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Application of SCAP to Drug Design. 1. Prediction of Octanol-Water Partition Coefficients Using Solvent-Dependent Conformational Analyses

Anton J. Hopfinger*[1]

Department of Macromolecular Science, Case Western Reserve University, Cleveland, Ohio 44106

and Robert D. Battershell

T. R. Evans Research Center, Diamond Shamrock Corporation, Painesville, Ohio 44077. *Received July 28, 1975*

The solvent-dependent conformational analysis procedure (SCAP) has been used to predict the octanol–water partition coefficients of 20 different compounds with an average absolute error of 9%. SCAP predicts partition coefficients almost as well as the Hansch procedure using π constants where the absolute error for the 20 compounds is 5%. In addition to estimating partition coefficients, SCAP allows direct calculation of the corresponding solute–solvent interaction free energies. Moreover, binding free energies, based upon hydrophobic and polar interactions, may also be computed. Such free energies are not calculable using other available methods. SCAP also allows solvation free energies to be compared to, or analyzed with, the various intramolecular free energies of the solute molecule as well as all other associated conformational properties.

The basis for quantitative structure–activity relationships (QSAR) in drug research has been approached from two extremes. The most extensively applied techniques are those which attempt to relate biological activity to free-energy contributions, most notably the relative free-energy changes which are associated with the transport of the drug through different environmental phases.[2-5] The most significant of this class of methods is Hansch analysis.[4] Steric and conformational effects are considered in only marginal, grossly simplified ways.[4] The other major approach to establishing QSAR is based solely upon preferred molecular conformation in free space. Most often molecular orbital (MO) techniques have been employed to perform two-dimensional conformational analyses of drug molecules.[6] Environmental interactions and associated transport and absorption properties are completely neglected in these analyses.

Overall, Hansch analysis and some associated methods[7-9] have had considerably more success in the establishment of QSAR than investigations based upon MO calculations. Part of the success of Hansch analysis as compared to MO studies must be attributed to the very important role which transport and absorption play in drug activity. Still, empirical indicator variables related to stereochemistry have often been required in Hansch analysis in order to optimize the QSAR. Moreover, certain MO indices have been shown to correlate quite well with activities in some classes of compounds.[6] Thus, as one might have ultimately anticipated, both environmental thermodynamics and intramolecular structural chemistry need to be considered in the development of a general QSAR theory. In other words, a reliable and computationally quick technique which incorporates all the assets found in these two extreme approaches would be quite desirable in molecular design studies.

It is our contention that the solvent-dependent conformational analysis procedure (SCAP) developed in our laboratories meet these requirements. Conformational analysis is performed using empirical potential energy functions which are optimized so as to reproduce experimental results, principally crystal packing structures and preferred solution conformations.[10-13] SCAP computes conformational energetics using additive pair potentials which account for intramolecular (a) dispersion, (b) electrostatic, (c) hydrogen bonding, and (d) valence bond distortion interactions. In addition, the shapes of molecular orbitals are considered through intrinsic torsional potential functions. A hydration shell model is used to compute the free energy of solvation as a function of conformation. This potential function is discussed in detail in the next section. SCAP is a partitioned technique which consequently allows the user to directly employ any one of a variety of MO methods as part of the analysis procedure. A common practice is to locate minimum energy conformations using empirical energy calculations and then to extract the useful MO indices using a MO method for each of the minimum energy structures. Preferred minimum energy conformations may be found by (a) uniformly scanning any, or all, of conformational hyperspace, (b) random energy minimization via Monte Carlo simulation analysis, or (c) any one of six different exact multidimensional minimization procedures. The major component of SCAP is the CAMSEQ software system which allows the investigator to use extremely flexible and simple input data. In essence, only the molecular connection table of the molecule along with output format instructions is necessary to carry out a complete conformational analysis. Output from CAMSEQ is quite comprehensive and can include (a) all conformational–geometric data, (b) a wide range of intramolecular and environmental thermodynamic

quantities, (c) a set of MO indices from each of the interfacing molecular orbital software packages, (d) cathode ray tube or graphic plotter stick-ball illustrations of the preferred conformations of the molecule, and (e) data packages of the above-mentioned quantities for inclusion into statistical software procedures along with equivalent data packages from other molecules in order to generate QSAR. Empirical conformational analyses are 300–5000 times faster than MO techniques. The actual computational advantage depends upon the particular MO method. Empirical conformational analysis is being used in the study of small molecules and the successes and reliability of such calculations are becoming well documented.[10,11] In addition, empirical conformational analysis has been usefully applied to structural studies of macromolecules.[12-18]

