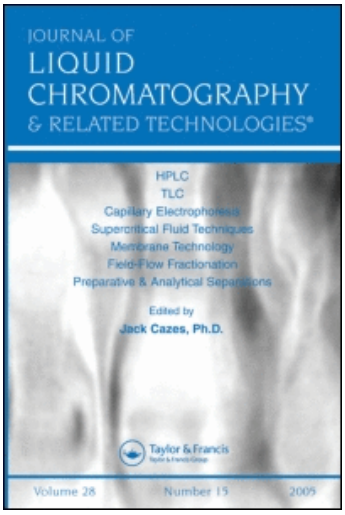

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Comparison of Octadecyl-Bonded Alumina and Other Stationary Phases for Lipophilicity Estimation by High Performance Liquid Chromatography

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COMPARISON OF OCTADECYL-BONDED ALUMINA AND OTHER STATIONARY PHASES FOR LIPOPHILICITY ESTIMATION BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A recently developed octadecyl-bonded alumina stationary phase (ODA) was evaluated for determining the lipophilicities of organic compounds by high performance liquid chromatography. Using a column packed with this material and mobile phases consisting of methanol and aqueous buffers, the correlation between the octanol-water partition coefficients (log P's) of compounds of various chemical classes and the logarithms of their chromatographic capacity factors (log k's) was found to be superior to that obtained using columns packed with octadecylsilica, polybutadiene-coated alumina or octadecyl-derivatized polystyrene-divinylbenzene copolymer. In contrast to results obtained with other columns, phenols and other hydrogen-bonding compounds did not need to be treated as a separate data set on the ODA column to obtain good correlations between log k's and log P's. The resistance of ODA to degradation by alkaline solvents allowed the use of a basic mobile phase (pH > 10) for suppressing ionization and determining the lipophilicities of organic bases which could not be evaluated within the stable pH range of ODS (pH 2-8). The log P's of five basic pharmaceutical compounds determined in this manner were found to be significantly higher than previously reported values. Evidence is presented which indicates that the previously reported log P values of these compounds are inaccurate, due to improper correction for ionization.

INTRODUCTION

Evaluating the lipophilicities of organic compounds is important in pharmaceutical, environmental and physical-organic chemistry. The most commonly used index of lipophilicity is the octanol-water partition coefficient (log P), which has been quantitatively correlated with the activities of compounds in many biological systems (1-3).

Because it is more convenient than direct methods of determination, there has been considerable interest in the estimation of log P values of compounds by correlation with the logarithm of their high performance liquid chromatographic (HPLC) capacity factors (log k'). Such methods are based upon similarities in the hydrophobic partitioning processes occurring in octanol-water mixtures and reversed-phase HPLC (4). Log P values obtained by HPLC correlation methods have been successfully used in a number of quantitative structure - activity relationship (QSAR) studies of drugs (4-6).

Although the distribution coefficients (log D's) of organic ions have found some utility in the design of pharmacologically active compounds (7,8), log P values are generally defined and correlated with biological activity in terms of the unionized state of the compound. As a result, most current HPLC methods are incapable of directly measuring partition coefficients for compounds which are substantially ionized in the stable pH range of the commonly-used octadecylsilane (ODS) columns (pH 2-8). This leaves out a number of important biologically active weak bases, such as alkaloids, with pK_a's between 7 and 10. The scope of the HPLC correlation method for general evaluation of lipophilicities of organic compounds is thus severely limited. Efforts have been made to extrapolate values obtained for partially ionized bases to their fully unionized states (9), but these have produced unreliable results (8). Complications arise from the effects of

mobile phase ionic strength on retention of organic ions and interactions of basic solutes with acidic silanol sites on ODS columns. Since these mechanisms have no effective counterpart in an octanol-water system, inaccurate estimates of partition coefficients for such compounds can result, even for those basic compounds which are not substantially ionized in the working pH range of ODS (10).

The inaccuracies and restricted scope of most of the current HPLC correlation methods for estimating partition coefficients are caused by the limited pH stability of silica-based columns and the presence of retention mechanisms (e.g., silanol interactions) that have no analogy in an octanol-water system. Reversed-phase column packings that are not based on silica have recently been developed, and a number of these have been investigated for their potential in estimating partition coefficients of organic compounds by correlation. Columns that have been investigated for this application include those based on polystyrene-divinylbenzene (PRP) copolymer (11), octadecyl-derivatized polystyrene-divinylbenzene (ACT-1) (12,13) , and polybutadiene-coated alumina (14,15). Various degrees of success have been achieved with these materials. Especially noteworthy is the work of Kaliszan and coworkers (14,15) with polybutadiene-coated alumina. The high pH stability of this material enabled them to employ a highly alkaline (pH 11.5) mobile phase to suppress the ionization and evaluate the log P 's of a number of basic pharmaceutical compounds with reasonably good accuracy.

