# CORRELATIONS BETWEEN OCTANOL–WATER PARTITION COEFFICIENTS AND REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY CAPACITY FACTORS

## CHLOROBIPHENYLS AND ALKYLBENZENES

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## SUMMARY

The capacity factors ($k'_\varphi$) of 4 chlorobiphenyls and 39 alkylbenzenes ($C_1$–$C_{10}$) were determined using reversed-phase high-performance liquid chromatography at eight different mobile phase compositions ($\varphi = 50$–$90\%$ acetonitrile in water). The predicted capacity factors in water (log $k'_0$) were determined by linear regression of log $k'_\varphi$ and the acetonitrile concentration. Comparison of log $k'_0$ data from two solvent systems (acetonitrile–water, methanol–water) with published data indicates that this parameter is dependent on both the mobile phase and the chromatographic system used in determining log $k'_\varphi$.

The determined log $k'_0$ values and *n*-octanol–water partition coefficients (log $P_{oct}$) taken from the literature were analyzed by linear regression. Log $P_{oct}$ estimates made from separate regressions using the individual and combined compound classes are presented and compared. The slopes of the lines for the two compound classes were similar, but each had distinctly different intercepts. Log $P_{oct}$ estimates resulting from the individual compound class regressions agreed more closely with published data than did estimates derived by combining the two classes during regression. It is recommended that separate regressions be developed for each compound class of interest.

Log $P_{oct}$ estimates for the alkylbenzenes were also made using fragment constants. The fragment constants were compared with structural group factors derived from the log $k'_0$ based estimates. It is noted that the substitution pattern of the benzene ring affects these group factors.

## INTRODUCTION

Reversed-phase high-performance liquid chromatography (RP-HPLC) has been used to estimate *n*-octanol–water partition coefficients (log $P_{oct}$), and recent

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reviews have discussed the merits of this method[1-4]. RP-HPLC avoids many of the potential problems associated with the traditional shake flask method for direct determination of log $P_{oct}$. More important, it allows the estimation of log $P_{oct}$ values (*i.e.*, log $P_{oct} > 6$) whose direct measurement is difficult because of analytical limitations[1-4].

In this study RP-HPLC was used to estimate log $P_{oct}$ for a variety of alkylbenzenes and selected chlorobiphenyls. Log $P_{oct}$ values for several short chain alkylbenzenes have been determined directly[5-8] or estimated by RP-HPLC[9-13]. We wanted to extend this database in order to enhance our understanding of their environmental distributions.

The RP-HPLC estimation method is based on the linear regression of a compound's log $P_{oct}$ and the logarithm of its RP-HPLC aqueous capacity factor (log $k'_0$). Others have reported good correlations using pooled data for several classes of compounds in this regression[6,9,12,14,15]. We had originally intended to extend the log $P_{oct}$ range beyond that of the short chain alkylbenzenes for which data are available by using selected polychlorophenyls (PCBs). The latter were chosen because they span a wide range of log $P_{oct}$ values and are relatively well characterized[16]. Recently however, Opperhuizen *et al.*[17] suggested that each compound class yields a distinct relationship between log $k'_0$ and log $P_{oct}$. Thus, greater estimation errors could result if the data are combined during linear regression. In this paper we verify this increase in estimation error by presenting log $P_{oct}$ − log $k'_0$ correlations for alkylbenzenes and PCBs using both acetonitrile and methanol mobile phases. The resulting correlation lines are compared with relationships developed using published log $k'_0$ values[13,17].

Log $P_{oct}$ estimates made using the acetonitrile log $k'_0$ data, as well as estimates made using the fragment constants of Hansch and Leo[5] (as discussed by Lyman[18]) are presented and compared with each other and available literature data.

## MATERIALS AND METHODS

### Chemicals

The alkylbenzenes used in this study were obtained from Aldrich Chemical, Supelco, Alfa/Morton Thiokol, Alltech Assoc. and the American Petroleum Institute. The PCBs were from Ultra Scientific. All analytes were of the highest purity available (95 to 99 + %) and purity was verified by high-resolution gas chromatography prior to use. Double distilled deionized water, filtered through a 0.45-$\mu$m membrane filter (Nylon 66, Supelco), and HPLC-grade methanol or acetonitrile (J. T. Baker) were sparged with helium before use.

### Apparatus

A Perkin-Elmer (PE) Series 400 liquid chromatograph and a PE LC-15B UV (254 nm) detector were used. The chromatograph was equipped with a Rheodyne 7125 injector, a 20-$\mu$l loop, and a 125 mm × 4.6 mm PE HS-5-$C_{18}$ (5 $\mu$m silica based octadecyl) column, operated at a flow-rate of 1.5 ml/min.

Void volumes were determined using two approaches: (1) injections of a sodium nitrate solution and (2) linearization of data for an alkylbenzene homologue series. It has been suggested that the latter procedure gives a more reliable estimate of the void volume[17,19,20]. The column's solvent volume was also determined via differential

weighing[19,21] with methanol and dichloromethane as solvents. This volume is the maximum void volume ($V_{0,max}$) since it includes mobile phase in the solvation layer of the stationary phase[19,21].