Perhaps the most unique and promising aspect to SCAP, from the point of view of potential drug design, is the capacity to carry out *solvent-dependent* conformational studies. Thus, Hansch-type analysis, as a detailed function of molecular geometry *and* conformation, is an integral part of the method. Up until recently SCAP had been calibrated for five solvents: water, methanol, ethanol, formic acid, and acetic acid. We have just completed calculation of the octanol (1-octanol) solvation parameters so that direct comparison with Hansch studies is now possible. The method of computing solute–solvent free energy is based upon the hydration shell model proposed by Hopfinger[19] and documented in several reports.[19-22] SCAP has been tested for one class of molecules by computing the conformational properties of acetylcholine and several of its homologs in aqueous solution and comparing these findings to high-resolution NMR data.[11] However, additional testing of the solute–solvent interaction free-energy model is still in order. The purpose of this paper is to report the results of such a test. We have computed the octanol–aqueous partition coefficients for 20 compounds using SCAP.

Method and Theory. A. Determination of the Hydration Shell Parameters for SCAP. The hydration shell model is well documented in ref 19–22. For clarity, a short discussion of the model is presented here.

In adopting a hydration shell model it is assumed that a characteristic solvation sphere can be centered about each solute group of the solute molecule. The size of the sphere, which defines the hydration shell, is dependent upon the solvent molecule and solute group of the solute molecule. A particular change in free energy is assigned to the removal of a solvent molecule from the hydration shell. The size of the hydration shell and the shape of the solvent molecule dictates how many solvent molecules can occupy the hydration shell. The sum of the intersections of the van der Waals volumes of the atoms of the solute molecule with the hydration shell results in an excluded volume which determines how many solvent molecules are removed from the hydration shell when the solute molecule is in a particular conformation. Thus the hydration shell free energy is sensitive to conformation via excluded hydration shell volumes.

The hydration shell model is a four parameter system where n = the maximim number of solvent molecules which can occupy the hydration shell, Δf = the change in free energy associated with the removal of one solvent molecule from the hydration shell, R_v = the effective radius of the hydration shell, and V_f = the free volume of packing associated with one solvent molecule in the hydration shell.

The hydration shell parameters for water, methanol, ethanol, formic acid, and acetic acid have been determined by solute–group–solvent–molecule configurational energy calculations described in ref 20 and 22. Numerical values of the parameters are also reported in these references. This method of calculating the hydration shell parameters could not be used to determine the octanol hydration shell parameters. The size of the 1-octanol molecule along with its preferred all-trans conformation makes complete configurational analyses impractical. Consequently, the 1-octanol hydration shell parameters were estimated by extrapolating the methanol, ethanol, and 1-butanol (calculated as part of this work in the manner presented in ref 20 and 22) parameters, using a quadractic function, to 1-octanol. The most recent compilation of the aqueous and octanol hydration shell parameters is presented in Table I.

B. Calculation of Octanol–Water Partition Coefficients. For dilute solutions, as is implicitly assumed in SCAP calculations, the partition coefficient for water (w) and 1-octanol (o) is given by

$$P_{wo} = C_o/C_w = a_o/a_w \tag{1}$$

where C indicates the concentration of solute and a indicates the activity of the solute. The solute activity is always expressable as

$$a = \exp[(F - F^0)/RT] \tag{2}$$

where F is the free energy of the solute in the solvent at temperature T, F^0 is the free energy of the standard state, and R is the gas constant. Ln (P_{wo}) can, consequently, be expressed in terms of the solute-solvent free energies.

$$\ln (P_{wo}) = \frac{1}{RT}(F_w{}^0 - F_o{}^0) - \frac{1}{RT}(F_w - F_o) \tag{3}$$

We define the standard state as the minimum free-energy conformation in free space, thus

$$F_w{}^0 = F_o{}^0 \tag{4}$$

and $F_o \equiv$ global minimum free energy for the solute molecule in octanol as a function of solute conformation. F_w is defined analogously to F_o.

Assuming the partition coefficients are measured at room temperature, T = 300 K, the operational form of eq 3 becomes

$$\log (P_{wo}) = -0.735(F_w - F_o) \tag{5}$$

In applying eq 5 we neglect cross-interactions between octanol, water, and/or the solute which likely arise in a completely water-saturated 1-octanol solution used in the experimental determination of log (P_{wo})'s. This has been necessary because quantitative modeling and weighing of cross-interactions have not proved possible. The good results (see Table II) achieved in the direct application of eq 5 might be considered as pragmatic justification for neglecting cross terms.

