of hydrochlorothiazide tablets composed of lactose and povidone did not change after 1 year at room temperature supports this implication.

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ACKNOWLEDGMENTS

Abstracted in part from a dissertation submitted by Paul J. Jarosz to the Graduate College, University of Iowa, in partial fulfillment of the Doctor of Philosophy degree requirements.

Determination of Octanol–Water Equivalent Partition Coefficients of Indolizine and Substituted 2-Phenylindolizines by Reversed-Phase High-Pressure Liquid Chromatography and Fragmentation Values

CLAUDIO L. K. LINS, JOHN H. BLOCK ˣ, ROBERT F. DOERGE, and GERARD J. BARNES

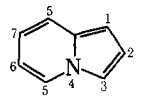
Received May 19, 1980, from the *School of Pharmacy, Oregon State University, Corvallis, OR 97331.* Accepted for publication July 27, 1981.

Abstract □ Octanol–water partition values were calculated using fragmentation values and measured rapidly by high-pressure liquid chromatography (HPLC) on bonded octadecylsilane supports. Log *P* for indolizine, π, and fragment (*f*) values for the indolizinyl substituents were determined using both methods. Good agreement was obtained for all three values.

Keyphrases □ Partition coefficient—indolizine and 2-phenylindolizines, determination by high-pressure liquid chromatography and fragmentation values □ Indolizine—substituted 2-phenylindolizines, partition coefficients determined by high-pressure liquid chromatography and fragmentation values □ High-pressure liquid chromatography—determination of partition coefficients of indolizine and 2-phenylindolizines □ Fragmentation values—determination of partition coefficients of indolizine and 2-phenylindolizine

There is considerable interest in partition coefficient determination in the area of rational drug design (1). The partition coefficient, log *P*, represents the distribution of a substance between an organic and aqueous phase. Several methods may be used to determine partition coefficients including the shake-flask method, liquid–liquid chromatography on liquid impregnated plate technique, and high-pressure liquid chromatography (HPLC).

No studies have been done on the log *P* of indolizines. Indolizine (I) is a 10π aromatic heterocyclic compound with the nitrogen at the bridge head position. It is nearly electrically neutral and weakly basic with a pKa value of 3.94 (2).



I

For the normal shake-flask method, octanol and water have been used previously as the biological lipid and aqueous phases, respectively, in partition determination (3). Due to the instability of the indolizine nucleus, measuring log *P* values of this compound by this technique has proven difficult. The shake-flask procedure (4) is a tedious, time-consuming process and subject to purity, stability, and mass-balance problems from the compounds being measured.

BACKGROUND

Liquid chromatography on paper or lipid-impregnated plates has been used as an alternative to octanol–water partition. Martin (5) derived Eq. 1 for thin-layer or paper chromatography (TLC):

0022-3549/82/0600-0614$01.00/0

Table I—Estimated Log *P* Values on HPLC Using Octanol-Saturated Water as Mobile Phase

Compounds	Log *k'*	Log *P*	
		Literature[a]	HPLC[b]
Anisole	0.518	2.08	2.08
p-Chloroacetophenone	0.711	2.35	2.29
p-Bromoacetophenone	0.884	2.43	2.48
Toluene	1.09	2.71	2.71
Chlorobenzene	1.24	2.84	2.87
Benzophenone	1.49	3.18	3.15
Indolizine (I)	0.894	—	2.49 ± 0.02[c]

[a] Reference 18. [b] Equation 3. [c] Standard error of the estimate from Eq. 3.

$$\log P = \log K + R_m \qquad \text{(Eq. 1)}$$

where K is a constant for the system, $R_m \approx \log [(1/R_f) - 1]$ where R_f has the usual meaning.

Reversed-phase HPLC has been used to measure the lipophilicity of several compounds. In HPLC, the capacity factor k' replaces R_m and is defined as:

$$k' = \frac{(t_r - t_0)}{t_0} = \frac{(V_r - V_0)}{V_0} = \frac{(d_r - d_0)}{d_0} \qquad \text{(Eq. 2)}$$

where:

t_r = retention time of the compound
t_0 = retention time of the solvent
V_r = retention volume of the compound
V_0 = retention volume of the solvent or dead volume
d_r = distance between the peak of the compound and peak of the solvent front
d_0 = distance between the point of injection and the peak of the solvent front.

