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Calculation of Drug Solubilities by Pharmacy Students

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A method of estimating the solubilities of drugs in water is reported which is based on a principle applied in quantitative structure-activity relationships. This procedure involves correlation of partition coefficient values using the octanol/water system and aqueous solubility. After identifying the atoms or groups comprising a compound the students need to employ but a few approximate hydrophilic or lipophilic numbers assigned to these in calculating the log P value of the drug or chemical and then place the agent in the appropriate soluble or insoluble category. Although this method does not always provide exact categorization it does so in a great majority of cases and permits the student to recognize certain potential chemical and therapeutic incompatibilities.

One of the most frequent questions asked medicinal chemistry faculty by pharmacy students is, "How do I know if a drug is soluble or insoluble in water?" These students were cognizant of the importance of such information in predicting chemical and therapeutic incompatibilities. Prior to the introduction of the procedure described in this paper, along with a discussion of the acid-base character of drugs, many students were incapable of determining if an insoluble material will be formed during a reaction and whether or not water can be used as the solvent for a certain drug. A method, therefore, was devised to enable the students to estimate a drug's solubility by assigning a numerical value to a molecule which relates to this property. This procedure, which is based on a scientific rationale, requires the use of only a few numerical values and a brief calculation time.

PROCEDURE

With the advent of quantitative structure-activity relationship (QSAR) concepts has come an increased awareness and use of physiochemical parameters such as partition coefficients and steric and electronic factors for correlation with biologic properties. The former constant is deemed most critical to a drug's overall effect and most students are exposed to this principle during their pharmacy education.

Most work has been done with partition coefficients based on the octanol/water system expressed as the \log_{10} or log P. Although this is a measure of the solubility characteristics of the whole molecule, one normally uses the sum of the fragments of the molecule which have been assigned relative hydrophilic-lipophilic values, (π), to calculate log P. Using this procedure, a positive value for π means the substituent, relative to H, favors the octanol phase (*i.e.*, lipophilic). And negative π value indicates its greater affinity for water (*i.e.*, hydrophilic).¹ The environment of the substituent can influence the relative π value, but for the most part, these values are small and can be

introduced while teaching a course in the medicinal chemistry sequence to about 80 second professional year students and then applied to those agents being discussed throughout the semester. The students learned eight π values as follows: C (aliphatic or C1²) = 0.5; phenyl = 2.0; C(=O)O or C(=O)N = -0.7; O or N (in amines, hydroxyls and ethers but not in hydrazines or N-O compounds) = -1.0; and -S- = 0. These numbers were obtained by rounding off literature values; exceptions being the sulfide³ and the amido group.⁴ The students then needed only to identify these fragments in the molecule and calculate the sum of the π values to calculate an approximate log P. After being given several examples in lecture and solving problems themselves at the chalkboard all students knew the π values and the only difficulty they occasionally experienced was identification of the appropriate fragments in a molecule (*e.g.*, in cyclic drugs).

The USP provides official definitions of water solubilities wherein "soluble" is defined as 3.3 to 10 percent. For our purposes therefore, those drugs with solubilities above 3.3 percent are considered soluble and those below, insoluble. The solubilities of drugs used in this paper were taken from the *Merck Index*(1), *Remington's Pharmaceutical Sciences*(2) or the *Handbook of Chemistry and Physics*(3). The octanol/water log P values were from Hansch and Leo(4) and the π values are from three different sources(4, 5 and 6).

Having a definition of solubility and a means of calculating log P, what remains is a method of correlating these two parameters. Through the examination of a large number of log P and solubility values, an arbitrary stan-

¹The term " π " more correctly refers to the system of substituting atoms or groups for hydrogen while the fragment system of calculating log P values involves the summing of appropriate structural elements. In approximating log P values this distinction normally is not critical.

²Average of 0.71 (aromatic) and 0.39 (aliphatic) values.

³Taken from aliphatic SCH₃ (0.45) and aromatic SCH₃ (0.61), each minus a methyl (0.5).