It is recognized that certain adjustments are required in some π constants in order to account for the nonadditive factors inherent to such terms. Most significant of these are firstly, the immediate covalently bonded environment, be it aliphatic, aromatic, or polar, in which the group is located, and, secondly, the need to compensate for topological sterorestrictions, i.e., different π values for 1,-2-dimethyl ring substitutions as opposed to, say, 1,4-dimethyl ring substitutions. Hansch[4] has made several such

Table I. Aqueous and 1-Octanol Hydration Shell Parameters for SCAP

Solute group		Contact radius	Solvent							
			Water				1-Octanol			
Name	Symbol	r, Å	n	Δf,[a] kcal/mol	R_v, Å	V_f, Å^3	n	Δf,[a] kcal/mol	R_v, Å	V_f, Å^3
Amide		1.35	2	0.63	4.3	35.8	2	0.18	6.4	53.6
Amide		1.50	2	0.63	3.9	14.3	2	0.15	5.9	60.6
Ester		1.50	2	0.46	3.9	38.3	2	0.16	5.9	60.5
Carbonyl	=O	1.35	2	1.88	3.9	67.8	2	0.90	6.3	52.4
Ester	-O-	1.35	1	0.21	3.9	59.6	1	0.12	6.2	88.9
Hydroxyl	-O-	1.35	2	1.58	3.9	55.2	1	0.52	5.6	56.6
Carboxyl	-O-	1.35	2	4.20	4.1	64.1	1	1.10	6.1	46.8
Carboxylate anion	-O	1.35	4	4.20	4.1	42.5	2	2.45	6.5	60.9
Amide	-H	1.20	2	0.31	3.5	31.3	1	0.28	5.7	51.7
Hydroxyl	-H	1.20	2	0.31	3.5	54.7	1	0.52	4.3	53.8
Carboxyl	-H	1.20	2	0.31	3.5	54.7	1	0.88	6.1	51.6
Bromo	-Br	2.00	6	-0.12	6.6	93.5	3	-0.04	7.7	138.6
Chloro	-Cl	1.80	6	0.12	4.9	53.2	3	0.28	6.7	70.8
Fluoro	-F	1.35	3	0.21	4.3	69.7	2	0.18	5.5	44.5
Sulfide	-S-	1.85	8	-0.05	6.2	79.3	3	-0.06	7.8	99.2
Sulfoxide		2.20	4	0.71	5.8	58.8	1	0.88	7.0	82.3
Sulfone		2.35	6	0.95	6.1	46.6	2	0.89	7.1	69.9
Sulfonate		2.50	6	1.38	6.3	38.9	3	0.72	7.4	59.6
Sulfate		2.60	8	1.45	6.4	26.5	4	0.70	7.6	37.9
Nitro		1.35	2	0.56	4.3	35.8	2	0.32	6.4	53.6
Nitro	-O	1.35	2	2.70	4.1	42.5	2	2.55	6.5	70.1
Cyano	-C≡N	2.10	6	0.71	5.7	96.8	3	0.83	7.2	89.6
Acetylene		2.15	2	0.53	5.5	123.6	2	0.46	7.0	133.7
Ammonium ion	$-N^+H_3$	1.80	3	15.40	4.3	22.1	...[b]	...	...	...
Trimethylammonium ion	$-N^+(CH_3)_3$	2.10	9	2.08	7.3	54.0	...	...	...	...
Phosphate ester oxygen		1.75	2	2.68	3.8	47.8	...	...	...	...
Phosphate ester PO_2^-		2.05	4	2.82	4.9	73.5	...	...	...	...
Aromatic	>C—H	1.65	3	0.11	3.9	3.3	2	0.40	6.5	48.6
Aromatic	>C—X≠H	1.50	2	0.06	3.9	43.6	2	0.36	6.5	56.7
tert-Butyl carbon		1.60		0.00				0.00	6.5	
Methine		1.75	2	-0.13	5.5	104.8	2	0.36	7.1	56.7
Methylene		1.85	4	-0.10	5.5	60.8	3	0.39	7.4	36.8
Methyl		2.05	8	-0.13	5.5	41.8	4	0.41	7.1	31.5
Vinyl	>C=C<	2.35	2	0.26	5.5	89.6	2	0.51	6.7	103.6
Methoxy	-O-	1.35	2	1.18	4.2	68.5	1	0.20	6.1	72.3

[a] The convention used to report Δf is stating the amount of free energy required to *remove* the solute group from the hydration shell and place it in the bulk solvent medium. [b] ... indicates the calculation has not been made.

corrections for various π-constant group classifications. An initial π constant for a group has evolved into a set of π constants for the group, each reflecting the particular topologically bonded medium about the group. Rekker and Nys[23-25] have taken this concept to the point of defining a new hybrid set of group partition coefficients

Table II. Values of Log (P_{wo}) for 20 Compounds Determined Experimentally, by Hansch Analysis, and by the SCAP-Drug Design Software System. Also Included are Values for the F_o and F_w of the SCAP Calculations as Well as the Relative Errors in the Log (P_{wo})'s Based upon % Rel Error = [(Obsd − Calcd)/Obsd] × 100.

