

## Liquid-Liquid Partition Coefficients by High-Pressure Liquid Chromatography

John M. McCall

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001. Received November 21, 1974

Lipid-water partition values can be rapidly and reliably measured by high-pressure liquid chromatography (HPLC) on bonded octadecylsilane supports. This method has been developed and applied to a family of hypotensive triaminopyrimidine 3-oxides. The measured column retention values for this class of compounds correlate well with the values calculated by the Hansch method. We believe that this technique is an important addition to the methodology of Hansch analysis.

The lipophilic-hydrophilic balance of a compound, which is expressed by a partition coefficient, is critical for drug absorption and transport. Octanol and water have become the model for biological lipid and aqueous phases in partition processes.<sup>1</sup> Liquid-liquid chromatography on paper or lipid impregnated plates is a useful alternative to octanol-water partition. Martin deduced on theoretical grounds that for such plate or paper chromatography

$$\log P = \log K + R_m$$

where  $P$  is the partition coefficient,  $K$  is a constant for the system, and  $R_m$  is the log of  $(1/R_f) - 1$  where  $R_f$  is the retention in the system.<sup>2</sup> In work with HPLC, a compound's retention is routinely expressed by a term  $k'$  which is defined as

$$k' = (t_R - t_0)/t_0$$

where  $t_R$  is the elution time of a retained peak and  $t_0$  is the elution time of an unretained peak. The terms  $k'$  and  $(1/R_f) - 1$  are analogous. Therefore, for partition between a stationary and mobile phase

$$\log P = \log K + \log k'$$

Thus, for HPLC with a stationary lipid phase and an aqueous mobile phase,  $k'$  should be linearly related to a measured liquid-liquid partition coefficient. For compounds with small  $k'$  values, it is critical that  $k'$  be differentiated from elution time for this relation to hold. Recently, Haggerty and Murrill reported the determination of partition coefficients of a family of nitrosoureas by liquid-liquid HPLC.<sup>3</sup>

### Results and Discussion

**Model Study.** A selected group of compounds of known partition coefficient were examined by liquid-liquid partition chromatography. Under appropriate conditions,  $k'$  and  $P$  were linearly related. The conclusions which follow from this relationship were tested in order to demonstrate the utility of the method. This work is described below.

Corasil C-18<sup>4</sup> was used as the stationary chromatographic phase. This hydrolytically stable, reverse phase packing material is a pellicular silica gel to which octadecyl chains have been chemically bonded. A silyl ether terminates one end of the octadecyl chain. This terminus is more hydrophilic than the other which is alkyl and therefore more lipophilic. This combination of polar and lipid properties is less extreme than that of octanol. However, because octanol-water is the standard partition combination, we will compare our data to octanol-water log  $P$  values.

Corasil C-18<sup>4</sup> has a low percentage of active silanol sites. These silanol sites will interfere with the desired liquid-liquid partition process. We blocked potentially offending silanol sites by treating Corasil C-18<sup>4</sup> with hexamethyldisilazane (HMDS) and trimethylsilyl chloride (TMSCl) in hot pyridine. This vigorously silylated column gave a better correlation between  $k'$  and  $P$  than untreated Corasil C-18.<sup>4</sup> The evaluation of support behavior is discussed below.

Selected compounds were chromatographed on the silylated Corasil C-18<sup>4</sup> support (Table I). The preferred mobile phases were 1% triethylamine (TEA) in water and 15% CH<sub>3</sub>CN in H<sub>2</sub>O. The difference between log  $P$  and log  $k'$  (i.e., log  $K$ ) was determined for each compound with each eluent. The measured log  $K$  values for a particular eluent were normalized with respect to the log  $K$  of benzene with that eluent. A term  $K_N$  is defined as the ratio of the log  $K$  values of a compound and benzene in a given solvent system.

$$K_N = (\log K)_{\text{compound}} / (\log K)_{\text{benzene}}$$

For a pure liquid-liquid interaction between the eluted compound and the stationary octadecylsilane phase, the difference between log  $P$  and log  $k'$  (i.e., log  $K$ ) should be constant. Simple aromatic hydrocarbons such as benzene should enjoy such a pure liquid-liquid interaction. Their log  $K$  values will approach a value which is representative of an exclusive liquid-liquid partition. For such compounds,  $K_N$  will approach unity. However, if a compound interacts with the few active silica gel sites on the column,  $k'$  will increase. Consequently, log  $K$  will decrease relative to the log  $K$  of benzene and  $K_N$  will be less than unity. If  $K_N$  values are consistently close to one, the system has good predictive power for liquid-liquid partition coefficients.