⁴Although the literature π values are -1.49 (aromatic) and -1.71 (aliphatic)

dard was adopted whereby those drugs with positive log P values over 0.5 are considered water-insoluble and those with less than 0.5 log P are deemed soluble. An early use of log P and π in correlating chemical structure with aqueous solubility involved free-energy changes of liquids(7). Although this study included only four of 156 compounds with log P values less than 0.5, the dividing line between soluble and insoluble appears to be in the same range. Although this method is applicable to a large number of drugs it is, of course, restricted to those containing only C, Cl, N and O. Other limitations should also be recognized, chief among these is the acid-base character of drugs. When dealing with acids or bases, log P values are normally determined at a pH, either very acid or alkaline, so that ionization is suppressed and only the neutral, most lipophilic form is present. Since most drugs are either weak acids or bases this possible discrepancy must be taken into consideration. Scherrer and Howard(8) have pointed out that when an ionizable compound is equilibrated in a two-phase system at a pH at which it is partially ionized, its concentration in the organic phase is not determined by log P alone. These investigators, therefore, introduced distribution coefficients (log D) as a correction based on the pK_a of the compound. Log D is also termed the apparent partition coefficient (P_{app}), which is in turn related to the true (corrected) partition coefficient (P_{corr}), P_{corr} is equal to $P_{app}/(1-\alpha)$, where α is the degree of ionization. Although this correction is not readily adaptable to our estimation method there have been a few drugs whose log P values have been determined using octanol/water at pH values that approximate those imparted to water by these agents and some examples will be presented later.

APPLICATIONS AND DISCUSSION

This method was initially applied to those CNS drugs covered in the medicinal chemistry course and described by the textbook(9). This consisted of 29 sedative-hypnotics, six central relaxants, three benzodiazepines, 14 phenothiazines, 12 anticonvulsants and 12 miscellaneous drugs. A few more such agents could have been included if π values for Br and F were introduced. Of this total the solubilities of 72 (95 percent) were correctly determined with three anomalies and one 'borderline' estimation. The success rate with this classification of drugs is not unexpected in view of the relationship between their log P values and depressant activity. It has been established that most organic drugs affecting the CNS require a log P of approximately 2 to pass the blood-brain barrier and gain access to the brain(10). A partition coefficient of this magnitude would translate to a water-insoluble compound. Considering all drugs, there are relatively few that are soluble in the non-salt form, a situation that should make easier the teaching of solubilities. To simply state that drugs in their free form are insoluble is not, however, satisfactory. In addition, there are situations when it is important to be cognizant of relative solubilities, a comparison made possible using the calculation method.

Since one of the larger members of this class of CNS depressants are barbiturates it might be instructive to examine the heterocycle common to these and at least one specific agent. Being cyclic ureides the barbiturates contain

acid portion(10). The most water-soluble drug is diethylbarbital with a calculated log P of 0.6. This agent is also one of the few weakly acidic drugs whose log P has been determined in octanol/water at other than a low pH. At pH 8.1 its log P value is 0.18 and has a log P value of 0.71 at pH 5. An environment closer to neutrality on the acid side would have been preferred for our comparison purposes but the value falls in the insoluble range according to the established definition; the actual solubility is 0.7 percent.

An examination of the anomalies and 'borderline' drugs, which fall in the anticonvulsant and central relaxant classes, may also be of interest ethosuximide, containing an amido group, six carbons and a carbonyl oxygen, has an estimated log P of 1.3 but is water-soluble. Trimethadione, a neutral drug with one each amido and carboxy groups and six carbons, calculates to 0.6 and is 5 percent soluble and is considered 'borderline'. The carbamates methocarbamol, 2.5 percent soluble, and chlorphenesin carbamate, almost insoluble, have simplified and incorrect calculated log P values of -0.7 and 0.3, respectively. This discrepancy can be accounted for on the basis that the infrequently encountered carbamyl moiety actually has a π value of -1.15 instead of the -1.7 used and an aromatic methoxy π value is -0.2 as compared to our value of -0.5. This situation exemplifies the errors that can be introduced when an attempt is made to simplify the calculation process.

The method was completely successful when applied to the 35 local anesthetics described in the student's text. Interestingly, the basic drug procaine which was recorded log P (octanol/water) values of -0.32 (pH 7) and 0.14 (pH 8) is only 0.5 percent soluble. Our calculated value places this drug in the correct water-insoluble category. The procedure was also correct in assigning 34 analgesics and analgesic antagonists, 30 antihistamines and 25 nonquaternized autonomic blocking agents, all water-insoluble.