Haggerty and Murrill (6) measured log *P* values for a family of nitrosoureas using a column packed with octadecylsilane bonded to silica[1] and eluted with 30% acetonitrile in pH 7.41 buffer solution. Another study (7) obtained good correlation between log *k'* and log *P* of some substituted phenol and aniline derivatives using bonded[2] columns with various mixtures of distilled water and acetone as the eluent. Exhaustive silylation of octadecylsilane reversed-phase columns were reported to give a better correlation between *k'* and log *P* than the untreated packing material (8). The rationale is that exhaustive silylation eliminates adsorption phenomena due to free SiOH sites.

The lipophilicities of 1,4-benzodiazepine derivatives were determined using oleyl alcohol supported on a porous silica[3] as an HPLC procedure and the results were compared with reversed-phase TLC techniques (9). Similar work was done (10) using 1-octanol supported on diatomaceous earth[4] with octanol-saturated water as the eluent.

Various HPLC techniques were compared (11) using three different columns: one reversed-phase[1], one unmodified absorption system[5], and one nonbonded porous silica[6] coated with 1-octanol or squalene. Several good correlations between log *k'* and log of biological activity were reported. Investigators using these techniques were warned to be careful in interpreting these correlations. Unger *et al.* (12) had near perfect agreement between shake-flask and reversed-phase HPLC procedures over a log *P* range of 3.5 units, using octanol-saturated pH 7.00 (0.01 *M*) phosphate buffer as the mobile phase, and silylated octadecyl-bonded silica[1] as the stationary phase.

The latter HPLC procedure (12) was used in the present study to determine the log *P* of unstable indolizine. Then, a modified HPLC method was developed to measure partition coefficients of 3.5 to 5.0. Using this method, the π and fragment values for the indolizinyl substituent were also determined.

EXPERIMENTAL

Solvents were analytical reagent quality, and the 1-octanol for chromatographic purposes was purified according to reported procedures (13). Standards were obtained from commercial sources. Indolizine and 2-phenylindolizines were synthesized by the Boekelheide (14) method and *via* the Chichibabin-Stepanow (15, 16) route, respectively.

[1] Corasil C18, Waters Associates, Milford, Mass.
[2] Porasil B, Waters Associates, Milford, Mass.
[3] Porasil C, Waters Associates, Milford, Mass.
[4] Hyflosupercel, Johns-Manville.
[5] Corasil II, Waters Associates, Milford, Mass.
[6] Porasil A, Waters Associates, Milford, Mass.

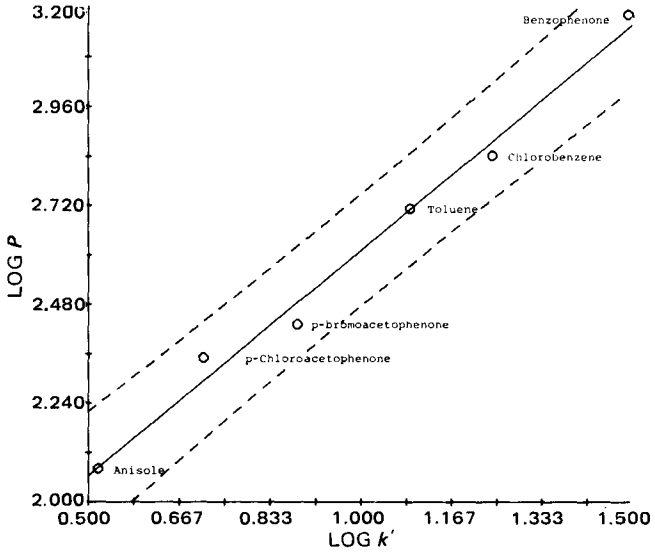


Figure 1—*Literature log* P *values* versus *log* k' *determined by octanol-coated octadecylsilyl-bonded support with octanol-saturated water as mobile phase. Key: (- - -) the 95% confidence limits of the predicted line; (○) standards are from Table I.*

Samples were dissolved in water-saturated octanol and/or a minimal amount of methanol. Sodium nitrate in octanol-saturated water was used as a suitable nonretained compound to define dead volume, V_0. Sample concentrations were adjusted so that the relative peak areas remained approximately constant.