Two linearization methods were used: (1) the procedure recommended by Berendsen et al.[19], and (2) two versions of a procedure recommended by Van Tulder et al.[20]. These linearization methods have been applied to the n-alkylbenzene series[17,19,20], and will be briefly described below. For a more thorough discussion the reader is referred to the original references[19,20]. Compounds for which retention data were available included benzene and the n-alkylbenzenes from toluene to n-pentadecylbenzene (excluding n-pentylbenzene and n-heptylbenzene). Retention times for the latter two compounds were estimated by linear interpolation of the retention times of n-butyl-, n-hexyl- and n-octylbenzene. To estimate the error associated with these interpolations we also interpolated values for n-propyl- and n-nonylbenzene. The interpolated retention times for these compounds exceeded the actual retention times by 0.61% and 2.67% respectively. The second linearization procedure presented by Van Tulder et al.[20] allowed the use of only the even numbered n-alkylbenzenes. Thus, these results are not dependent on interpolation.

Both linearization methods utilize the retention times of consecutive homologues $n$ and $n + 1$. The procedure of Berendsen et al.[19] uses linear regression of the equation

$$t_{R,n+1} = At_{R,n} - (A - 1)t_0 \tag{1}$$

Where $t_{R,n}$ and $t_{R,n+1}$ are the retention times of homologues $n$ and $n + 1$ respectively, $A$ is a constant and $t_0$ is the void time.

The procedure of Van Tulder et al.[20] is based on the equation

$$\ln(t_{R,n} - t_0) = b^0(z^0 + n) + c \tag{2}$$

Where $n$ is the number of additional carbons, $z^0$ is the number of carbons in the basic group (in this case benzene), and $b^0$ and $c$ are constants. The sequence number of the homologue is $i$ such that $i = 1, 2, \ldots, N$ ($N = 16$ homologues). This then leads to derivation of the following equations:

$$\ln(t_{R,i+1} - t_{R,i}) = b^0 i + c'' \tag{3}$$

where $c''$ is an operational constant, and

$$t_{R,i} = t_0 + pq^i \tag{4}$$

with $q = e^{b^0}$. Linear regression of $\ln(t_{R,i+1} - t_{R,i})$ against $i$ (eqn. 3) gives $b^0$ as the slope. This is then used to derive $q^i$ which is regressed against $t_{R,i}$ (eqn. 4). The intercept of eqn. 4 yields $t_0$. The second linearization procedure discussed by Van Tulder et al. is a variation which allows the use of non-consecutive homologues as long as they are equally spaced. For example, in our work only the even numbered n-alkylbenzenes were used, with $i$ being replaced by $j$ such that $j = 2i$. Retention times are converted to retention volumes via multiplication by the flow-rate.

RESULTS AND DISCUSSION

*Determination of the void volume*

The capacity factor ($k_\varphi'$) at each concentration ($\varphi$) of organic modifier is dependent on the retention volumes of the solute and of an unretained compound:

$$k_\varphi' = (V_{R,\varphi} - V_{0,\varphi})/V_{0,\varphi} \tag{5}$$

where $k_\varphi'$ = capacity factor, $V_{R,\varphi}$ = retention volume of the solute, $V_{0,\varphi}$ = retention volume of an unretained compound. Because of the importance of the void volume ($V_{0,\varphi}$) in determining $k_\varphi'$, we utilized and compared several methods for estimating this parameter. These methods were described briefly above. The resulting estimates of $V_{0,\varphi}$ are shown in Table 1. Differential weighing indicated $V_{0,max}$ to be 1.88 ml.

The retention volumes of sodium nitrate generally decreased with increasing water content for both mobile phases. The retention volume at 90% methanol is anomalous (low) compared to the rest of the sodium nitrate data. However, multiple determinations under these conditions agreed within 0.02 ml.

The linearization methods gave inconsistent results. With the acetonitrile–water mobile phase, linearization of the data yielded void volumes that had no apparent relationship with $\varphi$. In the methanol–water mobile phase the linearization methods both produced relationships between $\varphi$ and $V_0$. The resulting values however, differed from one another and were inversely related to those determined using sodium nitrate.

TABLE I

COMPARISON OF ESTIMATED VOID VOLUMES, $V_0$

$V_{0,max}$ was determined to be 1.88 ml via differential weighing, see text for details.