The silylated column gave mean  $K_N$  values of 0.94 for both 1% TEA in H<sub>2</sub>O and 15% CH<sub>3</sub>CN in H<sub>2</sub>O for the 21 compounds of Table I. These  $K_N$  values show standard deviations of 0.071 and 0.12 and average deviations from unity of 0.075 and 0.11. In contrast, untreated Corasil C-18<sup>4</sup> which was eluted with 1% TEA in water and 15% CH<sub>3</sub>CN in water gave mean  $K_N$  values of 0.84 and 0.85, respectively. Thus, a vigorously silylated octadecylsilane support was a prerequisite for linear behavior between  $k'$  and  $P$ .

A few of the silanol sites for the Corasil C-18 support are probably sterically protected from silylating reagents. Effective silylation will block the more accessible silanol sites. In chromatography, small, very basic molecules should be able to overcome the steric barrier for remaining sites. Such molecules will bind to the silanol sites and behave most poorly on the column. These compounds will test the success in blocking active silanol sites. Large, bulky amines, on the other hand, should behave well under most conditions. Such molecules reach the active silanol sites with greater difficulty. These conclusions are confirmed by the data of Table I. The bulky dimethylaniline has similar  $K_N$  values for both solvent systems (i.e., 0.97 and 0.94). However, the small and basic amino group of 2-phenylethylamine can penetrate the steric barrier. For this amine 1% TEA in H<sub>2</sub>O and 15% CH<sub>3</sub>CN in H<sub>2</sub>O give  $K_N$  values of 0.80 and 0.64. Presumably, the TEA in the mobile phase is competitively adsorbing onto and blocking the silanol sites. This should diminish the interaction between 2-phenylethylamine and these silanol sites. Thus, for small, basic molecules

**Table I.**  $K_N$  Determinations. Correlation of  $k'$  and  $P$  on C-18 HPLC Columns<sup>c</sup>

Compd	Log $P^a$	1% TEA-H <sub>2</sub> O		15% CH <sub>3</sub> CN-H <sub>2</sub> O	
		$k'^b$	$K_N^b$	$k'$	$K_N$
Benzene	2.13 <sup>d</sup>	7.04	1.00	5.32	1.00
Toluene	2.69 <sup>d</sup>	25.02	1.01	17.16	1.04
Nitrobenzene	1.85 <sup>d</sup>	4.30	0.95	4.20	0.88
Anisole	2.11 <sup>d</sup>	7.97	0.94	5.98	0.95
Benzaldehyde	1.48 <sup>e</sup>	1.90	0.94	1.91	0.86
Acetophenone	1.58 <sup>d</sup>	2.40	0.93	2.62	0.83
Benzyl alcohol	1.10 <sup>d</sup>	1.03	0.85	0.69	0.90
Ethyl benzoate	2.62 <sup>f</sup>	26.97	0.93	18.20	0.97
2-Phenylethylamine	1.41 <sup>g</sup>	2.48	0.80	3.26	0.64
<i>o</i> -Toluidine	1.32 <sup>h</sup>	1.77	0.84	1.58	0.80
<i>m</i> -Toluidine	1.40 <sup>d</sup>	1.97	0.86	1.72	0.83
<i>p</i> -Toluidine	1.39 <sup>d</sup>	1.91	0.87	1.70	0.83
<i>o</i> -Chloroaniline	1.92 <sup>h</sup>	5.09	0.92	3.35	0.99
<i>m</i> -Chloroaniline	1.88 <sup>d</sup>	6.62	0.83	3.57	0.95
<i>p</i> -Bromoaniline	2.26 <sup>i</sup>	8.90	1.02	4.51	1.14
<i>N,N</i> -Dimethylaniline	2.31 <sup>d</sup>	11.65	0.97	9.66	0.94
2-Bromopyridine	1.42 <sup>j</sup>	1.49	0.98	1.25	0.94
3-Bromopyridine	1.60 <sup>j</sup>	2.33	0.96	1.74	0.97
Benzimidazole	1.34 <sup>k</sup>	1.17	0.99	0.59	1.12
Quinoline	2.03 <sup>g</sup>	4.50	1.07	2.82	1.12
Indole	2.25 <sup>l</sup>	9.74	0.98	5.40	1.08