The high-pressure liquid chromatograph[7] consisted of a pump[8] and injector[9]. A UV–visible spectrophotometer[10] with low dead volume flow cells was used as detector. Standards and indolizines were analyzed at 260 nm. Peaks were measured on a 25-cm dual pen recorder[11]. The column packing of silica particles (37–50 μm) with an octadecylsilane-bonded coating[1] was persilated by McCall's method (8). Stainless steel columns (2-mm i.d.) in lengths of 5, 10, 30, and 60 cm were packed using published "tap-fill" procedures (17), and then mounted onto the liquid chromatograph.

Two methods were used to determine log *P*. One system followed Unger's procedure (12). The second procedure was patterned after reported methods (6–8) using persilated octadecylsilane columns[1] with 40% (v/v) acetonitrile in water as the mobile phase to determine large log *P* values (range 3.5 to 5.0) of standards and 2-phenylindolizines. Samples were dissolved in acetonitrile and/or a minimal amount of methanol. For both procedures, all solutions containing solute were first filtered[12] to reduce contamination or column clogging. All experiments were performed at ambient temperature (25°).

Log *P* values for unknowns obtained from HPLC data were determined by calculation using regression analysis derived from literature log *P* values (18) *versus* their log *k'* obtained experimentally. Daily standards were run with excellent reproducibility. Statistical analyses were performed using a statistical package[13].

RESULTS AND DISCUSSION

Log *P* Determination of Indolizine by HPLC—Due to the instability of indolizine, its log *P* value was estimated using HPLC techniques. Compounds possessing physical properties similar to those of indolizine were selected. These reference compounds (the first six compounds in Table I) were electrically neutral and had partition coefficients close to the estimated value for indolizine (log *P* 2.45 calculated by the fragment method). These compounds were chromatographed on a silylated column[1] coated with octanol. The mobile phase was octanol-saturated water

[7] Model ALC/GPC 201 Liquid Chromatograph, Waters Associates, Milford, Mass.
[8] Model M6000A, Waters Associates, Milford, Mass.
[9] Model U-6K, Waters Associates, Milford, Mass.
[10] Varian Model 635.
[11] Soltec.
[12] Fritted Disc, 10–15μ, Pyrex.
[13] Oregon State University Statistical Interaction Programming System (SIPS).

Table II—Estimated Log *P* Values on HPLC Using 40% (v/v) Acetonitrile in Water

Compound	Log *k'*	Log *P*	
		Literature[a]	HPLC[b]
o-Dibromobenzene	0.580	3.64	3.60
m-Dibromobenzene	0.732	3.75	3.93
Dibenzofuran	0.748	4.12	3.96
Fluorene	0.857	4.18	4.21
Diphenylacetylene	1.10	4.78	4.76

[a] Reference 18. [b] Equation 4.

using a 10-cm column. A linear relationship between log *P* values and their log *k'* values (Fig. 1) is given by:

$$\log P = 1.516\ (\pm\ 0.059) + 1.094\ (\pm\ 0.057) \log k' \qquad \text{(Eq. 3)}$$

$$n = 6, s = 0.0453, r^2 = 0.9893, F_{1,4} = 370$$

The values in parentheses are the standard errors, *n* is the number of compounds, *s* is the standard error of the corrleation, r^2 is the coefficient of determination, and *F* is the overall significance parameter with the indicated degrees of freedom.

Unger *et al.* (12) showed that nitrogenous compounds capable of hydrogen bonding with nonsilated silanol sites deviated from the calculated regression line. Pyridine and certain substituted pyridines deviated the most. Quinoline did not deviate as much. Acridine, 2,6-lutidine, and *N,N*-dimethylaniline fit the regression model. It appears that as the pKa of an amine decreases and steric hindrance about the nitrogen increases the ability to adsorb onto an open silanol site decreases. Indolizine has a reported pKa of 3.94 (2), far lower than that for pyridine (5.19) or quinoline (4.90). Furthermore, protonation of indolizine occurs on carbons 1 and 3, not on the nitrogen atom (19). The ring nitrogen is sterically hindered. Finally, in some unreported earlier work[14] the use of shift reagents was investigated in an attempt to simplify the proton NMR spectrum of indolizines. No noticeable change in the chemical shifts of any of the protons was obtained, which is strong evidence of a very weakly basic and/or sterically hindered nitrogen (20). For these reasons, reference compounds containing nitrogen capable of hydrogen bonding to silanol sites on the HPLC column were omitted.