In addition to the polybutadiene-coated alumina phase employed by Kaliszan and coworkers in their studies, new phases have been developed in which alkyl groups are directly bonded to the surface of alumina (16-18). Recent studies have shown that these new phases exhibit retention properties that are very similar to alkyl-bonded silica, while exhibiting higher pH stability (18,19). These properties clearly make these phases potentially useful for estimating log P's by the HPLC correlation method. In this report, we describe the evaluation of one such

stationary phase, octadecyl-bonded alumina (ODA) (17, 19), for determining the log P's under both neutral and alkaline conditions. We have compared the log P - log k' correlations obtained with the ODA and other reversed-phase stationary phases, and determined the partition coefficients of some basic pharmaceutical compounds obtained by employing the correlation method using an ODA column and a highly alkaline mobile phase.

EXPERIMENTAL

Materials

All solvents used were glass distilled, obtained from E. M. Science (Cherry Hill, NJ). Codeine, procaine, thebaine, and cocaine were obtained as methanolic solutions (1 mg/mL) from Sigma Chemical Co. (St. Louis, MO). All other compounds were obtained from Aldrich Chemical Co. (Milwaukee, WI).

Apparatus

The HPLC system consisted of a Perkin-Elmer Series 410 solvent delivery system, a Rheodyne Model 7125 injector (20 microliter loop) and a Perkin-Elmer Model LC-135 diode array UV-visible detector. Unless otherwise specified, the wavelength monitored was 220 nanometers. Chromatographic data were recorded and processed on a Perkin-Elmer Omega data system.

Four chromatographic columns were used in these studies:

Octadecylalumina (ODA): This column was obtained as a gift from the Biotage Company (Charlottesville, VA). It was packed with an experimental (not yet available for purchase) monomeric octadecyl bonded Alcoa Unisphere™ alumina stationary phase, as described by Haky *et al* (19). The stationary phase particle size was 8 microns, and the column dimensions were 250 mm x 4.6 mm I.D.

Octadecylsilica (ODS): This column, obtained from Alltech Associates (Deerfield, IL) was packed with "Econosil" octadecylsilica. The stationary phase particle size was 10 microns, and the column dimensions were 250 mm x 4.6 mm I.D.

Polybutadiene-Coated Alumina (PBD): This column, now commercially available, was obtained from the Biotage Company (Charlottesville, VA). It was packed with polybutadiene-coated Alcoa Unisphere™ alumina. The polymer was immobilized on the alumina surface by crosslinking reactions similar to those described by Schomberg and coworkers (20,21). The stationary phase particle size was 8 microns, and the column dimensions were 250 mm x 4.6 mm I.D.

Octadecyl-Modified Polystyrene-Divinylbenzene (ACT-1): This column, packed with octadecyl-modified Macrophase MP-1 was obtained from Interaction Chemicals (Mountain View, CA). Dimensions were 150 mm x 4.6 mm I.D.

Capacity Factor Determinations For General Octanol-Water Coefficient Correlation

Retention times for samples (injected as 1 mg/mL solutions in methanol) were determined on each column using the mobile phases and flow rates listed in Table 1. For each column, enough methanol was used in the mobile phase to give a capacity factor between 4 and 6 for benzene, a compound of moderately high lipophilicity (22). The mobile phases were buffered at pH 7.4 using standard sodium phosphate buffer, except in the case of the ODA column, where a zwitterionic buffer, 4-morpholinopropanesulfonate (MOPS), was used due to the instability of ODA to phosphate ion (19). In contrast to other reports (8,12), no significant differences in the log P - log k' correlations were observed by adding amines or octanol to the mobile phases for any of the columns.

The capacity factor, k', of each compound was calculated by the formula $k' = (t-t_o)/t_o$, where t is the compound's retention time and t_o is the retention time of an unretained substance, determined by injection of a sample of pure methanol.