<sup>a</sup>Log  $P$  = literature value for log octanol-water partition coefficient. <sup>b</sup> $K_N$  and  $k'$  were defined in the text. <sup>c</sup>The 2 ft × 1/8 in. column was packed with C-18 Corasil which was vigorously silylated. <sup>d</sup>T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964). <sup>e</sup>D. Nikaitani and C. Hansch, unpublished results cited in ref 235 of ref 1a. <sup>f</sup>M. S. Tute, see reference from ref 1b. <sup>g</sup>J. Iwasa, T. Fujita, and C. Hansch, *J. Med. Chem.*, 8, 150 (1965). <sup>h</sup>Private communication from M. Tichya and K. Bocek, cited in ref 301 of ref 1a. <sup>i</sup>Y. Ichikawa, T. Yamono, and H. Fujishima, *Biochim. Biophys. Acta.* 171, 32 (1969). <sup>j</sup>Private communication from M. Tute, cited in ref 276 of ref 1a. <sup>k</sup>S. Anderson and C. Hansch, unpublished results cited in ref 218 of ref 1a. <sup>l</sup>K. S. Rogers and A. Cammarata, *J. Med. Chem.*, 12, 692 (1969).

**Table II.** Log  $P$  and Log  $k'$  Correlation for Acidic Compounds

Compd	Log $P$	Log $k'^a$	Log $K$	$K_N$
Phenol	1.46	0.91	1.50	1.07
Thiophenol	2.52	9.44	1.41	1.01
Salicylamide	1.26	0.71	1.54	1.10
Benzene	2.13	5.32	1.40	1.00
Toluene	2.69	17.16	1.45	1.04

<sup>a</sup>These values were measured with a vigorously silylated Corasil C-18 column which was eluted with 15% CH<sub>3</sub>CN in water.

TEA in water is a better eluent than acetonitrile in water. Support silylation is a necessity. A column which was packed with untreated Corasil C-18<sup>4</sup> gave a  $K_N$  value of 0.4 for 2-phenylethylamine when eluted with 1% TEA in water.

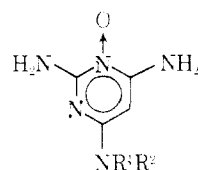
Table II illustrates that the technique described above is valid for phenolic compounds. The reference log  $K$  values which benzene and toluene provide correspond well with the log  $K$  values of phenol, thiophenol, and salicylamide. We have not yet applied the method to carboxylic acids.

The data from Tables I and II demonstrate that, for vigorously silylated Corasil C-18,<sup>4</sup>  $K_N$  and consequently log  $K$  are very nearly constant for a variety of compounds. Thus, log  $P$  values for unknown compounds can experimentally be determined quite easily. For a particular column and eluent, log  $K$  is determined from the elution times of standards of known log  $P$ . This calibrates the column. Log  $k'$  for the compounds of interest is then determined. The partition coefficient can be determined from the sum of log  $K$  and log  $k'$ . Compounds with widely variant lipophilicities can be measured by altering the components of the mobile

phase. In such a situation, determination of log  $P$  by direct partition has a definite advantage. With this technique, the ratio of the volumes of the two phases can be varied to accommodate divergent lipophilicities. The solvent system remains the same. This guarantees more continuity. In addition, there is no danger of a silanol type interaction in direct partition.

Because of the correspondence between retention ( $k'$ ) values and octanol-water partition values, log  $k'$  values can be calculated by the  $\pi$  additivity method of Hansch analysis.<sup>1,5</sup> This conclusion was tested with a series of hypotensive agents with which we have been involved.

**Test of Method.** Minoxidil (2,4-diamino-6-piperidopyrimidine 3-oxide), In (see structure 1), is a potent vasodi-



- 1a. NR'R<sup>2</sup> = methylamino
- b. NR'R<sup>2</sup> = ethylamino
- c. NR'R<sup>2</sup> = *n*-butylamino
- d. NR'R<sup>2</sup> = *n*-decylamino
- e. NR'R<sup>2</sup> = cyclohexylamino
- f. NR'R<sup>2</sup> = dimethylamino
- g. NR'R<sup>2</sup> = diethylamino
- h. NR'R<sup>2</sup> = di-*n*-propylamino
- i. NR'R<sup>2</sup> = diallylamino
- j. NR'R<sup>2</sup> = di-*n*-butylamino
- k. NR'R<sup>2</sup> = dicyclohexylamino
- l. NR'R<sup>2</sup> = morpholino
- m. NR'R<sup>2</sup> = pyrrolidino
- n. NR'R<sup>2</sup> = piperidino

