

# Substituent Contribution to the Partition Coefficients of Substituted Benzenes in Solvent-Water Mixtures

**Keyphrases** □ Partition coefficients—substituted benzenes in solvent-water mixtures, substituent contribution □ Solvent-water mixtures—substituent contribution to the partition coefficients of substituted benzenes □ Benzenes—substituted, substituent contribution to the partition coefficient, solvent-water mixtures

## To the Editor:

In the course of correlation analysis for biological activities, octanol-water partition coefficients ( $P$ ) have been used widely to express the lipophilic interactions of organic compounds with biological substrates. The contribution of a given substituent to the partitioning of a molecule is measured by a substituent constant,  $\pi$ , that is derived empirically from partition coefficients (1). Since discrepancies are found between some  $\pi$  values from different parent compounds and these variations depend also on the nature of the solvent-water system being used (2, 3), it is of interest to examine the relationship between  $\pi$  and pertinent physicochemical properties to identify the factors that account for the discrepancies.

By convention (1), the substituent constant  $\pi_X$  for a functional group attached to a reference compound (benzene or a benzene derivative) is defined as:

$$\pi_X = \log P_X - \log P_R \quad (\text{Eq. 1})$$

where  $P_X$  is the octanol-water partition coefficient of the compound containing substituent(s)  $X$ , and  $P_R$  is the partition coefficient of the parent or unsubstituted molecule. The extent to which  $\pi_X$  varies with various parent compounds was found to be relatively small for most nonpolar and weakly polar substituents (1), whereas more variation is observed for polar substituents. The values of  $\pi_X$  were analyzed in terms of the net partition free energies of the substituents and the free energies of interactions of the substituents with the parent aromatic structure. Because the values of the assumed free energy terms are not readily available for verifying the results, no specific rules have been constructed to indicate that  $\pi_X$  derived from different reference systems for a given functional group would be either constant or related in some simple way. The following analysis considers the factors affecting  $\pi_X$ .

Since  $\pi_X$  is a derived quantity, the factors that affect  $\pi_X$  must be contained in the expression for  $\log P$ . In the absence of solute association or dissociation, the partition coefficients of slightly water-soluble organic solutes between an organic solvent and water, in which the solvent has small solubility in water, can be expressed as (4):

$$\log P = -\log S_w - \log \gamma_0^* + \log(\gamma_w^*/\gamma_w) - \log \bar{V}_0^* \quad (\text{Eq. 2})$$

where  $S_w$  is the water solubility (moles/liter) of the liquid (or supercooled liquid) solute,  $\gamma_0^*$  is the activity coefficient (Raoult's law convention) in the water-saturated solvent phase,  $\gamma_w$  is the activity coefficient in water at saturation,  $\gamma_w^*$  is the activity coefficient in solvent-saturated water, and  $\bar{V}_0^*$  is the molar volume (liters/mole) of the water-