| Mobile phase composition | NaNO$_3$ (ml) | Linearization methods | | | | | | | | |
| | | Van Tulder et al.[20] | | | | | | Berendsen et al.[19] | | |
| | | $V_0$ (i=1) (ml) | $R^2$ | $n$ | $V_0$ (i=2) (ml) | $R^2$ | $n$ | $V_0$ (ml) | $R^2$ | $n$ |
| *Acetonitrile–water* | | | | | | | | | | |
| 90:10 | 1.35 | 1.56 | 0.9999 | 14 | 1.56 | 0.9999 | 8 | 1.66 | 0.9999 | 15 |
| 85:15 | 1.35 | 1.49 | 0.9997 | 14 | 1.52 | 0.9998 | 8 | 2.15 | 0.9999 | 15 |
| 80:20 | 1.28 | 1.34 | 0.9997 | 14 | 1.43 | 0.9997 | 8 | 1.93 | 0.9999 | 15 |
| 75:25 | 1.26 | 1.51 | 0.9999 | 13 | 1.53 | 1.000 | 8 | 1.90 | 0.9999 | 14 |
| 70:30 | 1.26 | 1.66 | 0.9999 | 9 | 1.83 | 0.9999 | 6 | 1.73 | 0.9976 | 10 |
| 65:35 | 1.23 | 0.97 | 0.9991 | 7 | 1.79 | 1.000 | 5 | 0.61 | 0.9888 | 8 |
| 60:40 | 1.22 | 1.06 | 0.9998 | 8 | 4.17 | 0.9956 | 5 | 0.39 | 0.9946 | 9 |
| 50:50 | 1.19 | 1.93 | 0.9999 | 5 | — | | | 2.11 | 0.9998 | 4 |
| *Methanol–water* | | | | | | | | | | |
| 90:10 | 1.32 | 1.07 | 0.9989 | 4 | — | — | | 1.20 | 0.9891 | 3 |
| 85:15 | 1.40 | 1.15 | 0.9988 | 4 | — | — | | 1.30 | 0.9910 | 3 |
| 80:20 | 1.38 | 1.18 | 0.9987 | 4 | — | — | | 1.34 | 0.9875 | 3 |
| 75:25 | 1.35 | 1.28 | 0.9991 | 4 | — | — | | 1.50 | 0.9940 | 3 |
| 70:30 | 1.35 | 1.33 | 0.9992 | 4 | — | — | | 1.60 | 0.9941 | 3 |

    In RP-HPLC the alkyl chains of the stationary phase are solvated to some extent by the organic modifier[21,22]. The extent of this solvation is dependent on both the solvent strength of the modifier and the composition of the mobile phase (*i.e.* water content). Thus, at the same mobile phase composition, acetonitrile will associate with the stationary phase to a greater extent than methanol[21]. Changing the organic modifier concentration in the mobile phase will alter the amount of modifier available to partition into the stationary phase. This change may affect the degree to which water is associated with the stationary phase, since it has been shown with acetonitrile, that the amount of associated water decreases as the bulk mobile phase water content increases[22]. A decrease in the concentration of organic modifier associated with the stationary phase could increase the self-association of the ($C_{18}$) alkyl chains. Mobile phase access to pore spaces in the particles may be restricted if these are blocked by the collapsed alkyl chains. This would result in a shorter retention time for an unretained component (*i.e.*, smaller $V_{0,\varphi}$) given a constant flow-rate.

    Except for the anomalous point for 90% methanol, the trends of the sodium nitrate $V_0$ data fit the processes just discussed, and are similar to those found by McCormick and Karger[21] for $^2H_2O$ with mobile phases of the same composition. The differences between the sodium nitrate determined void volumes in the two mobile phases is hard to explain in terms of the processes discussed above, however the difference between the hydrophobicity of these two modifiers may affect the relative amount of water associated with the stationary phase, and thus be reflected in the void volume determinations. The results obtained by linearization of the data, as previously noted, were inconsistent, and both linearization procedures gave $V_0$ values greater than $V_{0,max}$ at one or more acetonitrile concentrations. Therefore, we chose to utilize the $V_0$ values derived using sodium nitrate in our determination of $k_\varphi'$.

*Determining log $k_0'$ from log $k_\varphi'$*

    The capacity factor in water (log $k_0'$), of each compound was estimated from the capacity factors (log $k_\varphi'$) at each modifier concentration $\varphi(\varphi = 90\%$ methanol was not used) using least squares linear regression of the equation:
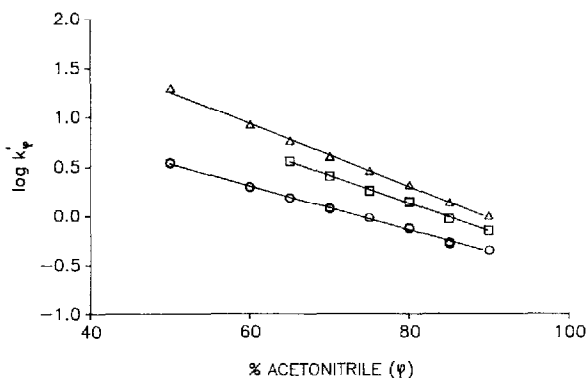
$$\log k_\varphi = b(\varphi) + \log k_0' \qquad (6)$$



Fig. 1. Log $k_\varphi'$–$\varphi$ relationships for benzene ($\bigcirc$), biphenyl ($\square$), and *n*-butylbenzene ($\triangle$) at $\varphi = 50$–90% acetonitrile.