**Table III.** Minoxidil Analogs  $k'$  and Calculated Log  $P$  Values

Compd	Measd $k'$ values (eluent) <sup>a</sup>	Rel eluting power <sup>b</sup>	$k'$ values in 1% TEA-H <sub>2</sub> O <sup>c</sup>	Log $P$ (log $k'$ + 1.28)
1a	0.67 (A)		0.017	-0.49
1b	1.88 (A)		0.048	-0.04
1c	20.27 (A), 2.85 (B)	A/B = 7.11	0.52, 0.59	1.02
1d	31.82 (D)		632	4.08
1e	2.21 (C)		2.21	1.62
1f	2.92 (A)		0.075	0.16
1g	3.67 (B)		0.76	1.16
1h	36.8 (B), 7.36 (C)	B/C = 5.00	7.67, 7.36	2.16
1i	9.91 (B), 2.15 (C)	B/C = 4.61	2.06, 2.15	1.60
1j	81.21 (C), 4.09 (D)	C/D = 19.85	81.21	3.19
1k	20.67 (D)		410	3.89
1l	4.67 (A), 0.58 (B)	A/B = 8.10	0.12, 0.12	0.36
1m	14.97 (A), 1.64 (B)	A/B = 9.12	0.38, 0.34	0.84
1n	4.42 (B)		0.92	1.24

<sup>a</sup>A  $\frac{1}{8}$  in.  $\times$  2 ft steel column was packed with vigorously silylated Corasil C-18 and eluted with solvents A, B, C, or D. Solvent A is H<sub>2</sub>O, B is 0.2% TEA in H<sub>2</sub>O, C is 1% TEA in H<sub>2</sub>O, and D is 1% TEA-40% MeOH-H<sub>2</sub>O. <sup>b</sup>Ratio of  $k'$  values of one substrate in two solvents. Discussed in text. <sup>c</sup>Based on retention ratios,  $k'$  (1% TEA-H<sub>2</sub>O) =  $k'$  (0.2% TEA-H<sub>2</sub>O)/4.80 =  $k'$  (H<sub>2</sub>O)/38.93 =  $k'$  (1% TEA-40% MeOH-H<sub>2</sub>O)  $\times$  19.85.

lator which is useful in the clinical management of hypertension.<sup>6</sup> We have prepared a variety of minoxidil analogs of widely different lipophilicities (see structure 1).<sup>7</sup> These compounds differ only in the amine substituent at the 6 position. They provide a difficult test for the HPLC measurement of partition coefficients.

Because of the diverse lipophilicities of these compounds, a single solvent system could not be used for all members of the series. Therefore, a vigorously silylated Corasil C-18<sup>4</sup> column was eluted with a spectrum of solvents. The lipophilicity of these solvents was gradually increased. The most hydrophilic analogs were eluted with either water or 0.2% TEA in water. The more lipophilic analogs were eluted with 1.0% TEA in water or with 1.0% TEA in 40% MeOH-water. The measured  $k'$  values for these compounds are recorded in Table III. These  $k'$  values are listed with respect to the solvent system in which they were measured. Before these  $k'$  values from the four solvent systems can be compared, the eluting power of each solvent system must be related to that of the others. The ratio of the eluting power of two solvents for a particular column is equal to the ratio of measured  $k'$  values for a single substrate in the two solvent systems.

$$\frac{\text{solvent A eluting power}}{\text{solvent B eluting power}} =$$

$$\frac{k' \text{ of substrate in solvent B}}{k' \text{ of same substrate in solvent A}}$$

Selected members of this series were chromatographed in two solvent systems of similar eluting strength. In this manner, the various eluents were contrasted to each other. Compounds 1c, 1l, and 1m were chromatographed in both H<sub>2</sub>O and 0.2% TEA in H<sub>2</sub>O. The respective  $k'$  ratios for these compounds in these two eluents were 7.11, 8.10, and 9.12 (standard deviation = 1.00; see Table III). The average ratio is 8.11. Likewise, compounds 1h and 1i were examined in 0.2% TEA in water and 1% TEA in water.  $k'$  ratios of 5.00 and 4.61 (average 4.8) were obtained. Finally, 1j was eluted with 1% TEA and 1% TEA-40% MeOH-H<sub>2</sub>O. The latter solvent has 19.85 times the eluting power of the former.