The salicylic acid derivatives, aspirin, salicylamide and salicyclic acid itself, were also examined. A true calculation of the latter requires the introduction of an additional π value, that for intramolecular hydrogen bonding (IMHB). Without this factor salicyclic acid log P value easily calculates as 0.3 but is only 0.2 percent soluble. If the 0.65 IMHB value is added we get a log P value of 0.95 which places it in the correct water-insoluble category. The literature value for this acid is 0.95 (pH 4); the pH of a saturated solution is 2.4. The need for applying the IMHB factor is infrequent but can be used during instruction in emphasizing this phenomenon which is of importance in biological action. It could also be pointed out that the isomer, p-hydroxybenzoic acid, cannot undergo IMHB and is eight times more soluble. Salicylamide has very close values in all respects to salicyclic acid while aspirin, 0.3 percent soluble, calculates to 1.1 log P without IMHB. As was the case with procaine, our procedure gives correct categorization of solubility while the experimental log P values for aspirin of -0.02 (pH 5) and -0.9 (pH 5.6) would not. It appears that there are situations when exact, or even simplified, calculated values are more meaningful than experimentally derived ones. One reason for this is the many experimental values, supposedly measured under like conditions but in different laboratories, that may vary for the same compound by as much as 1.5 log units. A variance of 0.5 units is common.

Table I. Additional representative solubilities

Drug or chemical	Log P Calculated	Log P Observed	Predicted solubility	Literature solubility
Chlorpromazine	5.0	5.3	I ^b	I
Dibucaine	4.3	4.2	I	I
Phenytoin	3.1	2.5	I	I (1.5%)
Amphetamine	2.5	1.8	I	SS ^e
Phenoxymethyl penicillin	2.4	2.1	I	I (0.08%)
Amobarbital	2.1	2.1	I	I (0.08%)
Phenacetin	1.8	1.5	I	I (0.1%)
Phenobarbital	1.6	1.6	I	I (0.1%)
Parachlorophenol	1.5	2.4	I	SS (2.7%)
Ethyl chloride	1.5	1.4	I	I (0.57%)
Benzoic acid	1.3	2.0	I	I (0.33%)
Thiazole	0.5	0.4	B ^c	SS
Propanol	0.5	0.3	B	S
Acetylacetone	0.5	0.3	B	S (12.5%)
Ethanol	0.0	-0.3	S ^d	S
Nicotinamide	-0.2	-0.4	S	S
Lactic Acid	-0.7	-0.6	S	S
Glycerol	-1.5	-1.7 ^a	S	S
Citric Acid	-1.6	-1.7	S	S

^aFrom Pomona College Medicinal Chemistry Project data. ^bInsoluble. ^cBorderline solubility. ^dSoluble. ^eSlightly soluble.

in this category and may be considered exceptions to the SAR requirement. Chloral hydrate is highly ionized as a result of the inductive influence of the chlorine atoms and is very soluble. Neither its log P, nor that of paraldehyde, has been determined in octanol/water but it calculates by our method to 0.5 or 'borderline'. Doubtless the true value is considerably lower because of the halogen effect. The neutral paraldehyde calculates correctly giving a 0 log P and is 12 percent soluble. The solubilities of some additional drugs and chemicals, arranged by increasing hydrophilicity and containing a variety of chemical groupings, are shown in Table I.

After mastering the determination of drug solubilities using the eight constants the students will be able to proceed to drugs containing atoms or groups not yet considered. Examples of these are the nitro and nitrate groups. The former has a π value of -0.85 (aliphatic) and -0.28 (aromatic) which can be averaged and rounded off to -0.6, and not the -0.3 calculated by the previous method. Similarly the nitrate group, found in several vasodilators, has a π value of ca. 0.2 and not -4.0.

It should be emphasized that this simplified method of estimation has only general application and cannot, without becoming cumbersome, be applied with success in all cases. This is particularly the case when electronic factors play an important role. When examining the amphoteric antibacterial sulfonamides, for example, we find that the addition of one or two methyl groups to the pyrimidine of sulfadiazine to give sulfamerazine and sulfamethazine yields a progressive increase, instead of the expected decrease, in solubility. The effect of the methyl is to increase the lability of the N¹ amide hydrogen and, thus the molecule's hydrophilicity.

In general, the log P of heterocycles, such as those found in sulfonamides, can be estimated by subtracting 0.5 from phenyl ($\pi = 2.0$) or naphthalene ($\pi = 3.4$) for each carbon substituted by a heteroatom and adding the π value for the latter. Thus, the calculated π values for pyridine and isoquinoline are 0.5 (0.64 observed) and 1.9 (2.0 observed), respectively, and permit the solubility determination of such drugs as nicotinamide and dibucaine, Table I.

This method of determining drug solubilities has been enthusiastically received by the pharmacy students in our medicinal chemistry course. It has done much to dispel confusion and to increase their confidence in dealing with drugs as chemicals capable of causing therapeutic and dispensing problems. Provided its limitations are considered, it can be a useful tool in the teaching of an important and relevant topic.

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