TABLE II

DIRECTLY DETERMINED LOG $P_{oct}$ VALUES AND ESTIMATED AQUEOUS CAPACITY FACTORS (LOG $k'_0$) OF THE ALKYLBENZENES AND CHLOROBIPHENYLS WHICH WERE USED IN THE REGRESSION ANALYSIS

| Compound | Log $P_{oct}$ values* | Ref. | Log $k'_0$ values | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | Acetonitrile (this report) | Methanol | | Ref. 13** |
| | | | | This report | Ref. 17 | |
| *Alkylbenzenes* | | | | | | |
| Benzene | 2.13, 2.15, 2.15 | 5 | 1.649 | 2.019 | 0.993 | 2.389 |
| Toluene | 2.65, 2.65, 2.69, 2.73 | 5,6,8 | 1.936 | 2.559 | 1.536 | 3.027 |
| Ethylbenzene | 3.13, 3.13, 3.15 | 5,6,8 | 2.200 | 3.066 | 2.093 | 3.535 |
| n-Propylbenzene | 3.68, 3.69, 3.69, 3.69 | 5,6,8 | 2.533 | 3.658 | 2.655 | 4.174 |
| n-Butylbenzene | 4.26, 4.28, 4.29 | 5,6,8 | 2.846 | | 3.212 | 4.760 |
| *Chlorobiphenyls* | | | | | | |
| Biphenyl | 3.76, 3.89, 4.09 | 16 | 2.389 | 3.231 | 2.121 | 4.278 |
| 4-Monochlorobiphenyl | 4.49, 4.61 | 16 | 2.738 | 4.078 | 2.947 | |
| 2,4,6-Trichlorobiphenyl | 5.47 | 16 | 3.190 | 4.875 | 4.110 | |
| 2,2′,4,5,5′-Pentachlorobiphenyl | 5.92, 6.11, 6.50 | 16 | 3.703 | 5.873 | 4.861 | |
| 2,2′,4,4′,5,5′-Hexachlorobiphenyl | 6.72, 6.90 | 16 | 4.040 | 6.537 | 5.480 | |

* Repetitions of log $P_{oct}$ values were considered independent when they had different original sources.

** Transformed from ln $k'_0$ to log $k'_0$.

Estimation of log $k_0'$ by eqn. 6 has two potential sources of error. The first possibility is that the relationship could be non-linear. Work by Karger *et al.*[23] investigating the relationship between $\varphi$ and log $k_\varphi$ for alcohols, resulted in the suggestion[9] that eqn. 6 is valid only for acetonitrile concentrations below 50%. However, we found linearity over the range of 50 to 90% as demonstrated in Fig. 1 for benzene, *n*-butylbenzene, and biphenyl in acetonitrile. The squared correlation coefficient (the coefficient of determination, $R^2$) for all regressions using eqn. 6 with an acetonitrile mobile phase was 0.997 or greater. Consequently, we used the linear model to determine log $k_0'$. It is possible that the relationship is non-linear below 50% and that our extrapolated value for log $k_0'$ is not, in fact, the capacity factor in water. This will be discussed further below. We report the coefficient of determination rather than the correlation coefficient ($r$) because $R^2$ better measures the strength of the linear relationship between the two variables[24].

The second potential source of error to estimates of log $k_0'$ is interaction of the organic modifier with water or the stationary phase. Log $k_0'$ values derived using eqn. 6 for both acetonitrile and methanol mobile phases are shown in Table II. We found that the log $k_0'$ values were dependent on the mobile phase used to determine log $k_\varphi'$ (and hence log $k_0'$). This effect has been reported before[25,26] and was suggested to result from differences in the modifier's ability to hydrogen bond with water[25], or to interact with the stationary phase[26]. The difference in the log $k_0'$ values we determined using acetonitrile and methanol mobile phases (Table II, log $k_0'$ columns 1 and 2, respectively) lead us to conclude that these log $k_0'$ values are not the capacity factors in water. Whether this results solely from a mobile phase interaction, or interaction and non-linearity is uncertain.

The direct measurement of log $k_0'$ would be impractical for most of these compounds. Since the data fit the linear model so well, we felt we could use these estimates in the correlation with log $P_{oct}$ without pursuing the source of these differences further.

*Correlation of log $k_0'$ and log $P_{oct}$*

Log $P_{oct}$ data for the alkylbenzenes were collected from the literature[5-8]. Values for the PCBs were taken from a recent compilation by Shiu and Mackay[16]. All literature values used in the regression equations were determined by either shake flask or generator column methods and are listed in Table II. The literature data for log $P_{oct}$ and the experimentally determined log $k_0'$ values were fit to the equation:

$$\log P_{oct} = b \log k_0' + a \qquad (7)$$

using a geometric mean linear regression[27]. This is the appropriate regression model when measurement error is associated with both variates (log $P_{oct}$ and log $k_0'$). A regression was developed for benzene and the *n*-alkylbenzenes from toluene to *n*-butylbenzene because of the quantity of log $P_{oct}$ data available for these compounds. The value of *n*-hexylbenzene (5.52) fell outside the 95% confidence intervals[28] of this line. Since this log $P_{oct}$ value is in the range where direct determination becomes difficult, *n*-hexylbenzene was not added to the regression. Separate regressions were performed for the alkylbenzenes and the PCBs to allow comparison of the slopes and intercepts of the lines for these two compound classes. The derived regression lines for the log $P_{oct}$ — log $k_0'$ relationships are listed in Table III.