**Table I—Values for  $\Delta$ ,  $\pi$  (Octanol-Water), and  $\pi$  (Heptane-Water) Derived with Respect to Benzene**

Compound	Function	$\Delta^a$	$\pi$ (octanol-water) <sup>b</sup>	$\pi$ (heptane-water) <sup>c</sup>
Benzene	—	0	0	0
Toluene	CH <sub>3</sub>	0.60	0.56	0.59
Styrene	C <sub>2</sub> H <sub>3</sub>	0.83	0.82	0.85
Ethylbenzene	C <sub>2</sub> H <sub>5</sub>	1.20	1.02	1.17
<i>o</i> -Xylene	1-CH <sub>3</sub> -2-CH <sub>3</sub>	1.08	0.99	1.13
<i>m</i> -Xylene	1-CH <sub>3</sub> -3-CH <sub>3</sub>	1.09	1.07	1.28
<i>n</i> -Propylbenzene	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	1.66	1.55	1.85
1,3,5-Trimethylbenzene	1,3,5-(CH <sub>3</sub> ) <sub>3</sub>	1.46	1.29	1.79
<i>tert</i> -Butylbenzene	<i>tert</i> -C <sub>4</sub> H <sub>9</sub>	1.96	1.98	2.15
Fluorobenzene	F	0.16	0.14	0.19
Chlorobenzene	Cl	0.72	0.71	0.69
Bromobenzene	Br	0.91	0.86	0.84
Iodobenzene	I	1.14	1.12	1.07
<i>o</i> -Dichlorobenzene	1-Cl-2-Cl	1.34	1.22	1.19
<i>m</i> -Dichlorobenzene	1-Cl-3-Cl	1.40	1.25	1.28
1,2,4-Trichlorobenzene	1,2,4-(Cl) <sub>3</sub>	1.93	1.89	1.80
$\alpha,\alpha,\alpha$ -Trifluorotoluene	CF <sub>3</sub>	0.88	0.88	1.05
Aniline	NH <sub>2</sub>	-1.24	-1.23	-2.22
<i>m</i> -Chloroaniline	1-NH <sub>2</sub> -3-Cl	-0.27	-0.25	-1.55
<i>o</i> -Toluidine	1-NH <sub>2</sub> -2-CH <sub>3</sub>	-0.83	-0.84	-1.72
<i>m</i> -Toluidine	1-NH <sub>2</sub> -3-CH <sub>3</sub>	-0.79	-0.73	-1.72
Phenol	OH	-1.70	-0.67	-3.18
Benzoic acid	COOH	-0.73	-0.28	-2.98
Phenylacetic acid	CH <sub>2</sub> COOH	-1.15	-0.83	-3.33
Anisole	OCH <sub>3</sub>	0.21	-0.02	-0.16
Acetophenone	COCH <sub>3</sub>	-0.33	-0.40	-1.12
Benzaldehyde	CHO	-0.23	-0.65	-1.21
Nitrobenzene	NO <sub>2</sub>	0.14	-0.28	-0.77
Benzonitrile	CN	-0.26	-0.57	-1.36

<sup>a</sup> The  $\Delta$  values are calculated from the respective  $\gamma_w$  values of the compounds at  $\sim 25^\circ$  and  $\log \gamma_w = 3.38$  for benzene as the standard (Ref. 7). Data for halobenzenes, dichlorobenzenes, 1,2,4-trichlorobenzene, *m*-chloroaniline, and toluidines are taken from the citations given in Ref. 4; anisole and benzonitrile from Ref. 8; and the remainder from the citations in Ref. 6. <sup>b</sup> The  $\pi$  (octanol-water) values are based on  $\log P = 2.13$  for benzene (Ref. 1) as the standard and the  $\log P$  data from the citations in Refs. 1 and 9 for all compounds, except for 1,2,4-trichlorobenzene from Ref. 4. <sup>c</sup> The  $\pi$  (heptane-water) values are calculated from the respective  $\log P$  values of the compounds using  $\log P = 2.26$  for benzene (Ref. 9) as the standard. Data for toluene, xylenes, aniline, *m*-chloroaniline, *m*-toluidine, benzoic acid, and anisole are from the citations in Ref. 9 and the rest from this work.

saturated solvent. The  $\log \bar{V}_0^*$  term is essentially constant for solutes in dilute solution.

In octanol-water systems, it has been shown (4, 5) that the primary determinant of the solute partition coefficient is the extent of solute solubility in water ( $S_w$ ), followed in decreasing order by solute incompatibility with octanol ( $\gamma_0^*$ ) and the alteration of solute water solubility by dissolved octanol ( $\gamma_w^*/\gamma_w$ ). The  $\log(\gamma_w^*/\gamma_w)$  term is relatively small for those solutes that have comparable or greater solubility in water than octanol (solvent) in water, and thus can be neglected for many simple aromatic liquids.

Substituting Eq. 2 into Eq. 1 gives:

$$\pi_X \approx \log[(S_w)_R/(S_w)_X] - \log[(\gamma_0^*)_X/(\gamma_0^*)_R] \quad (\text{Eq. 3})$$

or

$$\pi_X \approx \log[(\gamma_w)_X/(\gamma_w)_R] - \log[(\gamma_0^*)_X/(\gamma_0^*)_R] \quad (\text{Eq. 4})$$

where the solubility ratio in Eq. 3 may be replaced by the inverse of the activity coefficient ratio (4, 5). The magnitude of  $\pi_X$  for a functional group in a reference compound thus is equal to the difference between  $\log[(\gamma_w)_X/(\gamma_w)_R]$  and  $\log[(\gamma_0^*)_X/(\gamma_0^*)_R]$ , *i.e.*, between the effects of the substituent on solute compatibility with water and with octanol (solvent).