Compound	Log (P_{wo}) obsd[a]	Log (P_{wo}), Hansch analysis[b]		SCAP calculations			
				Log (P_{wo}) calcd		F_o,	F_w,
		Value	% rel error[c]	Value	% rel error[d]	kcal/mol	kcal/mol
Benzene	2.13	2.13	0.0	2.23	−4.7	4.65	1.62
Aniline	0.90	0.90	0.0	0.92	−2.2	5.44	4.19
Propylbenzene	3.68	3.63	+1.4	3.52	+4.4	5.55	0.76
2-Butanone	0.29	0.29	0.0	0.24	+17.2	3.80	3.47
Cyclohexanol	1.23	1.07	+13.0	1.22	+0.8	4.21	2.55
2,2-Dimethyl-propanol	1.36	0.94	+30.9	1.43	−5.1	3.98	2.03
2-Butanol	0.61	0.61	0.0	0.50	+18.0	3.05	2.37
Ethyl acetate	0.73	0.73	0.0	0.59	−19.2	3.96	3.16
Chloroform	1.97	1.67	+15.2	2.11	−7.1	4.65	1.78
Chlorobenzene	2.84	2.84	0.0	2.82	+0.7	6.01	2.17
2-Methyl-2-butanol	0.89	0.91	−2.2	0.75	+15.7	3.08	2.06
Propionitrile	0.16	0.16	0.0	0.19	−18.8	3.71	3.44
1-Pentyne	1.98	1.98	0.0	1.96	+1.0	2.80	0.13
Benzyl alcohol	1.10	1.47	−33.6	1.37	−24.5	7.01	5.05
Chlorobutane	2.39	2.39	0.0	2.17	+9.2	3.82	0.87
Toluene	2.69	2.63	+2.2	2.62	+2.6	4.64	1.08
Ethylbenzene	3.15	3.21	−1.9	3.01	+4.4	5.04	0.96
Flourobenzene	2.27	2.27	0.0	2.28	−0.4	5.23	2.13
Nitrobenzene	1.85	1.85	0.0	2.08	−12.4	15.38	12.66
Pentane	2.50	2.50	0.0	2.17	+13.2	4.20	1.25

[a] As reported in ref 23. [b] From π values given in ref 4. In some instances the π values used were taken from the log (P_{wo}) obsd experiments. Hence, agreement is forced and artificial. [c] Average absolute error = 5.0%. [d] Average absolute error = 9.0%.

called f constants. The SCAP calculations, at least in principle, take into account *all* nonadditive, secondary-structure corrections in computing partition coefficients. This is a consequence of the geometry assigned to the hydration shells coupled with the interaction of the hydration shells with the solute molecular geometry.

Lastly, we are cognizant that some important chemical groups have not been subjected to hydration shell analysis. That is, Table I is incomplete. We anticipate that as the methods reported here are extended to additional compounds, Table I will evolve into a more nearly complete set of parameters.

Results and Discussion

A significant test of SCAP is to see how well it predicts log (P_{wo}). Table II lists log (P_{wo}) values determined experimentally,[26] computed by Hansch analysis, and computed by SCAP for 20 different solute species, along with the respective relative errors. Also reported in Table II are the individual free energies of solute–octanol, F_o, and solute–water, F_w, interactions as determined directly from the SCAP calculations.

The most significant observation made from an inspection of Table II is the good agreement between the observed log (P_{wo}) values and those computed using SCAP. The maximum difference, for benzyl alcohol, is 24.5% while the average difference is approximately 9%. An inspection of Table II suggests that SCAP predicts log (P_{wo}) values with almost the same reliability as that obtained using π constants.