TABLE III

REGRESSION EQUATIONS FOR THE LOG $P_{oct}$ — LOG $k_0'$ CORRELATIONS

| Mobile phase | Compound | $n$ | Regression equation | $R^2$ |
|---|---|---|---|---|
| Methanol | *Alkylbenzenes* | | | |
| | This report | 14 | Log $P_{oct}$ = 0.937 ± 0.045 log $k_0'$ + 0.265 | 0.999 |
| | Opperhuizen[17] | 17 | Log $P_{oct}$ = 0.947 ± 0.038 log $k_0'$ + 1.198 | 0.998 |
| | Harnisch[13]* | 17 | Log $P_{oct}$ = 0.895 ± 0.030 log $k_0'$ − 0.020 | 0.998 |
| | *Polychlorobiphenyls* | | | |
| | This report | 11 | Log $P_{oct}$ = 0.886 ± 0.135 log $k_0'$ + 1.012 | 0.979 |
| | Opperhuizen[17] | 11 | Log $P_{oct}$ = 0.859 ± 0.129 log $k_0'$ + 2.042 | 0.980 |
| Acetonitrile (this report) | Alkylbenzenes | 17 | Log $P_{oct}$ = 1.759 ± 0.050 log $k_0'$ −0.744 | 0.999 |
| | PCBs | 11 | Log $P_{oct}$ = 1.757 ± 0.263 log $k_0'$ −0.278 | 0.980 |
| | Combined | 28 | Log $P_{oct}$ = 1.987 ± 0.133 log $k_0'$ −1.159 | 0.979 |

\* Data transformed from ln $k_0'$ to log $k_0'$.

Selected log $P_{oct}$ — log $k_0'$ relationships are plotted in Figs. 2 and 3. The lines in Fig. 2 are for log $k_0'$ values from methanol–water mobile phase systems, with data from this work and that reported by Opperhuizen *et al.*[17] and Harnisch *et al.*[13]. Fig. 3 compares the log $P_{oct}$ — log $k_0'$ relationships we developed using methanol–water and acetonitrile–water mobile phases to estimate log $k_0'$.

Initial inspection of the lines in Fig. 2 suggests that the slopes of the alkylbenzene and PCB lines are similar, but that the intercepts vary. Comparison of the lines in Fig. 2 and Table III indicate that the intercepts depend on both the chromatographic system used and the compound class investigated. Braumann[1] showed that when a methanol–water mobile phase and six different *n*-alkyl-bonded stationary phases were used the log $k_\varphi$ — $\varphi$ relationship for benzene exhibited similar slopes, but different intercepts. Since this intercept is usually taken to represent log $k_0'$, this would explain the dependence of the log $P_{oct}$ — log $k_0'$ relationship on the chromatographic system.



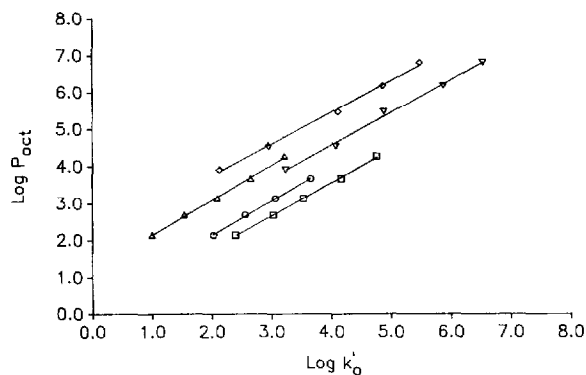Fig. 2. Comparison of the log $P_{oct}$ — log $k_0'$ relationships developed using a methanol–water mobile phase to estimate log $k_0'$. Alkylbenzenes: (○) this report; (△) ref. 17; (□) ref. 13. PCBs: (▽) this report; (◇) ref. 17.
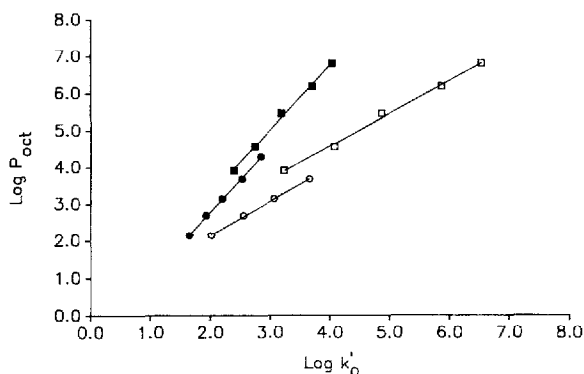
Fig. 3. Comparison of the log $P_{oct}$ — log $k_0$ relationships developed for our alkylbenzene and PCB data from the methanol–water (open symbols) and the acetonitrile–water (closed symbols) mobile phases. ($\bigcirc$, $\bullet$) Alkylbenzenes; ($\square$, $\blacksquare$) PCBs.