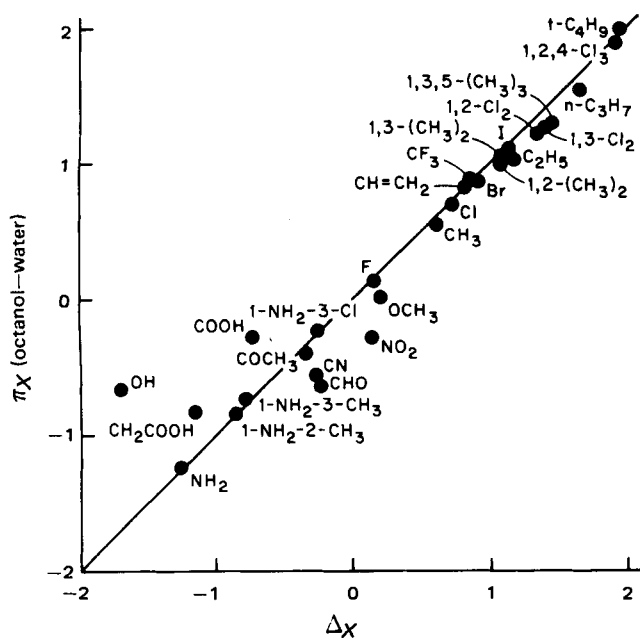


Figure 1—A comparison of  $\Delta_X$  and  $\pi_X$  (octanol-water) values for common substituents with benzene as the reference standard. Key: (—)  $\pi_X$  (octanol-water) =  $\Delta_X$ .

To illustrate the relative effects of these two terms on the values of  $\pi_X$  for some substituents in the octanol-water system, benzene is chosen as the reference compound. For both benzene and benzene substituted with nonpolar and weakly polar groups (such as  $X$  = halogens, alkyl groups, and amino), the logarithmic effects on activity coefficients in octanol ( $\log \gamma_0^*$ ) are considerably less than in water ( $\log \gamma_w$ ) (4, 5). For example, the  $\log[(\gamma_w)_X/(\gamma_w)_R]$  values with benzene as reference are  $-1.24$ ,  $0.72$ ,  $0.91$ , and  $1.66$  for  $X$  =  $\text{NH}_2$ ,  $\text{Cl}$ ,  $\text{Br}$ , and  $n\text{-C}_3\text{H}_7$ , respectively, and the corresponding  $\log[(\gamma_0^*)_X/(\gamma_0^*)_R]$  values are  $\sim 0.00$ ,  $0.01$ ,  $0.05$ , and  $0.10$  calculated following a previously described method (4). Consequently, the magnitude of each  $\pi_X$  should be essentially equal to the value of  $\log[(\gamma_w)_X/(\gamma_w)_R]$ , which is designated for brevity as  $\Delta_X$  (6).