TABLE 1

Mobile Phase Compositions and Flow Rates Used For Each Column

Column	Mobile Phase	Flow Rate, mL/min
ODA	70% MOPS buffer (0.01M), pH 7.4; 30% methanol	2.00
ODS	45% phosphate buffer (0.05), pH 7.4; 55% methanol	2.00
PBD	75% phosphate buffer (0.05 M), pH 7.4; 25% methanol	2.00
ACT-1	20% phosphate buffer (0.05 M), pH 7.4; 80% methanol	1.00

Capacity Factor Determinations of Model Compounds on ODA Column and Log P Calculation

Capacity factors for the organic bases listed in Table 5 were determined from their retention times obtained on the ODA column as 1 mg/mL solutions using a mobile phase consisting of 30% methanol and 70% aqueous sodium hydroxide (0.1M) and a flow rate of 2.00 mL/min. Log P's were then determined by mathematical interpolation of a linear log P - log k' correlation line established by chromatographing a calibration mixture consisting of four non-ionizable standards:

TABLE 2

Empirical Calculation of Log P of Procaine,

$(CH_3CH_2)_2NCH_2CH_2O(CO)C_6H_4(p\text{-}NH_2)$

Structural Subunit	Substituent Constant	Number of Subunits	Sum of Substituent Constants
CH_3	0.702	2	1.404
CH_2	0.530	4	2.120
N (aliphatic)	-2.16	1	-2.16
COO (aromatic)	-0.431	1	-0.431
C_6H_4	1.688	1	1.688
NH_2	-0.854	1	-0.854
proximity effect (Aliphatic N and O)	0.574	1	0.574
Total		Log P =	2.34

benzyl alcohol (log P = 1.16), acetophenone (log P = 1.66), toluene (log P = 2.74) and naphthalene (log P = 3.37).

Empirical Calculation of Partition Coefficients

Empirical log P values for the compounds in Table 5 were calculated by the method described by Rekker (23), in which the chemical structures of the compounds are broken into structural subunits and tabulated 'fragmental constants' for each unit are then summed. A 'proximity effect' correction is made for

electronegative atoms separated by 2 or less carbon atoms. Calculation of the log P of procaine is outlined in Table 2.

Shake-flask Determination of Log P of Benzylamine

Three drops of benzylamine and one drop of nitrobenzene (internal standard with log P = 1.85) were mixed in a tube containing a biphasic mixture of 1 mL of octanol and 4 mL of aqueous sodium hydroxide (0.1 M). The layers were separated, analyzed, and the log P was calculated according to the HPLC method described by Nahum and Horvath (24).

RESULTS AND DISCUSSION

General Log P - Log k' Correlations

Evaluating the partition coefficients of organic compounds by HPLC correlation is best performed under conditions which maximize the similarities in the retention mechanisms in the chromatographic process and the partitioning mechanisms occurring in a biphasic octanol-water system. Although this ideally requires employing a totally aqueous mobile phase in the HPLC system, the excessively long retention times which would be obtained for lipophilic compounds under these conditions make such an approach impractical. Methanol-water mobile phases have been found to give good estimates of log P's by HPLC correlation while allowing lipophilic compounds to elute with reasonable retention times (13,25). Several researchers have advocated extrapolating retention data obtained at several methanol-water mobile phase compositions to obtain capacity factors at totally aqueous conditions for log P estimation (10,12,26). Although this approach occasionally gives superior results to those obtained by correlation with a single methanol-water mobile phase, the multiple experiments required for

TABLE 3
Experimental Capacity Factors and Literature Octanol-Water Partition Coefficients#

Compound	Lit. Log P	Log k'ODA	Log k'ODS	Log k'PBD	Log k'ACT-1
m-aminophenol	0.17	-0.275	-0.663	-1.136	-0.468
benzamide	0.65	0.044	-0.274	-0.756	-0.092
resorcinol	0.80	0.373	-0.021	-0.784	-0.560
aniline	0.90	0.079	-0.058	-0.576	-0.685
benzyl alcohol	1.16	0.230	0.088	-0.516	-0.685
acetanilide	1.16	0.066	0.031	-0.525	--
picoline	1.20	0.016	0.154	-0.629	--
phenol	1.46	0.373	-0.022	-0.405	-0.029
ethyl propionate	1.50	0.230	0.338	-0.274	--
benzonitrile	1.56	0.376	0.185	-0.064	0.452
acetophenone	1.66	0.447	0.285	--	0.321
p-cresol	1.94	0.728	0.363	-0.097	-0.255
m-cresol	1.96	0.692	0.351	-0.095	-0.251
benzene	2.01	0.772	1.731	0.633	0.743
quinoline	2.03	0.655	0.433	0.058	0.218
anisole	2.04	0.782	0.581	0.577	0.697
methyl benzoate	2.18	0.861	0.608	0.515	0.991
trichloroethylene	2.29	1.045	0.855	0.971	0.687
methyl salicylate	2.46	1.252	0.852	0.797	1.072
chlorobenzene	2.49	1.249	1.071	1.161	0.818
ethyl benzoate	2.64	1.200	1.007	0.873	0.991
1-naphthol	2.71	1.461	0.769	0.684	0.651
toluene	2.74	1.183	0.946	1.061	0.996
2-naphthol	2.84	1.366	0.705	0.619	0.546
bromobenzene	2.99	1.386	1.142	1.314	1.205
thymol	3.30	1.625	1.213	0.968	0.701
naphthalene	3.37	1.641	1.358	*	*
biphenyl	4.06	*	1.625	*	*
phenanthrene	4.46	*	1.807	*	*