The log *k'* value for indolizine (0.894) was measured under the same conditions used for the standards (Table I) and a log *P* value of 2.49 was calculated using Eq. 3.

Determination of π Value of the Indolizinyl Moiety by HPLC—Because the 2-phenylindolizines are more stable than indolizine their log *P* determinations using the traditional shake-flask procedure (4) were attempted without success. These compounds degrade in solution with changes detectable in the UV spectrum within 1 hr. Undoubtedly agitation in the octanol–water system hastened this degradation. Thus, an HPLC procedure was devised.

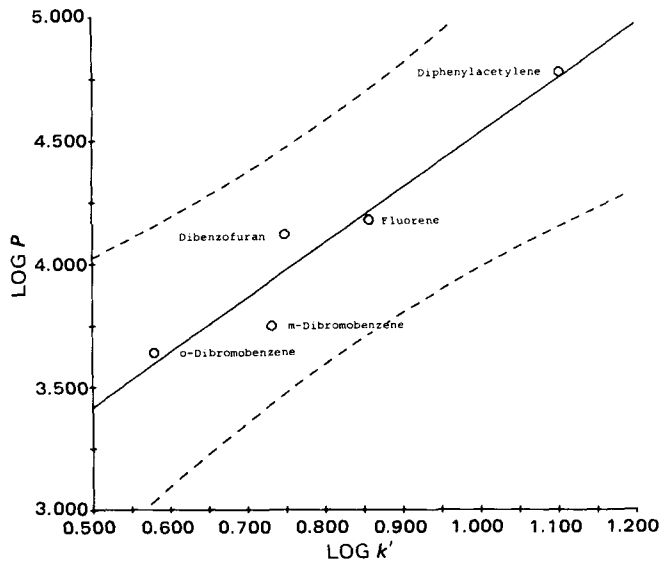


Figure 2—*Literature log* P *value* versus *log* k' *determined by 10-cm column*[1] *using 40% (v/v) acetonitrile in water as the mobile phase. Key: (- - -) the 95% confidence limits of the predicted line; (○) standards are from Table II.*

[14] J. H. Block, unpublished.

Table III—Estimated Log *P* on HPLC of 2-Phenylindolizines

Compound	X	Y	Log *k'*[a]	Log *P* HPLC[b]
II*a*	H	H	0.892	4.29 (±0.07)
II*b*	OCH_3	H	0.851	4.20 (±0.07)
II*c*	H	OCH_3	0.826	4.14 (±0.06)
II*d*	CH_3	H	1.19	4.96 (±0.16)
II*e*	H	CH_3	1.15	4.87 (±0.14)
II*f*	Cl	H	1.30	5.20 (±0.19)
II*g*	H	Cl	1.27	5.14 (±0.18)
II*h*	Br	H	1.40	5.43 (±0.23)
II*i*	H	Br	1.35	5.31 (±0.21)

[a] Values measured on a persilated column[1] (10 cm) using 40% (v/v) acetonitrile as the eluant. [b] Equation 4; numbers within the parentheses are the standard error of the estimate.

The octanol–water HPLC system is limited to compounds having a log *P* of 3.15 which is the log *P* of octanol itself (18). Any compound with a greater log *P* would, in theory, remain on the HPLC column indefinitely. Using either the π or fragment approach of calculating log *P* values, the log *P* values for the 2-phenyl substituted indolizines were estimated to be in the range of 4–5.