In summary, for this series of compounds, retention in

**Table IV.** Log Correction ( $\pi$ ) Factors for Hansch Calculations<sup>a</sup>

Group	$\pi$
CH <sub>2</sub>	0.50
Double bond	-0.30
Amine ring closure	-0.48
-O-	-0.98
Branching at amine	-0.34
Ring closure	-0.09

<sup>a</sup>The origin of these terms is explained in the text.

H<sub>2</sub>O is 8.11 times that in 0.2% TEA-H<sub>2</sub>O, retention in 0.2% TEA-H<sub>2</sub>O is 4.80 times that of 1% TEA-H<sub>2</sub>O, and retention in 1% TEA-H<sub>2</sub>O is 19.85 times that of 1% TEA-40% MeOH-H<sub>2</sub>O. From this information, all the solvent systems were related to 1% TEA in water (see Table III).

This method for relating different eluents for a family of related compounds is convenient and tends to minimize the effect of unusual interactions between substrate and chromatographic system. Members of a given series calibrate relative eluting powers of the solvents with which they will be chromatographed. Although these ratios may not be the same for substrates of a different class, they are good working parameters for the class of compounds which is being considered.

After the log  $k'$  values were expressed in terms of a single solvent (1% TEA-H<sub>2</sub>O), the log  $P$  values for the minoxidil family were calculated (log  $P$  = log  $k'$  + constant). The difference between log  $P$  and log  $k'$  for benzene in the 1.0% TEA-water system is 1.28. Thus, for the minoxidil analogs, log  $P$  (the octanol-water partition coefficient) is equal to the sum of the log  $k'$  and 1.28. The calculated log  $P$  values are listed in Table III.

The observed log  $k'$  values can be calculated readily by the Hansch  $\pi$  additivity method.<sup>1,5</sup> Table IV lists the log substituent constants,  $\pi$ , which are necessary for these calculations. These  $\pi$  factors are obtained from literature sources where possible.<sup>1</sup> In special cases, they are calculated from model systems.

For example, for ring closure to form a cyclic amine,  $\pi$  equals the difference (i.e., -0.48) between the log  $P$  values

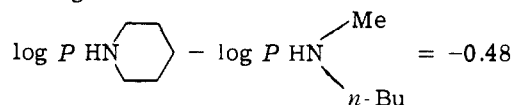
Table V. Calculation of Log  $k'$  Values<sup>a</sup>

Compd	Calcd log $k'$	Measd log $k'$
1a	Model compound	-1.77
1b	-1.28	-1.32
1c	-0.28	-0.26
1d	2.73	2.80
1e	0.30	0.34
1f	Model compound	-1.12
1g	-0.12	-0.12
1h	0.88	0.88
1i	0.28	0.32
1j	1.88	1.91
1k	3.14	2.61
1l	-0.89	-0.92
1m	-0.60	-0.44
1n	-0.10	-0.04

<sup>a</sup>Examples of these calculations are in the text. The 6-dimethylamino and 6-methylamino analogs are used as models in these calculations.

for piperidine<sup>8</sup> (0.85) and methyl-*n*-butylamine<sup>8</sup> (1.33).

log  $P$  amine ring closure =



Likewise, the  $\pi$  for branching at an amine function is the difference (-0.34) between the log  $P$  value for isopropylamine (-0.03)<sup>8</sup> and the log  $P$  of *n*-butylamine (0.81)<sup>8</sup> which has been decreased 0.5 log units because of butylamine's extra methylene group. The method of log  $k'$  calculation is illustrated below.

log  $k'$  *n*-decylamino (1d) =

$$\log k' \text{ methylamino (1a)} + 9\pi_{\text{CH}_2} =$$

$$-1.77 + 4.50 = 2.73 \text{ (measured log } k' = 2.80)$$

log  $k'$  diallylamino (1i) =

$$\log k' \text{ dimethylamino (1f)} + 4\pi_{\text{CH}_2} + 2\pi_{\text{double bond}} =$$