The average absolute error using Hansch analysis is 5% and it is more accurate in the estimation of log (P_{wo}) for 16 of the 20 molecules than the SCAP procedure. Moreover, the test set used provides a natural bias toward the Hansch constants since a number of the compounds included were used to derive basic π values. It would appear 12 out of the 20 compounds fall into this category. Both methods appear adequate for semiquantitative usage. However, SCAP additionally provides estimates of the individual free-energy contributions from the aqueous and hydrophobic phases. Moreover, specific solute sites can be selectively allowed to interact with aqueous or hydrophobic media using SCAP. Thus, SCAP delivers the flexibility, not available in other design procedures, of comparing solute–solvent free-energy contributions. Optimum absorption binding free energies based upon hydrophobic and hydrophilic interactions can also be estimated.

It should be noted that most of the test species used in this study are relatively rigid and nearly independent of conformational freedom. Those molecules which possess potential conformational flexibility, for example, pentane, are still relatively rigid owing to intramolecular interactions. Consequently, it is not possible to discern from the work reported here how much better, if at all, the SCAP calculations will predict log (P_{wo}) than Hansch analysis in flexible molecules where the additive principle is least reliable and conformational effects are most pronounced.

SCAP appears to be computationally least reliable for molecules containing extensive aliphatic and/or polar groups. The source of error has been assigned to an incomplete modeling of the solvent organization about the solute molecule. Polar groups of the solute induce solvent-molecule structuring beyond the first hydration shell layer. The aliphatic groups order the first layer of solvent molecules *across* hydration shells of the respective aliphatic solute groups. For both classes of solute–group interactions intersolvent molecule organization beyond the first hydration shell layer of the solute groups is not considered in the SCAP solute–solvent free-energy functions leading to errors in the computed log (P_{wo})'s.

Nevertheless, it is significant to note that in many compounds the first layer hydration shell free-energy model accurately estimates the partition coefficient. This can be interpreted as indicating that the bulk of the solvation process involves only the first layer of solvent molecules about the solute groups. A second point to be made is that the parametric values used in the present

hydration shell model are the direct result of independent theoretical calculations which have not been optimized on the basis of experimental data as have the π constants. This suggests that the theoretical calculations, and the associated potential energy functions, used to estimate the hydration shell parameters are realistic. However, these theoretical values of the hydration shell parameters could be used as initial parametric estimates from which an optimized set of values could be generated by using available experimental log (P_{wo})'s. Since interactions from second and, perhaps, even additional layers of solvent molecules probably are required to describe solvation thermodynamics, the differences between the optimized and existing hydrations shell parameters might be thought of as the contributions which the additional solvent layers make to the solute–solvent interactions.

The SCAP is limited to the calculation of dilute solution properties of a solute molecule. Solutions in which solute molecules associate, or the solute concentration is sufficiently high so as to alter the structure of bulk solvent, probably cannot be treated by SCAP. Still, it is our hope that this paper will be the first in a series reporting the successful application of SCAP to problems in molecular design. Our immediate interests will focus upon the prediction of optimim binding energy between some agonists and their receptors and its significance in generating useful QSAR.

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Molecular Connectivity. 6. Examination of the Parabolic Relationship between Molecular Connectivity and Biological Activity

Wallace J. Murray,*[1] Lemont B. Kier,

Massachusetts College of Pharmacy, Boston, Massachusetts 02115

and Lowell H. Hall

Eastern Nazarene College, Quincy, Massachusetts 02169. *Received August 27, 1975*

The topologically derived, nonempirical molecular connectivity index, χ, for several classes of compounds is shown to be parabolically related to the biological activities of these compounds. Similar nonlinear relationships were previously shown between the octanol–water partition coefficients, expressed as log P, of the compounds and their biological activities. These and previous studies indicate that many physicochemical properties presently used in structure–activity studies may be intermediaries between the nonempirical molecular structure encoded in χ and measured biological activities.

The manner in which atoms in a molecule are arranged or connected is called molecular connectivity, a fundamental characteristic of any molecule. Many physical properties are dependent not only upon the number of atoms in a molecule (additive property) but also upon the arrangement of those atoms within the molecule (constitutive property). It is well established that simple lengthening of a hydrocarbon side chain by $-CH_2-$ units will correlate in a linear manner with most physical properties. However, branching in a hydrocarbon side chain has not previously been amenable to correlation. For example, pentyl alcohol, isopentyl alcohol, *sec*-pentyl alcohol, and *tert*-pentyl alcohol all have the same number of carbons and the same molecular weight but have different boiling points, molecular polarizabilities, solubilities, and partition coefficients.

For many years correlation of properties with branching has been attempted with but limited success.[2] Randic[3a] has recently formulated a branching index, later called χ or the molecular connectivity index,[3b] which seemingly encodes the additive and constitutive nature of a molecule. In the same way that the universal constant "π" is a