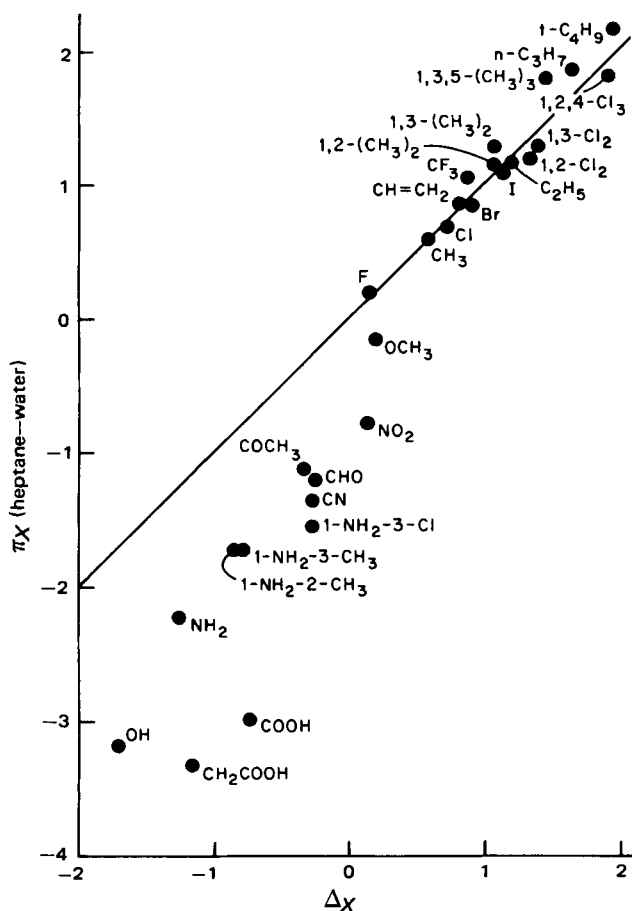
A comparison of  $\pi_X$  and  $\Delta_X$  values is shown in Table I, and a plot of  $\pi_X$  versus  $\Delta_X$  is shown in Fig. 1. The results indicate that when  $\pi_X$  approximates  $\Delta_X$  for substituent  $X$  and  $\pi_Y$  approximates  $\Delta_Y$  for substituent  $Y$  in monosubstituted benzenes, the values of  $\pi_{XX}$  (or  $\pi_{YY}$ ) and  $\pi_{XY}$  also approximate the corresponding values of  $\Delta_{XX}$  (or  $\Delta_{YY}$ ) and  $\Delta_{XY}$  for disubstituents  $X, X$  and  $X, Y$  attached to benzene. Supporting data are demonstrated with xylenes and dichlorobenzenes ( $\pi_{XX} \approx \Delta_{XX}$ ) and with toluenes and *m*-chloroaniline ( $\pi_{XY} \approx \Delta_{XY}$ ). It is recognized, however, that the magnitudes of  $\pi_{XX}$  and  $\pi_{XY}$  (or  $\Delta_{XX}$  and  $\Delta_{XY}$ ) in disubstitution are not necessarily equal to the sum of  $\pi_X$  and  $\pi_Y$  (or correspondingly of  $\Delta_X$  and  $\Delta_Y$ ). This is because the increment in solute activity coefficient with addition of a substituent may vary from compound to compound (*i.e.*, from benzene to a substituted benzene) and from solvent to solvent (in this case from water to octanol). Since the additivity rule may not be strictly obeyed when more than one substituent is present, it is better to consider the set of substituents as a whole rather than to treat them as a sum of independent components.

The value of  $\pi_X$  would be expected to deviate significantly from  $\Delta_X$  when a benzene derivative and benzene show appreciable differences in their respective compatibilities with octanol. If the derivative is more compatible than benzene with octanol, *i.e.*, if  $\log[(\gamma_0^*)_X/(\gamma_0^*)_R]$  is negative, then  $\pi_X$  will be greater than  $\Delta_X$ . The finding that  $\pi_X$  is significantly greater than  $\Delta_X$  for  $X$  =  $\text{COOH}$  and  $\text{CH}_2\text{COOH}$  is reasonable, because the addition of these highly polar groups to relatively nonpolar benzene should make for better compatibility with the partially polar octanol phase, which also contains  $2.3 M$  of water (10). Although phenol is expected to be more compatible with the octanol than benzene (*i.e.*,  $\pi_X > \Delta_X$  when  $X$  =  $\text{OH}$ ), the large difference between  $\pi_X$  and  $\Delta_X$  could partly be due to hydrate formation of phenol in water (11), which introduces inaccuracies into the value of  $\Delta_X$  (*i.e.*,  $\gamma_w$  for phenol) as calculated from the apparent phenol solubility in water.

With  $X$  =  $\text{NO}_2$ ,  $\text{CN}$ , and  $\text{CHO}$ , the values of  $\pi_X$  are much smaller than the respective values of  $\Delta_X$ . It is not clear whether these anomalies are caused by some specific interactions of octanol with nitrobenzene, benzonitrile, and benzaldehyde or by possible solute associations or dissociations in water and/or octanol. In general, although the  $\pi_X$  values for highly polar groups might deviate significantly from the respective  $\Delta_X$  values in octanol-water systems, the differences are usually well within  $\pm 1$  for simple aromatic compounds in the absence of association or dissociation. This may be attributed to the partially polar nature of the octanol medium that allows it to accommodate relatively indiscriminately a wide range of benzene derivatives of varying polarities (4, 5).

