J. Chem. Eng. Data **1995,** *40,* 959–962

Aqueous Solubilities and Octanol–Water Partition Coefficients of Chloroveratroles and Chloroanisoles

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The aqueous solubilities and octanol–water partition coefficients at 25 °C of veratrole (1,2-dimethoxybenzene), three chlorinated veratroles, and nine chlorinated anisoles (methoxybenzenes) were measured by a conventional shake-flask, batch-contacting method. The data indicate that both solubilities and octanol–water partition coefficients are well correlated with LeBas molar volume, yielding structure–property relationships which may be useful for predictive purposes. Correlation of supercooled liquid solubilities and octanol–water partition coefficients of a series of phenolic compounds suggests that in aqueous solution the chloroveratroles and chloroanisoles behave similarly to nonpolar aromatic compounds such as the chlorobenzenes and differently from the related chlorophenolic substances.

Introduction

A wide range of high and low molecular weight chlorinated organic compounds are produced during the pulp bleaching process by a series of complex reactions between chlorine and the lignin contained in the pulp (Kringstad and Lindström, 1984). Chlorinated phenols, guaiacols, and catechols are produced in significant amounts during softwood and hardwood pulping. Extensive studies by Neilson et al. (1983, 1984, 1989) and Remberger et al. (1986) have shown that these organochlorines may be biotransformed into chlorinated anisoles and veratroles as shown in Figure 1 (Brownlee and MacInnis, 1993). Trace amounts of 4,5-dichloroveratrole (45DCV), 3,4,5-trichloroveratrole (345TCV), and tetrachloroveratrole (TeCV) have been identified in bleached kraft mill effluent (Neilson et al., 1989; Brownlee and MacInnis, 1993). Chlorinated anisoles and veratroles are of environmental concern because they are more lipophilic and stable than the corresponding catechols and guaiacols. Furthermore, they are believed to be more toxic and to have a greater potential for bioaccumulation (Neilson et al., 1984).

The environmental fate and effects of chloroveratroles and chloroanisoles depend on their physical–chemical properties. There is thus a need to establish a sound data base of these properties by experimental determination and by development of predictive methods for use when data are unavailable or are suspect. Suntio et al. (1988) reviewed organochlorine compounds present in pulp mill effluent and emphasized the lack of reported physical–chemical properties, which prevents obtaining an adequate understanding of their environmental pathways and effects. Aqueous solubility is a crucial parameter for assessing environmental partitioning because it influences evaporation and sorption to biotic and abiotic phases. The dimensionless octanol–water partition coefficient (K_{OW}) is an important and frequently used descriptor of chemical behavior in the environment. It is a measure of hydrophobicity of organic compounds and has been demonstrated to be an important parameter in bioaccumulation.

There is a need to correlate environmentally relevant physical–chemical properties such as solubility and K_{OW} with appropriate molecular descriptors to establish quantitative structure–property relationships (QSPR). There is also an incentive to relate physical–chemical properties, particularly octanol–water partition coefficients, to toxicity data in order to assess the likelihood of adverse effects.

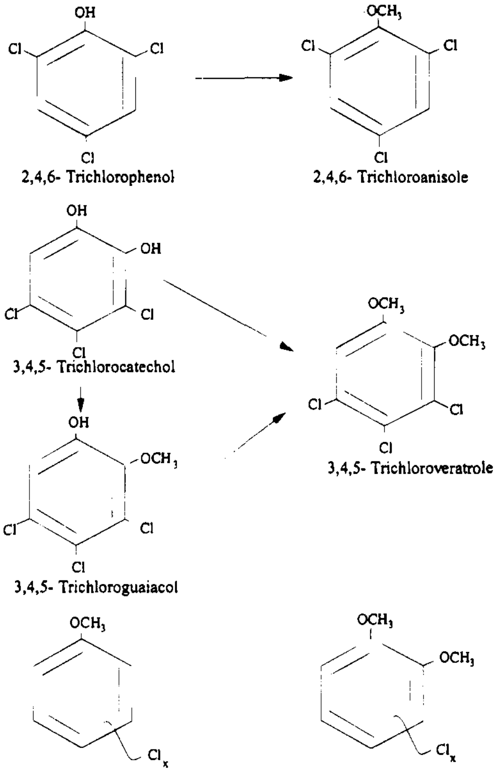

Figure 1. Structural formulas for chloroanisoles and chloroveratroles and the corresponding phenol, guaiacol, and catechol from which they can be produced by biological methylation.