Selected standards (Table II) with known log *P* values (18) in this range were chromatographed using several different solvent systems. These consisted of a reversed-phase persilated column[1] with different column lengths and different concentrations of acetonitrile in water as the mobile phase. Columns[1] varied in length from 5 to 10 cm and the solvent system consisted of acetonitrile concentrations in the range of 35–50%. Good linear relationships (Fig. 2) were found in a system using 40% acetonitrile in a 10-cm column[1]. The results are displayed in Table II and represented by:

$$\log P = 2.300\ (\pm\ 0.2967) + 2.234\ (\pm\ 0.360) \log k' \qquad \text{(Eq. 4)}$$

$$n = 5, s = 0.1416, r^2 = 0.9251, F_{1,3} = 37.0$$

A variety of 2-phenylindolizine analogs with widely different lipophilicities were prepared (Table III). These compounds have different substituents in the *para* and *meta* positions on the 2-phenyl groups. These substituted 2-phenylindolizines were chromatographed under conditions identical to those in Table II. Their log *k'* values were used to calculate their log *P* values using Eq. 4 (Table III).

π Value Correlation from HPLC Data—An investigation was conducted to determine whether the retention times of substituted 2-phenylindolizines using a persilated column[1] were proportional to their Hansch π constants (17). The previously described mobile phase of 40% acetonitrile in water using a 10-cm column was used. An excellent linear relationship was found between the log *P* values of the 2-phenyl substituents and log *k'*. The results are represented by:

$$\text{Log } P_{\text{substituent}} = 0.696\ (\pm\ 0.027) + 1.674\ (\pm 0.072) \log k' \qquad \text{(Eq. 5)}$$

$$n = 9, s = 0.0452, r^2 = 0.9874, F_{1,7} = 548.2$$

There is no complete set of π values for substituted phenyl compounds. That is, there are π values for CH_3, CH_3O, Cl, Br, and C_6H_5, but not tolyl, anisyl, *etc.* Since π_H is defined as zero, the log *P* values of the intact molecule (toluene, anisole, *etc.*) were used as an estimate of π to obtain Eq. 5.

The $\pi_{\text{indolizinyl}}$ values were calculated by subtracting the log *P* of the complete molecule, which represents the substituent (21) from the log *P* of the substituted indolizine (Table IV):

$$\pi_{\text{indolizinyl}} = \log P_{\text{substituted indolizine}} - \log P_{\text{substituent}} \qquad \text{(Eq. 6)}$$

The calculated $\pi_{\text{indolizinyl}}$ values vary from 2.03 and 2.44 with a mean of 2.41, a standard error of ±0.045, and a coefficient of variation of 6.0%.

Examination of the $\pi_{\text{indolizinyl}}$ results in Table IV shows that they can be placed into two groups. Compounds II*a*–II*e* compose one group with a mean of 2.14 and II*f*–II*i* have a mean of 2.36. The latter group contains the halogens. Hansch and Leo[15] have found that halogen adds about 0.2 units to π and fragment values. Correcting for the halogen effect, the mean $\pi_{\text{indolizinyl}}$ value becomes 2.15 (±0.024) with a coefficient of variation of 3.4%.

[15] A. Leo and C. Hansch, personal communications.

Table IV—$\pi_{indolizinyl}$ and $f_{indolizinyl}$ Values Using HPLC, 2-Phenyl Substituent [a]

Compound	Log $P_{substituent}$ [b]	$\pi_{indolizinyl}$ [c]	$f_{substituent}$ [d]	$f_{indolizinyl}$ [e]
IIa	2.13	2.16	1.90	2.39
IIb	2.11	2.09	1.88	2.32
IIc	2.11	2.03	1.88	2.26
IId	2.69	2.26	2.46	2.49
IIe	2.69	2.17	2.46	2.39
IIf	2.84	2.36 (2.16)	2.61	2.59 (2.39)
IIg	2.84	2.30 (2.10)	2.61	2.53 (2.33)
IIh	2.99	2.44 (2.24)	2.76	2.67 (2.47)
IIi	2.99	2.32 (2.12)	2.76	2.55 (2.35)

[a] See Table II for log k' and log P results obtained by chromatography. [b] Reference 18. [c] Equation 6; values within the parentheses are corrected for the presence of a halogen. [d] Reference 21; obtained by subtracting f_H (0.23) from log P of the 2-phenyl substituent. [e] Equation 8; values within the parentheses are corrected for the presence of a halogen.