Literature Values From Reference 3
* Compound did not elute for at least 100 minutes under the chromatographic conditions

this approach drastically increases the time required for each log P determination, and thus makes it unattractive for the rapid estimation of log P's of large numbers of compounds. For this reason, we chose to evaluate the applicability of the ODA and the other HPLC stationary phases for the estimation of partition coefficients employing single methanol-water mobile phase compositions.

Our initial comparisons of the correlation of log P with log k' on the ODA and other phases were obtained using compounds from the list shown in Table 3. Graphs of log k' vs log P for each of the four stationary phases studied are shown in Figures 1 and 2, and linear correlation parameters are shown in Table 4. The results show that the ODS and ODA columns give the best correlations between log k' and log P at neutral pH, indicating a greater similarity to the octanol-water partitioning processes with these monomeric alkyl-bonded phases than with the polymeric PBD and ACT-1 columns. While the lower correlation obtained for the PBD column is probably due to the relative dissimilarity of the structure of its polybutadiene coating to octanol, the even poorer correlations obtained with the ACT-1 column can at least partially be attributed to the high retention of compounds on this stationary phase. The large percentages of methanol in the mobile phase (80%) required to obtain acceptable retention times on thie ACT-1 column may interfere with hydrophobic expulsion mechanisms which generally control the retention of compounds under reversed phase HPLC conditions. Indeed, in previous studies with ACT-1, good correlations between partition coefficients and log k' were obtained only when specially-prepared columns of short length (5 cm) were employed (13), or extrapolated k's to totally aqueous mobile phases were used in the log P - log k' correlations (12).

Comparison of log P - log k' correlations obtained for phenolic and non-phenolic compounds on the ODA and other columns indicates that the effects of hydrogen bonding on retention of compounds on ODA is different from the ODS, PBD, and ACT-1 columns. As shown in Figures 1-2, the phenolic compounds exhibit a small but significant deviation from the correlation obtained for other compounds on the ODS, PBD and ACT-1 columns. In fact, the linear correlation coefficients (R^2) improve when phenolic compounds are removed from the data