Theoretical Background

The correlation between logarithms of K_{OW} and C^{S}_{W} was first proposed by Hansch et al. (1968) and was further discussed by Mackay et al. (1980), Miller et al. (1985), and Tewari et al. (1982). A simple relationship between K_{OW} and solubility in terms of activity coefficients can be derived by expressing the fugacity, f, of a solute in aqueous solution as

$$f = x_W \gamma_W f_R \tag{1}$$

where x_W is the solute mole fraction in solution, γ_W is the aqueous phase activity coefficient according to Raoult's law,

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0021-9568/95/1740-0959$09.00/0

and f_R is the reference fugacity or approximately the vapor pressure of the pure solute in liquid form at the system temperature. In dilute aqueous solution, the concentration, C_W ($mol \cdot m^{-3}$), is approximately x_W/v_W where v_W is the molar volume of the solution ($m^3 \cdot mol^{-1}$).

At saturation when the concentration is $C^S{}_W$, if it is assumed that the water dissolved in the saturated liquid solute phase has a negligible effect on the fugacity of the excess liquid solute, we can equate f to f_R; hence, from (1)

$$\gamma_W = 1/x_W = 1/C^S{}_W \nu_W \qquad (2)$$

When the solute partitions between a liquid phase such as octanol (subscript O) and water (subscript W), the fugacity is given as

$$f = x_O \gamma_O f_R = x_W \gamma_W f_R \qquad (3)$$

Hence

$$x_O \gamma_O = x_W \gamma_W \qquad (4)$$

The octanol–water partition coefficient (K_{OW}) is usually defined as the ratio of the solute concentration (mass/volume) in octanol saturated with water to its concentration in water saturated with octanol under equilibrium conditions as shown in eq 5. Substituting for x_O/x_W from eq 4 and γ_W from eq 2 gives

$$K_{OW} = C^S{}_O/C^S{}_W = (x_O/\nu_O)/(x_W/\nu_W) = \gamma_W \nu_W/\gamma_O \nu_O = 1/(\gamma_O \nu_O C^S{}_W) \qquad (5)$$

K_{OW} can also be viewed as a ratio of solubilities in octanol and water, in which case the solubility in octanol, $C^S{}_O$ is $1/\gamma_O v_O$.

These equations illustrate the fundamental inverse relationship between $C^S{}_W$ and K_{OW} which occurs when the activity coefficient in octanol, γ_O, or the solubility in octanol, $C^S{}_O$, remains constant. This has been used as a basis for correlating K_{OW} with $C^S{}_W$ in quantitative structure–property relationship plots (QSPRs). Equation 5 can be converted into the logarithmic form of eq 6 and correlation is usually of eq 7.

$$\log K_{OW} = -\log C^S{}_W - \log(\gamma_O \nu_O) \qquad (6)$$

$$\log K_{OW} = A - B \log C^S{}_W \qquad (7)$$

Equation 6 suggests that the regression coefficient B on $\log C^S{}_W$ should be close to unity. Yalkowsky and Valvani (1979) and Yalkowsky et al. (1979) fitted experimental data to equations of this form, obtaining experimental values of 0.88 for hydrocarbons and 0.987 for halobenzenes, confirming that the coefficient on $\log C^S{}_W$ is indeed close to unity. Mackay et al. (1980) suggested that the reason for the coefficient being less than 1.0 is that γ_O varies and tends to be larger specifically for substances of large molar volume with lower water solubilities.

In this work, experimental values are reported for $C^S{}_W$ and K_{OW} for chloroveratroles and chloroanisoles. The data are interpreted and correlated to elucidate the fundamental thermodynamic relationships between the aqueous solubility and octanol–water partition coefficient for these substances.

Experimental Section

Materials. Chloroveratroles (99+% purity) were obtained from Helix Biotech Corp. of Richmond, British Columbia. Chloroanisoles (of the highest commercial purity, 97–99%) were purchased from Aldrich Chemical Co. The chemicals were used as purchased without further purification. Doubly distilled water was used to prepare all saturated solutions. Methanol and hexane (both of HPLC grade) were obtained from Caledon Laboratories, Ontario. 1-Octanol (99+% purity) was purchased from Fisher Scientific. Milli-Q ultrapure deionized water was used with methanol as the mobile phase for HPLC analysis.