The foregoing analysis with benzene as reference also applies to systems with other compounds as reference standards. Again, the values of  $\pi_X$  and  $\Delta_X$  derived with respect to a new reference compound should be comparable with nonpolar and weakly polar functional groups. For instance, when aniline ( $\log P = 0.90$ ) is used as the reference, the values of  $\pi_X$  and  $\Delta_X$  are  $0.98$  and  $0.98$  for  $X$  =  $\text{Cl}$  (*meta*);  $0.39$  and  $0.42$  for  $X$  =  $\text{CH}_3$  (*ortho*); and  $0.50$  and  $0.46$  for  $X$  =  $\text{CH}_3$  (*meta*). With toluene ( $\log P = 2.69$ ) as reference,  $\pi_X$  and  $\Delta_X$  are  $0.43$  and  $0.48$  for  $X$  =  $\text{CH}_3$  (*ortho*) and  $0.51$  and  $0.49$  for  $X$  =  $\text{CH}_3$  (*meta*). These results agree with the earlier findings that the group contribution to partition coefficient derives mainly from the variation of the solute incompatibility with water, although  $\pi_X$  may vary from one reference standard to another. Again, significant (but not remarkable) differences between  $\pi_X$  and  $\Delta_X$  would occur if  $\log[(\gamma_0^*)_X/(\gamma_0^*)_R]$  should become significant.

While the values of  $\log[(\gamma_0^*)_X/(\gamma_0^*)_R]$  are relatively small and comparable for most substituents in the octanol-water system, they can be highly important for certain substituents in other solvent-water systems in which the solvent is sensitive to the polarity difference of the two partitioned solutes. This argument follows a general rule that components of similar polarities and structures usually form more ideal solutions than components of different polarities and structures (*i.e.*, like dissolves like). Consider now the  $\pi_X$  values for the substituents derived from the heptane-water system using again benzene as the parent compound (Table I). A plot of  $\pi_X$  (heptane-water) versus  $\Delta_X$  is given in Fig. 2. The extremely nonpolar structure of



**Figure 2**—A comparison of  $\Delta_X$  and  $\pi_X$  (heptane-water) values for common substituents with benzene as the reference standard. Key: (—)  $\pi_X$  (heptane-water) =  $\Delta_X$ .

heptane, as evidenced by small water content of  $3.3 \times 10^{-3} M$  at saturation (10), makes it sensitive to the difference in polarity between a substituted and parent (benzene) molecules. With  $X = \text{NH}_2, \text{CHO}, \text{NO}_2, \text{CN}, \text{COCH}_3, \text{COOH},$  and  $\text{CH}_2\text{COOH}$  attached to benzene, the observed  $\pi_X$  (heptane-water) values are markedly lower than the corresponding  $\Delta_X$  values. These results presumably from greatly increased polarities of the substituted benzenes (over that of benzene), which reduce the compatibilities of the substituted benzenes with heptane. Addition of alkyl groups to benzene (making the molecules more hydrocarbon-like) gives somewhat higher  $\pi_X$  (heptane-water) than  $\pi_X$  (octanol-water), as would be expected. Addition of halogen groups shows insignificant differences between the two sets of  $\pi_X$  values. In other words, the values of  $\log[(\gamma_0)_X/(\gamma_0)_R]$  in the heptane phase are reasonably close to zero for relatively nonpolar substituents but are very significant and positive for polar substituents. As a whole, those substituents which cause large differences between  $\pi_X$  (heptane-water) and  $\Delta_X$  are the same ones that show large differences between  $\pi_X$  (heptane-water) and  $\pi_X$  (octanol-water).

In conclusion, the correspondence between  $\Delta_X$  and  $\pi_X$  in heptane-water is less obvious than in octanol-water, because heptane shows greater sensitivity than octanol to the polarities of the substituted benzenes.

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## Effect of Water Deprivation on Chloramphenicol Disposition Kinetics in Humans

**Keyphrases** □ Kinetics, disposition—effect of water deprivation on chloramphenicol, humans □ Chloramphenicol—effect of water deprivation, disposition kinetics in humans

### To the Editor:

The first study of the effect of water deprivation on drug disposition kinetics was recently reported (1). Temporary water deprivation causes significant changes in drug metabolizing enzymes, hormones responsible for water balance in the body, and blood chemistry and physiology (2–4). Despite these significant changes, little has been reported in the literature on the effect of water deprivation resulting from various disease states and environmental factors on drug disposition kinetics.

The present study reports the effect of highly restricted water intake on chloramphenicol absorption and urinary elimination in humans.

The panel of subjects studied consisted of four healthy male volunteers (weight, 60–72 kg; age, 22–24 years). A total of 14 days was allowed for the conditioning of the subjects for the treatment studies. During the first 11 days,