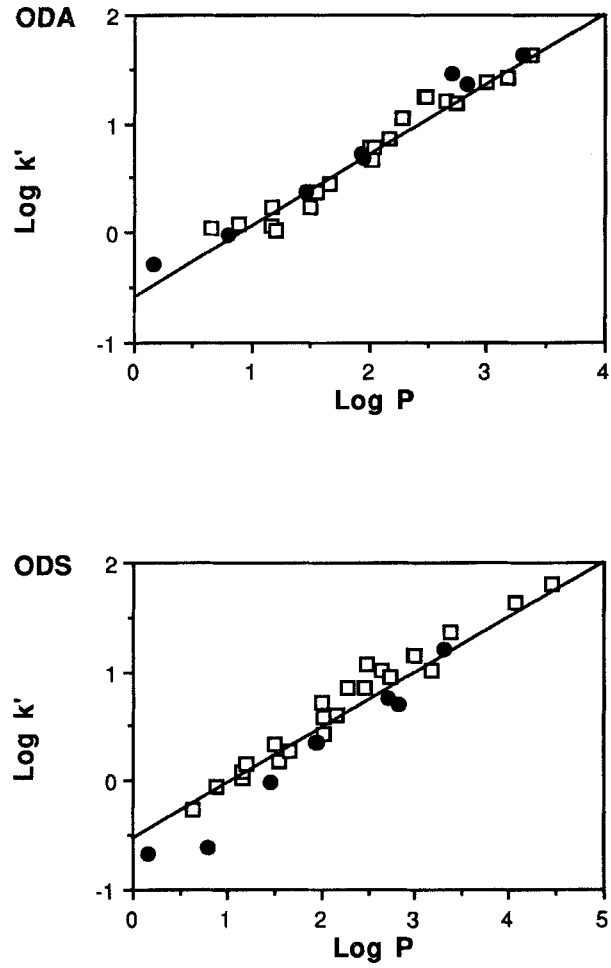

FIGURE. 1. Plots of the logarithms of the capacity factors (log k') of the compounds shown in Table 3 on ODA (upper graph) and ODS (lower graph) vs the logarithm of their octanol-water partition coefficients (log P).
Key: □ non-phenolic compounds; ● phenolic compounds

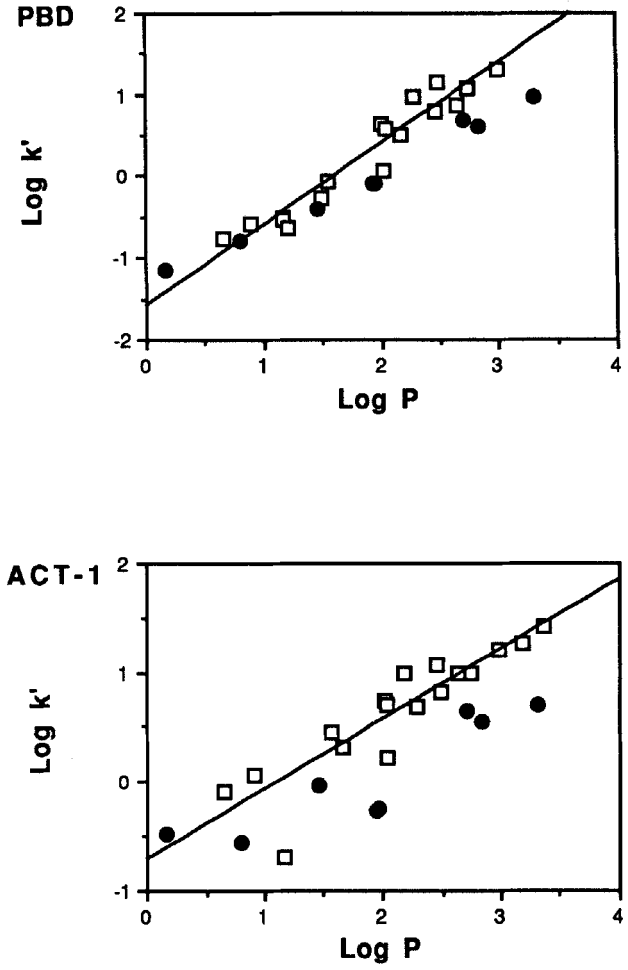

FIGURE 2. Plots of the logarithms of the capacity factors (log k') of the compounds shown in Table 3 on PBD (upper graph) and ACT-1 (lower graph) vs the logarithm of their octanol-water partition coefficients (log P).
Key: □ non-phenolic compounds; ● phenolic compounds

TABLE 4

Regression Parameters For Graphs of Log k' vs Log P

Data Set	Parameter	ODA	ODS	PBD	ACT-1
All compounds	Slope	0.661	0.580	0.840	0.583
	Intercept	-0.562	-0.673	-1.410	-0.742
	R^2	0.960	0.938	0.881	0.686
All except phenols	Slope	0.671	0.548	0.990	0.641
	Intercept	-0.601	-0.541	-1.593	-0.713
	R^2	0.953	0.964	0.933	0.804
Phenols only	Slope	0.653	0.614	0.694	0.435
	Intercept	-0.496	-0.901	-1.348	-0.783
	R^2	0.980	0.970	0.985	0.803

set for these three stationary phases (see Table 4). Data points for the phenols generally fall below the general log P - log k' correlation lines on ODS, PBD and ACT-1, indicating that phenols are retained on these columns slightly less than would be expected from their log P values. As suggested in an earlier paper (25), this can be attributed to differences in the hydrogen-bonding capabilities of these three stationary phases and the octanol used in the shake-flask determination of the partition coefficient values. On the other hand, there does not appear to be any deviations by phenolic compounds in the general log P - log k' correlations obtained on the ODA column (see Figure 1). As shown in Table 4, regression parameters are very similar for the log P - log k' correlations for phenolic and non-phenolic compounds on ODA, and inclusion of the phenolic compounds in the data