The slopes of our alkylbenzene and PCB regression lines within each organic modifier were tested for parallelism using a non-parametric procedure[29]. We also compared the slopes of our alkylbenzene log $P_{oct}$ — log $k_0$ correlation in methanol to those generated by regressing the log $k_0$ data of Opperhuizen et al.[17] and Harnisch et al.[13] against the literature log $P_{oct}$ values. We found no significant differences between the alkylbenzene and PCB slopes ($\alpha = 0.061$) for either mobile phase. Undoubtedly the variance of the PCB log $P_{oct}$ values obscures the apparent difference in these slopes in the methanol mobile phase. The slope of our alkylbenzene line for the methanol–water system was not significantly different from the slope derived using the data of Opperhuizen et al.[17] ($\alpha = 0.016$). The slope resulting from the log $k_0$ data of Harnisch et al.[13] failed the test for parallelism with both our methanol–water alkylbenzene line and that developed using the data of Opperhuizen et al.[17]. This may result from error associated with our transformation of their data from the natural logarithm to the base ten logarithm, or it may be from some other cause.

*Estimated log $P_{oct}$ values, comparison with the literature*

Log $P_{oct}$ estimates for benzene and 39 alkylbenzenes as well as biphenyl and 4 chlorobiphenyls were obtained using the separate acetonitrile log $P_{oct}$ vs. log $k_0$ regression lines. These estimates are shown in Table IV (estimate 1). Our *n*-alkylbenzene log $P_{oct}$ estimates are in good agreement with the available literature data. There are some differences evident for the substituted benzenes, and these will be discussed below. However, our estimates for these compounds are similar to the RP-HPLC estimates of Hammers et al.[9] and Harnisch et al.[13].

Also shown in Table IV are the log $P_{oct}$ estimates resulting from the regression line derived by combining the alkylbenzene and PCB data in the acetonitrile–water system (estimate 2). These estimates are usually higher for the alkylbenzenes and lower for the PCBs than the estimates determined from the individual compound class regressions. The combined regression estimate also usually deviates further from the available directly measured literature log $P_{oct}$ values.

The log $P_{oct}$ estimates made using the fragment constant approach[5,18] are also shown in Table IV. Beyond benzene these estimates were determined using our

TABLE IV

LOG $k'_0$ DATA, ESTIMATED LOG $P_{oct}$ VALUES AND LITERATURE DATA FOR THE TEST COMPOUNDS

| Compound | Log $k'_0$ | Log $P_{oct}$ estimates* | | Fragment constants[5] (pred. base compound) | Literature values (ref.)** |
|---|---|---|---|---|---|
| | | 1 | 2 | | |
| *Alkylbenzenes* | | | | | |
| Benzene | 1.649 | 2.16 | 2.12 | 2.13 | 2.20 (9), 2.13, 2.23 (13) |
| Toluene | 1.936 | 2.66 | 2.69 | 2.82 (benzene) | 2.78 (9), 2.65, 2.77 (13) |
| Ethylbenzene | 2.200 | 3.13 | 3.21 | 3.20 (toluene) | 3.26 (9), 3.17, 3.30 (13) |
| 1,2-Dimethylbenzene | 2.271 | 3.25 | 3.35 | 3.32 (toluene) | 3.12 (5), 3.13 (6,8), 3.19 (9) |
| 1,3-Dimethylbenzene | 2.317 | 3.33 | 3.45 | 3.32 (toluene) | 3.20 (5,8), 3.29 (9) |
| 1,4-Dimethylbenzene | 2.333 | 3.36 | 3.48 | 3.32 (toluene) | 3.15 (5), 3.18 (6,8), 3.28 (9) |
| n-Propylbenzene | 2.533 | 3.71 | 3.88 | 3.67 (ethyl) | 3.90 (9), 3.69, 3.84 (13) |
| (1-Methylethyl)benzene | 2.633 | 3.89 | 4.07 | 3.54 (ethyl) | 3.66 (5) |
| 1,2,3-Trimethylbenzene | 2.526 | 3.70 | 3.86 | 3.91 (1,2-dimethyl) | 3.55 (5), 3.66 (9) |
| 1,2,4-Trimethylbenzene | 2.596 | 3.82 | 4.00 | 3.91 (1,2-dimethyl) | 3.78 (9) |
| 1-Ethyl-2-methylbenzene | 2.571 | 3.78 | 3.95 | 3.79 (ethyl) | 3.53 (8) |
| 1-Ethyl-3-methylbenzene | 2.630 | 3.88 | 4.07 | 3.79 (ethyl) | |
| 1-Ethyl-4-methylbenzene | 2.639 | 3.90 | 4.09 | 3.79 (ethyl) | |
| n-Butylbenzene | 2.846 | 4.26 | 4.50 | 4.25 (n-propyl) | 4.44 (9), 4.21, 4.38 (13) |
| (1,1-Dimethylethyl)benzene | 2.840 | 4.25 | 4.49 | 4.19 (ethyl) | 4.11 (5) |
| (1-Methylpropyl)benzene | 2.947 | 4.44 | 4.70 | 4.12 (n-propyl) | |
| (2-Methylpropyl)benzene | 3.006 | 4.54 | 4.82 | 4.12 (n-propyl) | |
| 1-Methyl-2-(1-methylethyl)benzene | 2.844 | 4.26 | 4.49 | 4.55 (1-methylethyl) | |
| 1-Methyl-3-(1-methylethyl)benzene | 2.912 | 4.38 | 4.63 | 4.55 (1-methylethyl) | |
| 1-Methyl-4-(1-methylethyl)benzene | 2.940 | 4.43 | 4.68 | 4.55 (1-methylethyl) | |
| 1,2-Diethylbenzene | 2.865 | 4.30 | 4.54 | 4.33 (ethyl) | |
| 1,3-Diethylbenzene | 2.947 | 4.44 | 4.70 | 4.33 (ethyl) | |
| 1,4-Diethylbenzene | 2.954 | 4.45 | 4.71 | 4.33 (ethyl) | |
| 1-Methyl-2-propylbenzene | 2.913 | 4.38 | 4.63 | 4.37 (n-propyl) | |
| 1-Methyl-3-propylbenzene | 3.000 | 4.53 | 4.80 | 4.37 (n-propyl) | |
| 1-Methyl-4-propylbenzene | 3.013 | 4.56 | 4.83 | 4.37 (n-propyl) | |
| 1-Ethyl-2,3-dimethylbenzene | 2.820 | 4.22 | 4.45 | 4.45 (ethyl) | |
| 1-Ethyl-2,4-dimethylbenzene | 2.895 | 4.35 | 4.59 | 4.45 (ethyl) | |