$$-1.12 + 2.00 - 0.6 = 0.28 \text{ (measured log } k' = 0.32)$$

log  $k'$  morpholino (1l) = log  $k'$  dimethylamino (1f) +

$$2\pi_{\text{CH}_2} + -\text{O}- + \text{ring closure} = -1.12 + 1.00 -$$

$$0.98 - 0.09 = -1.19 \text{ (measured log } k' = -0.92)$$

log  $k'$  cyclohexylamino (1e) =

$$\log k' \text{ methylamino (1a)} + 5\pi_{\text{CH}_2} +$$

$$\pi_{\text{branching at amine}} + \pi_{\text{ring closure}} = -1.77 + 2.5 -$$

$$0.34 - 0.09 = 0.30 \text{ (measured log } k' = 0.34)$$

These calculations are completely analogous to the calculation of log  $P$  based on  $\pi$  additivity which is included in the Hansch method. Table V lists the results of these calculations. The excellent agreement between measured and calculated log  $k'$  values further substantiates the viability of this method.

The data which have been presented demonstrate that retention ( $k'$ ) values are linearly related to octanol-water

partition values for the compounds which were examined. Consequently, log  $P$  values can be obtained directly from log  $k'$  values. Thus, HPLC on columns which are packed with vigorously silylated octadecylsilyl supports and which are eluted with an aqueous solvent present a useful alternative to the often tedious octanol-water partition coefficient measurement. The HPLC technique is fast and reproducible. A typical compound can be assayed in less than 10 min. Because of such rapid analysis time, compounds which are unstable in solution can be assayed. Because solvent lipophilicity can be rapidly adjusted, compounds whose partition coefficients vary by several orders of magnitude can be quickly measured. Samples need not be pure since contaminants do not interfere with  $k'$  determinations. Finally, because both refractive index and uv HPLC detectors are available, any compound can be detected. We conclude that the technique should be a useful addition to the methodology of Hansch analysis. Further work will expand the list of tested compounds and hopefully establish more firmly the generality of this method.

### Experimental Section

All chromatography was performed on a Waters ALC 100 HPLC. Columns were stainless steel ( $\frac{1}{8}$  in.  $\times$  2 ft). The path to the detector was minimized to give the lowest possible dead volume. The dead volume between the end of the column and the uv detector was measured. A correction for this dead volume was made in retention calculations. Thus,  $k'$  values reflect only time on the column. Elution times were measured with a stopwatch for maximum accuracy. Samples were dissolved in MeOH at a concentration of 0.1%. Injections of 1  $\mu$ l of such solutions were made. The elution time of an unretained peak was regarded as equal to the elution time of the very hydrophilic formamide (log  $P$  = -1.69). Retention ( $k'$ ) values were calculated in the manner which was described in the text.

**Silylation.** HMDS and TMSCl. Corasil C-18<sup>4</sup> (5.0 ml) was stirred with 2.0 ml of HMDS and 1.0 ml of TMSCl in 10 ml of pyridine at 60° for 3 hr and at 100° for 2 hr. The packing was filtered and washed with CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>O, and MeOH. The material was dried in vacuo.

**Columns.** Stainless steel columns ( $\frac{1}{8}$  in.  $\times$  2 ft) were dry packed by adding the Corasil C-18<sup>4</sup> incrementally. The base of the column was tapped continuously during this process.

**Acknowledgment.** We are grateful to J. Attebery of Waters Associates for encouragement and advice.

### References and Notes

- (1) For reviews see (a) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971); (b) M. S. Tute, *Adv. Drug Res.*, **6**, 1 (1971).
- (2) (a) A. J. P. Martin, *Biochem. Soc. Symp.*, **3** and **4** (1949); (b) E. C. Bate-Smith and R. G. Westfall, *Biochem. Biophys. Acta*, **4**, 427 (1950).
- (3) W. J. Haggerty, Jr., and E. A. Murrill, *Res. Dev.*, **25**, 30 (1974). Our work differs from Haggerty and Murrill's. In order to establish the generality of the method, we have examined a more diverse group of model compounds. We have developed new methodology to minimize the silanol component of the chromatographic support. Finally, we emphasize the importance of  $k'$  rather than elution time for log  $P$  determinations.
- (4) Trademark, Waters Associates.
- (5) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).
- (6) (a) E. Gilmore, J. Weil, and C. Chidsey III, *N. Engl. J. Med.*, **282**, 521 (1970); (b) W. A. Pettinger and H. C. Mitchell, *ibid.*, **289**, 167 (1973).
- (7) The synthesis of these agents will be reported later.
- (8) S. C. Anderson and C. Hansch, unpublished analysis cited in ref 1a.