set actually improves the correlation coefficient for all compounds on ODA. This suggests that hydrogen-bonding partitioning properties of the ODA material are more similar to those of octanol than the other three stationary phases tested. The most likely sites for hydrogen bonding interactions on the ODA material are the oxygen atoms (hydrogen-bond acceptors) on its alumina backbone; similar interactions are known to occur at these sites in unmodified alumina (27). The existence of a small but detectable hydrogen bonding effect on the retention of solutes on the ODA material indicates that at least some of these oxygen atoms are accessible to solutes during their separation on ODA. Apparently, these types of oxygen atoms are not accessible to solutes on the other alumina-based column investigated in these studies, PBD, since the differences in correlations found between log k' and log P for phenols and nonphenols on PBD are more similar to those obtained on ODS and ACT-1 than those obtained on ODA (see Figure 2 and Table 4). At any rate, the data shown here clearly indicate that the ODA material has somewhat greater hydrogen-bond accepting properties than the other three phases investigated, and that it is these enhanced hydrogen-bonding properties which result in the superior correlations between log P and log k' on the ODA stationary phase.

Estimation of Log P's of Organic Bases Under Alkaline Conditions

The known resistance of ODA to degradation by alkaline solvents and the high degree of correlation between log P and log k' on ODA makes this stationary phase potentially useful for estimating partition coefficients of basic pharmaceutical compounds in their unionized states. Suppressing ionization of such compounds is possible on ODA columns by employing mobile phases of high alkalinity (pH 9-11). Such an approach is generally not possible with ODS and similar silica-based columns, owing to the dissolution of the stationary phase when these conditions are employed.

We evaluated the ODA column for this potential application by employing it for estimating the log P's of the five model compounds shown in Table 5. The compounds were chosen for the following reasons:

1. Similar to many pharmaceutically active organic bases, each of the model compounds' ionization constants (shown in Table 5) are over 8.0, requiring the use of a very alkaline (pH > 10) mobile phase to ensure complete suppression of ionization (28).

2. Reference log P's determined by classical shake-flask methods were available in the literature (2,3,22) for comparison with values obtained by correlation with log k' on ODA.

3. The structures of each of the model compounds could be broken into structural subunits whose log P 'fragmental constants' had been previously determined (23). This allowed the calculation of an additional set of reference log P's, determined empirically from the structures of the compounds according to the fragmental method of Rekker (23).

Additionally, four of the five model compounds are controlled substances which can legally be obtained only as methanolic solutions in milligram quantities without a government license. This simulates a common situation in pharmaceutical research laboratories, where sufficient quantities of experimental drug substances for log P determination by classical shake-flask methods are often not available, and indirect methods such as HPLC correlation must be employed.

Since a highly alkaline methanol-aqueous sodium hydroxide mobile phase could be employed to suppress ionization, estimation of the log P's of the model compounds by correlation with their capacity factors on the ODA column was straightforward. The log P values of these compounds determined for these compounds are listed in Table 5, along with their literature values and those empirically calculated by Rekker's fragmental method.

TABLE 5

Dissociation Constants and Partition Coefficients of Model Compounds

Compound	pK_a*	Lit.# Log P	ODA Log P	Empirical Log P	Shake-Flask Log P
Codeine	8.21	1.14	2.04	2.01	--
Procaine	8.91	1.90	2.21	2.34	--
Thebaine	8.15	1.91	2.38	2.51	--
Cocaine	8.39	2.09	2.92	2.51	--
Benzylamine	9.35	1.09	1.45	1.56	1.33

* Value from Reference 29
# Value from Reference 22

The original purpose for estimating the partition coefficients of the 5 model compounds under the conditions described here was to obtain log P values which could be compared with those in the literature as an evaluation of the accuracy and applicability of the ODA column for general log P estimation for organic bases. Surprisingly, however, the data which was obtained gave strong evidence that the literature log P values for these compounds are themselves inaccurate. A chromatogram of a mixture of four of the model compounds under the conditions similar to those used to estimate their partition coefficients is shown in Figure 3. The chromatogram shows excellent separation of peaks corresponding to procaine, thebaine, and cocaine. This is inconsistent with their similar literature log P values, on the basis of which they all would be expected to nearly co-elute. The log P values of the model compounds determined on the ODA column (Table 5) are also