| | | | | | |
|---|---|---|---|---|---|
| 1-Ethyl-3,5-dimethylbenzene | 2.939 | 4.43 | 4.68 | 4.45 (ethyl) | 4.11 (9) |
| 2-Fthyl-1,3-dimethylbenzene | 2.794 | 4.17 | 4.39 | 4.45 (ethyl) | 4.17 (9) |
| 2-Ethyl-1,4-dimethylbenzene | 2.874 | 4.31 | 4.55 | 4.45 (ethyl) | 4.00 (5) |
| 4-Ethyl-1,2-dimethylbenzene | 2.913 | 4.38 | 4.63 | 4.45 (ethyl) | 4.61 (7), 5.11 (9) |
| 1,2,3,4-Tetramethylbenzene | 2.864 | 4.30 | 4.53 | 4.36 (1,2,3-trimethyl) | 5.52 (6,8), 5.25, 5.45 (13) |
| 1,2,3,5-Tetramethylbenzene | 2.842 | 4.26 | 4.49 | 4.36 (1,2,3-trimethyl) | 6.29, 6.52 (13) |
| 1,2,4,5-Tetramethylbenzene | 2.768 | 4.13 | 4.34 | 4.48 (1,2,4-trimethyl) | |
| Hexamethylbenzene | 3.037 | 4.60 | 4.88 | 5.62 (1,2,3,4-tetramethyl) | 7.33, 7.60 (13) |
| n-Hexylbenzene | 3.411 | 5.26 | 5.62 | 5.34 (n-butyl) | |
| n-Octylbenzene | 4.031 | 6.35 | 6.85 | 6.42 (n-butyl) | |
| n-Nonylbenzene | 4.306 | 6.83 | 7.40 | 6.96 (n-butyl) | |
| n-Decylbenzene | 4.613 | 7.37 | 8.01 | 7.50 (n-butyl) | |
| *Polychlorobiphenyls* | | | | | |
| Biphenyl | 2.389 | 3.92 | 3.58 | | 4.04, 3.70, 3.79, 4.10, 3.75 (16), 3.93, 3.78 (13) |
| 4-Monochlorobiphenyl | 2.738 | 4.53 | 4.27 | | 4.34, 4.40, 4.69 (16) |
| 2,4,6-Trichlorobiphenyl | 3.190 | 5.33 | 5.17 | | |
| 2,2',4,5,5'-Pentachlorobiphenyl | 3.703 | 6.23 | 6.18 | | 6.85, 7.64, 6.15, 6.44, 6.42 (16) |
| 2,2',4,4',5,5'-Hexachlorobiphenyl | 4.040 | 6.82 | 6.85 | | 7.44, 6.93 (16) |

\* Estimate 1 results from the correlations of the individual compound classes, estimate 2 results from combining the compound classes in the regression analysis.

\*\* See also Table II, refs. 5–8 are directly determined, others are RP-HPLC estimates.

estimate 1 as the basic fragment. These estimates also seem good for the short chain
*n*-alkylbenzenes, and not as good for the poly-substituted benzenes.