Preparation of Saturated Solution. (i) Aqueous Solubility. Excess amounts of chloroveratroles or chloroanisoles were added to 50 mL Erlenmeyer flasks containing doubly distilled water. Samples were stirred or shaken gently for 24 h and allowed to settle at (25 ± 2) °C for at least 48 h before analysis.

(ii) Octanol–Water Partition Coefficient. A stock solution of approximately 1 mg/mL of the compound in 1-octanol was prepared. Except for monochloroanisoles, a 2 mL aliquot of stock solution and 20 mL of water were shaken for 48 h at 25 °C in a 60 mL separatory funnel. Saturated samples of monochloroanisoles were prepared in the same manner but using a 4 mL aliquot of stock solution and 40 mL of water.

Analytical Methods. (i) Aqueous Solubility. HPLC Measurements. Analysis was performed using a Waters Associates (Millford, MA) liquid chromatograph (HPLC system) consisting of a Model 6000 solvent delivery system, a Model M45 solvent delivery system, a Model 440 UV absorbance detector with 254 and 280 nm kits, and a Model 720 system flow controller. The system was operated in isocratic mode with a methanol and water mixture (85:15 by volume) as the mobile phase. The analytical column was a Waters 3.9 mm o.d. × 300 mm long μBondapak C_{18} column. Aqueous samples were directly injected onto the column. Peak areas were integrated and recorded by a Waters Model 730 data module. Calibration standards were prepared by dissolving known amounts of the chemical in methanol.

Gas Chromatographic Measurements. The saturated aqueous solution was extracted with hexane and then directly injected onto the gas chromatograph column. Analysis was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a ^{63}Ni electron capture (EC) detector. The analytical column was a 0.32 mm o.d. by 30 m long J&W DB-15 fused silica capillary column. The make-up and carrier gas was a 95:5 by volume argon–methane mixture. Operating conditions were the following: injection port at 250 °C, oven in isothermal mode with set point between 110 and 180 °C depending on the melting point of the chemical, detector at 300 °C. Peak areas were recorded on a Hewlett-Packard 3392A integrator.

(ii) Octanol–Water Partition Coefficient. Gas Chromatographic Measurement. The aqueous phase and octanol phase were first separated. The aqueous phase was centrifuged, extracted with hexane, and then directly injected onto the GC column. The octanol phase was diluted 10–100 times with octanol and was also analyzed by direct injection onto the GC column.

Results and Discussion

Table 1 summarizes the measured aqueous solubilities of veratrole, chloroveratroles, and chloroanisoles at 25 °C and previously reported values. The measured solubility data have a precision (standard deviation) of approximately ±5%. The measured aqueous solubilities for 345-TCV and TeCV are substantially different from Neilson's reported values (1984). Neilson's "approximate solubilities in water" were determined incidentally when preparing solutions for bioassays. No details were given about analytical methods or replications: thus, we regard these reported values as only approximate.

Table 1. Aqueous Solubilities of Chloroveratroles and Chloroansioles at 25 °C

compound	mol wt	mp/°C	LeBas mol vol/ $(cm^3{\cdot}mol^{-1})$	solubility/ $(g{\cdot}m^{-3})$	supercooled liq solubility $C^S{}_L/(mol{\cdot}m^{-3})$	method	lit. value/ $(g{\cdot}m^{-3})$	ref
veratrole	138	liq	158.6	6690 ± 59	48.9	HPLC−UV		
4,5-dichloroveratrole	207	83	200.4	71.9 ± 1.7	1.35	HPLC−UV		
				72.6 ± 1.9		GC−ECD		
3,4,5-trichloroveratrole	241.5	66	221.4	10.3 ± 0.8	0.11	GC−ECD	2.5	Neilson et al. (1984)
tetrachloroveratrole	276	90	242.3	1.59 ± 0.07	0.026	GC−ECD	0.7	Neilson et al. (1984)
2-chloroanisole	142.5	liq	148.3	490 ± 10	3.44	HPLC−UV		
3-chloroanisole	142.5	liq	148.3	235 ± 7.08	1.65	HPLC−UV		
4-chloroanisole	142.5	liq	148.3	237 ± 4.67	1.66	HPLC−UV		
2,3-dichloroanisole	177	32	169.2	86.9 ± 2.6	0.58	GC−ECD		
2,6-dichloroanisole	177	liq	169.2	140 ± 3.73	0.8	GC−ECD		
2,3,4-trichloroanisole	211.5	70	190.1	10.8 ± 0.26	0.141	GC−ECD		
2,4,6-trichloroanisole	211.5	61	190.1	13.2 ± 0.4	0.142	GC−ECD		
2,3,4,5-tetrachloroanisole	246	88	211.0	1.35 ± 0.05	0.023	GC−ECD		
2,3,5,6-tetrachloroanisole	246	84	211.0	1.82 ± 0.03	0.028	GC−ECD		