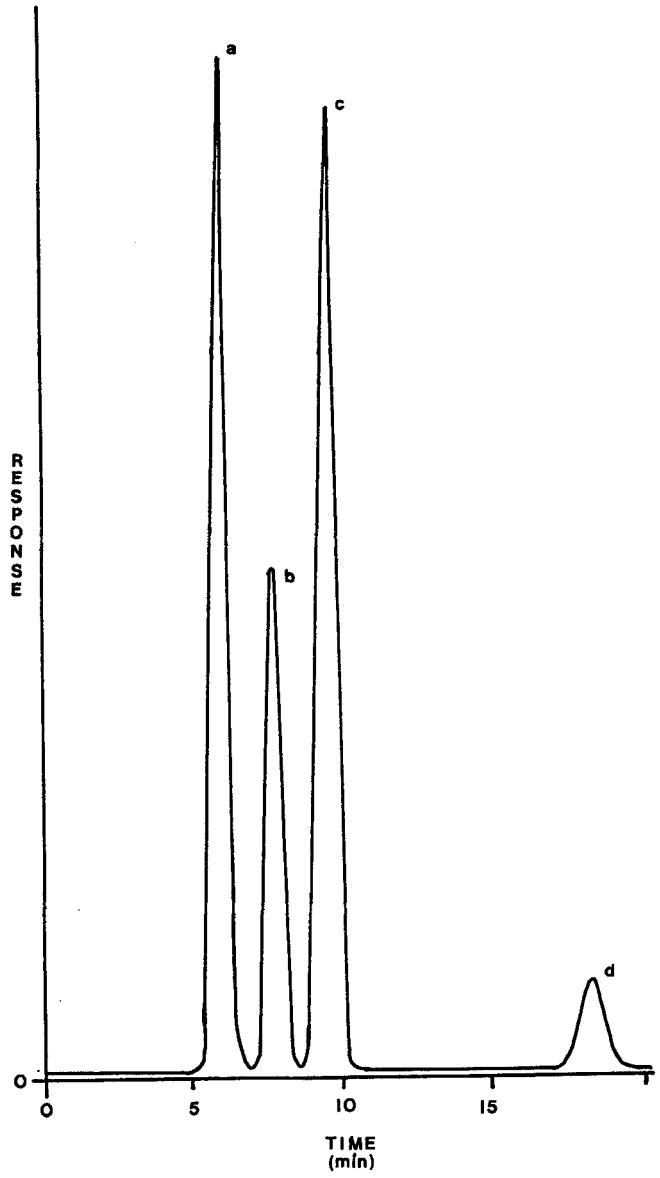

FIGURE 3. HPLC chromatogram of a drug mixture on ODA stationary phase using a mobile phase consisting of 35% methanol and 65% aqueous sodium hydroxide (0.1 M). Peaks: a = codeine; b = procaine; c = thebaine; d = cocaine

all significantly higher than the literature values, yet the partition coefficients determined on ODA are comparable to those calculated for each compound by Rekker's fragmental method. Additionally, the data in Table 5 also shows that the log P value of benzylamine determined in this study by the classical shake-flask method under alkaline conditions is more consistent with the values obtained by HPLC correlation on the ODA column and by Rekker's method than the literature log P value for benzylamine. It appears then, that previously-reported log P values compiled for the five compounds in Table 5 may be inaccurately low.

Inaccuracies in the literature log P values of the five model compounds may be due to the way in which they were calculated. Although the complete experimental details of how these values were determined are not available, it is stated by Hansch and Leo (2) that these values were first determined by the shake-flask method at neutral pH and then corrected for ionization using a form of equation 1,

$$\log D = \log P - \log [1 + ([H]/K_a]) \qquad (1)$$

where D is the distribution coefficient determined at neutral pH, [H] is the hydrogen ion concentration and K_a is the dissociation constant of the protonated base. This equation is based on the assumption that the protonated form of the base does not partition into the organic phase, which is valid only for small, very polar hydrophilic organic bases. Unger and coworkers (8,29) have shown that this equation can lead to inaccurate log P values for larger, more lipophilic bases, such as those investigated in the present study. They proposed the more complicated equation 2 for correcting partition coefficients for ionization, which takes into account a significant partition coefficient P' for the protonated base:

$$\log P = \log [P + P'[H]/K_a] - \log [1 + ([H]/K_a)] \qquad (2)$$

It is not possible to use equation 2 to correct the literature log P values for ionization, because use of this equation requires distribution coefficient values at at

least two pH's, and such data is not available. A more direct approach, of course, is to determine the log P using solvents at very alkaline pH's, where the protonated form of the base has been completely eliminated. The high pH stability of the ODA stationary phase allows this alternative approach to be successfully used for partition coefficient estimation, apparently giving more accurate log P values.