Log P of Indolizine Calculated by the Fragment Method—The log P of the indolizine nucleus can be also calculated by the fragment method using values from model systems (18).

For example, for the fused aromatic ring model, the aromatic carbon (f_{CH}) has a value of 0.35 and the bridgehead carbon next to a heteroatom (f_C^*) is 0.44. For the nitrogen, several values can be used depending on the specific location of the atom in the molecule. According to a previous report (21), the fragment constant for the nitrogen in a ring system such as indole or pyrrole (−0.67) lies between the values of the nitrogen attached to one aromatic ring (−1.03), and two aromatic rings (−0.03). The fragment value for N-phenyl pyrrole is −0.56. Indolizine (I) is a special case because the nitrogen is located at the bridgehead position of the molecule. The nitrogen in this system is more lipophilic than the usual heterocyclic nitrogen because the unshared electrons on the nitrogen resonate among all the atoms of the ring (22). The low pKa (3.94) and the fact that protonation occurs on carbons 1 and 3 is further evidence of the special nature of this nitrogen. For this reason, a fragment value of −0.44 was used as an approximation of the nitrogen constant for indolizine[15]. This value represents a nitrogen in an aromatic system attached to two aromatic rings. The addition of all these fragment values is illustrated below:

$$\log P = 7 f_{(CH)} + f_{(C)}^* + f\text{—}\underset{\phi}{\overset{|}{\underset{\phi}{N}}}\text{—}\phi \qquad \text{(Eq. 7)}$$

$$= 7\,(0.35) + (0.44) + (-0.44)$$

$$= 2.45$$

In a similar manner, the fragment substituents of 2-phenylindolizines were calculated by the fragment method (20) and listed in Table IV. Indolizinyl fragment values were calculated by subtracting fragment substituent values from log P values:

$$f_{indolizinyl} = \log P - f_{substituent} \qquad \text{(Eq. 8)}$$

The average indolizinyl fragment value is 2.47 with a sample standard error of ±0.044. The fragment values vary from 2.26 to 2.67 with a coefficient of variation of 5.4%.

As was done with the π determination, the fragment results in Table IV can be divided into two groups with the methyl and methoxy substituted compounds IIa–IIe in the first group and the halogen substituted compounds IIf–IIi in the second. The average fragment value for the nonhalogenated indolizines is 2.37 and for the halogenated indolizines is 2.59. Applying a correction of 0.2 for the halogenated compounds, the average decreases to 2.39. The average $f_{indolizinyl}$ for all 11 compounds then becomes 2.38(±0.024) with a coefficient of variation of 3.0%.

Both the fragment and π approach to calculating log P values assumes that partial partition coefficients are additive. They also assume that each substituent behaves independently in terms of any effect on lipophilicity; this is not true. To correct for interactions, the fragment approach uses correction terms or different fragment substituent values dependent on the type of parent molecule containing the substituent. Nevertheless, neither method differentiates between a *meta* and *para* substituent in terms of resonance *versus* inductive effects on lipophilicity. Furthermore, both approaches ignore any resonance or inductive effect that the indolizine ring might have on the phenyl ring.

In both the fragment and π approaches, the individual substituent values are derived from known compounds whose partition coefficients were obtained by the classical shake-flask procedures. There have been no reported studies on the partitioning behavior of indolizine. It is difficult to extrapolate this heteroaromatic to other heteroaromatic systems for the reasons already stated. Nevertheless, the results obtained for indolizine by the different methods described in this paper show good consistency and can be considered a measure of lipophilicity for future quantitative structure–activity relationship (QSAR) studies involving indolizine.

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ACKNOWLEDGMENTS

Presented in part before the Medicinal Chemistry and Pharmacognosy Section, APhA Academy of Pharmaceutical Sciencies, St. Louis meeting, March 31, 1981.

This paper constitutes a portion of C. L. K. Lins' Doctor of Philosophy degree requirements, Oregon State University, 1980.

This work was supported by the Oregon State University Research Office and from National Institutes of Health Biomedical Research Support Grant RR07079.

The authors thank Professors Corwin Hansch and Albert Leo for supplying a value for the halogen effect and an estimate for the fragment value for the indolizine nitrogen.