Table 2. Octanol−Water Partition Coefficients (K_{OW}) of Chloroveratroles and Chloroanisoles at 25 °C

compound	concn in aq phase/$(g{\cdot}m^{-3})$	concn in octanol phase/$(g{\cdot}m^{-3})$	log K_{OW}	method	lit. value log K_{OW}	ref
veratrole	4.87 ± 0.33	980 ± 10	2.18	HPLC−UV		
4,5-dichloroveratrole	0.8 ± 0.07	1057 ± 8.1	3.11	GC−ECD		
3,4,5-trichloroveratrole	0.1 ± 0.02	1030 ± 50	4.01	GC−ECD	4.6	Neilson et al. (1984)
tetrachloroveratrole	0.012 ± 0.001	986 ± 43	4.86	GC−ECD	5.8	Neilson et al. (1984)
					4.7	Sarrikoski et al. (1986)
anisole					2.11	Dunn et al. (1986)
2-chloroanisole	1.76 ± 0.06	1261.5 ± 24.4	2.5	HPLC−UV		
3-chloroanisole	1.8 ± 0.08	980 ± 30	2.6	HPLC−UV		
4-chloroanisole	2.06 ± 0.09	898 ± 28.6	2.7	HPLC−UV		
2,3-dichloroanisole	0.45 ± 0.04	982 ± 76	3.24	HPLC−UV		
2,6-dichloroanisole	0.34 ± 0.026	968 ± 5	3.14	HPLC−UV		
2,3,4-trichloroanisole	0.093 ± 0.003	1019 ± 62	4.03	GC−ECD		
2,4,6-trichloroanisole	0.087 ± 0.001	980 ± 58	4.02	GC−ECD		
2,3,4,5-tetrachloroanisole	0.019 ± 0.003	1002 ± 54	4.5	GC−ECD		
2,3,5,6-tetrachloroanisole	0.025 ± 0.002	997 ± 64.6	4.4	GC−ECD		

The variation in solubility in homologous series such as this depends on molecular size and shape as can be characterized by the additive LeBas molar volume (Reid et al., 1987). Table 1 also gives the molar volume V_M/$(cm^3{\cdot}mol^{-1})$ calculated using the additive LeBas method which can be expressed as a function of the number of chlorine atoms N as

$$V_M = 158.6 + 20.9N \quad \text{(chloroveratroles)} \qquad (8)$$

$$V_M = 127.4 + 20.9N \quad \text{(chloroanisoles)} \qquad (9)$$

where 20.9 represents the difference in atomic volume of chlorine and hydrogen. Correlation of QSPRs requires that the physical−chemical properties of the series be expressed in the same physical state, liquid or solid. With the exceptions of the parent compounds and some of the monochloro and dichloro isomers which are liquid at room temperature, the solid solubilities were converted to supercooled liquid ($C^S{}_L/(mol{\cdot}m^{-3})$) values by dividing by the fugacity ratio, F. The fugacity ratio, defined as the ratio of solid and supercooled liquid fugacities, f_S/f_L, was evaluated from the melting point and the estimated entropy of fusion of moderately sized rigid organic molecules. In the absence of reported entropy of fusion data, the fugacity ratio can be estimated using Walden's rule as discussed by Yalkowsky (1979) as

$$f_S/f_L = \exp[-6.79((T_M/T) - 1)] \qquad (10)$$

where f_S and f_L (Pa) are the fugacities of the solid and liquid of the solute, T_M is the melting point (K), and T is the system temperature (K).