CONCLUSIONS

In this study, a new monomeric octadecyl-bonded alumina based stationary phase, ODA, has been demonstrated to be useful for the estimation of the octanol-water partition coefficients of a wide variety of organic compounds by correlation with their capacity factors. Owing to the similarity of this phase to octanol in polarity, hydrogen-bonding abilities and hydrophobicity, correlations between the partition coefficients of various classes of compounds and their capacity factors on this stationary phase are more similar to each other than they are on octadecylsilica or other reversed-phase columns. Additionally, the high pH stability of ODA allows the use of alkaline mobile phases for the estimation of partition coefficients of organic bases in their unionized states. The log P values of some pharmaceutical compounds estimated in this manner appear to be more accurate than values previously reported.

Columns packed with the ODA stationary phase are not yet commercially available, and some of the details of the preparation of the ODA material are still proprietary and thus have not yet been reported in the open literature. Nevertheless, the work described here clearly indicates a great potential for such types of surface-modified alumina based stationary phases in the characterization and analysis of organic compounds by reversed-phase HPLC.

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REFERENCES

(1) Hansch, C. and Fujita, T. J. Am. Chem. Soc. 86, 1616, 1964.

(2) Leo, A.J., Hansch, C. and Elkins, D., Chem. Rev. 7, 525, 1971.

(3) Kaliszan, R. Quantitative Structure - Chromatographic Retention Relationships, Wiley, New York, 1987, pp. 232 - 278.

(4) Hansch, C. and Leo, A., Substituent Constants For Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979.

(5) Kaliszan, R., J. Chromatogr. Sci., 22, 362, 1984.

(6) Tomlinson, E., J. Chromatogr., 113, 1, 1975.

(7) Scherrer, R.A. and Howard, S.M., J. Med. Chem., 20, 53, 1977.

(8) Unger, S.H. and Chiang, G.H., J. Med. Chem. 24, 262, 1981.

(9) Unger, S.H. and Feurman, J. Chromatogr., 176, 426, 1979.

(10) El Tayar, N., Van De Waterbeemd, H., and Testa, B., J. Chromatogr., 320, 305, 1985.

(11) De Biasi, V., Lough, W.J. and Evans, M.B., J. Chromatogr., 353, 279, 1986.

(12) Minick, D.J., Brent, D.A. and Frentz, J., J. Chromatogr. 461, 177, 1989.

(13) Lambert, W.J. and Wright, L.A., J. Chromatogr., 464, 400, 1989.

(14) Kaliszan, R., Blain, R.W., and Hartwick, R.A., Chromatographia., 25, 5, 1988.

(15) Kaliszan, R., Petrusewicz, J., Blain, R. and Hartwick, R. A., J. Chromatogr., 458, 395, 1988.

(16) Knox, J.H. and Pryde, A., J. Chromatogr., 112, 171, 1975.

(17) Wieserman, L.F., Martin, E.S. and Cross, K., 39th Pittsburgh Conference on Analytical Chemistry, New Orleans, 1988, Paper No. 391.

(18) Pesek, J.J. and Lin, H.D., Chromatographia, 28, 565, 1989.

(19) Haky, J.E., Vemulapalli, S. and Wieserman, L.F. J. Chromatogr., in press.

(20) Bien-Vogelsang, U., Deege, A. Figge, H., Kohler, J. and Schomberg, G., Chromatographia, 19, 170, 1984.

(21) Heineman, G., Kohler, J. and Schomberg, G., Chromatographia, 23, 435, 1987.

(22) Hansch, C. and Leo, A., Log P and Parameter Database, Comtex Scientific Corporation, New York, 1983.

(23) Rekker, R.R. The Hydrophobic Fragmental Constant, Elsevier, Amsterdam, 1977.

(24) Nahum, A. and Horvath, C., J. Chromatogr., 192, 315, 1980.

(25) Haky, J.E. and Young, A.M., J. Liquid Chromatogr., 7, 675, 1984.

(26) Braumann, T., Weber, G. and Grimme, L.H., J. Chromatogr., 261, 329, 1983.

(27) Snyder, L.R., Principles of Adsorption Chromatography, Dekker, New York , 1968, Chapters 7,10, and 11.

(28) Perrin, D.D., Dissociation Constants of Organic Bases in Aqueous Solution, Butterworths, London, 1965.

(29) Unger, S.H., Drug Design, 9, 47, 1980.