butler, "Chemical Thermodynamics," 5th ed., Macmillan and Co., London, England, 1962, pp. 383–385.
(7) C. H. Deal, E. L. Derr, and M. N. Papadopoulos, *Ind. Eng. Chem. Fundam.*, **1**, 17(1962).
(8) S. D. Christian, A. A. Taha, and B. W. Gash, *Quart. Rev.*, **24**, 20(1970).
(9) A. H. Beckett and A. C. Moffatt, *J. Pharm. Pharmacol., Suppl.*, **21**, 144S(1969).
(10) M. H. Bickel and H. J. Weder, *ibid.*, **21**, 160(1969).
(11) M. Nakano, N. I. Nakano, and T. Higuchi, *J. Phys. Chem.*, **71**, 3954(1967).
(12) A. F. Michaelis and T. Higuchi, *J. Pharm. Sci.*, **58**, 201(1969).
(13) T. Higuchi, J. H. Richards, S. S. Davis, A. Kamada, J. P. Hou, M. Nakano, N. I. Nakano, and I. H. Pitman, *ibid.*, **58**, 661 (1969).

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BOOKS

REVIEWS

Analytical Metabolic Chemistry of Drugs (Medicinal Research Series, Vol. 4). By Jean L. Hirtz. Marcel Dekker, 95 Madison Ave., New York, NY 10016, 1971. xvii + 395 pp. 15.5 × 23.5 cm. Price $24.50.

Dr. Hirtz's object in compiling this volume was to provide a source of physical and chemical techniques that would enable the analyst to "separate, purify, identify and determine" drugs and their metabolites in biological media. It would thus seem to have been aimed primarily at laboratories involved in some way in drug metabolism studies. A fine line was drawn by excluding from consideration those methods concerned only with studies of "absorption, distribution, blood levels, *etc.*" Citing 1044 references, some 350 drugs and their metabolites are covered.

The book is divided into twenty chapters, all but two classing drugs by chemical structure. The two exceptions are the chapters on antibiotics and on miscellaneous drugs. Most will find the grouping convenient. The style is reportorial, a detailed accounting, in almost cookbook fashion in many instances, of the methods by means of which drug metabolites were separated from their congeners in biological fluids and purified for the purpose of identification and quantitation.

One would hope the author to have been less modest and allowed the spice of his own experience to flavor the book in critical appraisal of the material he presents. The most serious criticism, however, is one suffered in common by all authors of technical books and is offered here as a stimulus to Dr. Hirtz to speed the updating, now in progress, of the present volume. The latest reference date was 1966 and the intervening six years have seen no slacking off of drug metabolism studies nor end to improvements in analytical methodology. For example, his report on chlorpromazine, though exhaustive, would benefit by reference to the more recent studies by Holmstedt and by Curry.

Inclusion of gas chromatographic techniques employing the recently introduced nitrogen detector, and of isolation techniques employing the newer XAD resins, would have made the book of more immediate practical value. The author may also have inadvertently slighted the women's lib movement by omitting any reference to synthetic steroids. Despite these shortcomings, the book would make, as the author suggests, a suitable companion piece to R. T. Williams' classic *Drug Detoxications.*

The foreword was written by Prof. E. R. Garrett who apparently had a role in bringing the book to this country from France and in "Americanizing" the translation which reads smoothly, with but few lapses in spelling, grammar, or syntax.

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