The deviation of the estimated values of log $P_{oct}$ for the substituted benzenes,
relative to the directly determined values is intriguing. The magnitude of this deviation
may be affected by the substitution pattern of the ring. Our RP-HPLC estimates and
those using the fragment constants exceed the directly measured log $P_{oct}$ values for
most of the multi-substituted benzenes. Rapaport and Eisenreich[15] reported a similar
but opposite effect for the PCBs they studied. They found the RP-HPLC method
underestimated the log $P_{oct}$ values of PCBs having chlorines *ortho* to the phenyl bridge.
They proposed a correction factor which when applied to the RP-HPLC estimate
brought the value in line with those measured directly. Currently the database of
directly determined alkylbenzene log $P_{oct}$ values is insufficient to permit the estimation
of similar factors for the substituted benzenes. However, we feel that this matter should
be investigated more thoroughly, as it may lead to insights into the interaction of the
analyte with the stationary and mobile phases.

If we consider only differences between our RP-HPLC estimates for isomeric
structures, trends become more apparent. For example, isomers with *ortho* substitu-
tion have log $P_{oct}$ values about 0.1 log units lower than those having *meta* and *para*
substitution. The log $P_{oct}$ values of the trisubstituted benzenes seem to differ by this
amount for each *ortho* substitution. This pattern, however, is not readily apparent for
the tetramethylbenzenes.

The fragment constant method[5] adds a factor to the log $P_{oct}$ value for each

TABLE V

COMPARISON OF GROUP FACTORS FOR LOG $P_{oct}$, FROM THE FRAGMENT CONSTANT
METHOD[5,18] AND DERIVED FROM THE RP-HPLC ESTIMATIONS

|  | *Group being added:* | | | |
|---|---|---|---|---|
|  | *Methyl* | *Ethyl* | *1-Methylethyl* | *Propyl* |
| Fragment constants | 0.66 | 1.20 | 1.61 | 1.74 |
| RP-HPLC factors |  |  |  |  |
| *ortho* to: |  |  |  |  |
| Methyl | 0.59 | 1.12 | 1.60 | 1.72 |
| Ethyl | 0.65 | 1.17 | — | — |
| Propyl | 0.67 | — | — | — |
| 1-Methylethyl | 0.37 | — |  | — |
| *meta* to: |  |  |  |  |
| Methyl | 0.67 | 1.22 | 1.72 | 1.88 |
| Ethyl | 0.76 | 1.32 |  | — |
| Propyl | 0.82 | — |  | — |
| 1-Methylethyl | 0.49 | — | — | — |
| *para* to: |  |  |  |  |
| Methyl | 0.70 | 1.24 | 1.77 | 1.90 |
| Ethyl | 0.77 | 1.33 | — | — |
| Propyl | 0.85 | — | — | — |
| 1-Methylethyl | 0.54 | — | — | — |

additional structural fragment added to the molecule. Since our RP-HPLC estimates were used as the basic group for the fragment constant log $P_{oct}$ predictions, direct comparison of these results with the log $k_0'$ based estimates is useful only in evaluating the group factors added to the basic compounds. In Table V we make this comparison for the disubstituted benzenes. The difference between adding a group at the *ortho* position *versus* the *meta* and *para* positions is evident in this table. This comparison shows that the position of substitution can affect the log $P_{oct}$ value added by a fragment. For example the fragment constants for the addition of a methyl or ethyl group to toluene match the group factor for *meta* substitution, whereas the 1-methylethyl and propyl group additions match *ortho* substitution more closely. Also of interest in this table is the effect of the group already on the ring, an effect is evident for all groups but particularly the 1-methylethyl group. These data suggest that the log $P_{oct}$ value added by a structural group can be dependent on another structural group on the ring.

## CONCLUSIONS

Our void volume measurements suggest that the linearization procedures investigated do not always yield a better estimate of the void volume. Both linearization procedures occasionally gave volumes greater than the maximum solvent volume of the column as determined by differential weighing. This leads us to conclude that injection of a sodium nitrate solution gave a more reliable estimate of $V_0$.

The difference of log $k_0'$ values for a given compound, in the two mobile phases indicates that the values determined using this method are not the true aqueous capacity factor. When the aqueous capacity factor is desired, it should be determined directly.

Comparison of our log $k_0'$ results in methanol with literature data suggest that for a given mobile phase the slopes of the log $P_{oct}$ – log $k_0'$ regression lines are similar, but that the intercepts vary with chromatographic system used. This variability and the dependence on the organic modifier indicates that log $k_0'$ is not a good hydrophobic parameter by itself, as has been suggested[1], but is strongly correlated with log $P_{oct}$.

It appears that log $P_{oct}$ – log $k_0'$ correlations allow us to estimate log $P_{oct}$ of hydrophobic compounds reasonably accurately, however the correlation cannot be extended over different compound classes without some loss in predictive power. This should be of particular concern when using RP-HPLC to estimate log $P_{oct}$ values beyond the calibration range (log $P_{oct} > 4$–6).

The fragment constant method of Hansch and Leo[5] yields log $P_{oct}$ estimates similar to the RP-HPLC estimates. The fragment constant method needs to be adjusted to include ring substitution effects that it does not currently account for.

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