Table 2 gives the measured octanol−water partition coefficients for chloroveratroles and chloroanisoles at 25 °C. Available literature values for various chlorinated veratroles and anisoles are also included for comparison. The measured log K_{OW} values for 345-TCV and TeCV deviate quite substantially from values estimated by Neilson et al. (1984) using a HPLC retention time method. However, the measured log K_{OW} for TeCV is in good agreement with the Saarikoski et al. (1986) reported experimental value which was also determined by the conventional shake-flask method. Although the K_{OW} for anisole was not determined in this work, the value reported by Dunn et al. (1986) follows a consistent trend on QSPR plots when compared with experimental values in this work.

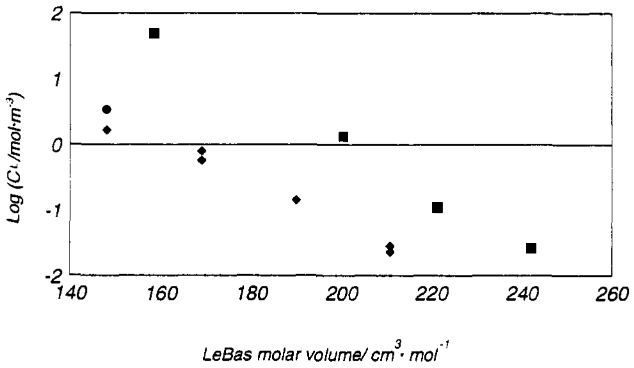

Figure 2. Supercooled liquid solubility $C^S{}_L$ versus LeBas molar volume V_L for veratrole, chloroveratroles (■), and chloroanisoles (◆).

Figure 2 is a plot of the logarithm of supercooled liquid solubilities versus the LeBas molar volume for chloroveratroles and chloroanisoles. The plot demonstrates log-linear behavior which is expected when addition of each chlorine results in a constant increase in the Gibbs free energy or equivalently a constant increase in the logarithm of the

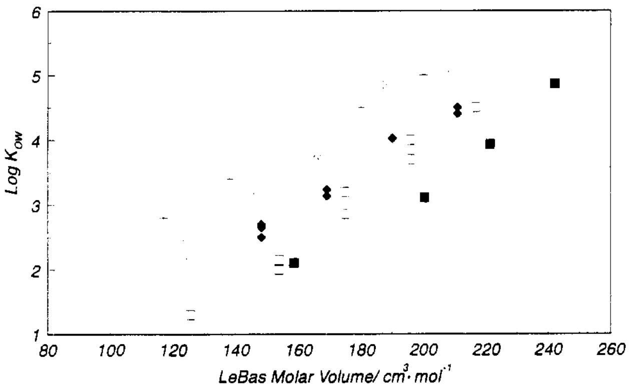

Figure 3. log K_{OW} versus LeBas molar volume V_L for chloroveratroles (■), chloroanisoles (◆), chlorophenols (×), chloroguaiacols (□), and chlorobenzene (+).

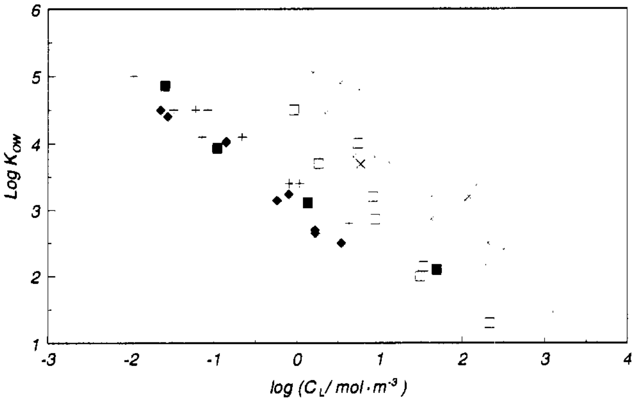

Figure 4. log K_{OW} versus log $C^S{}_L$ for chloroveratroles (■), chloroanisoles (◆), chlorophenols (×), chloroguaiacols (□), and chlorobenzenes (+).

activity coefficient. The slopes of the two plots reveal that for an increase in the LeBas molar volume of 20.9 $cm^3 mol^{-1}$, i.e., for every chlorine added, the solubility of the chloroanisoles drops by an average of 0.63 log unit or a factor of 4.3 while for the chloroveratroles the drop is 0.81 log unit or a factor of 6.5.

Figure 3 is a plot of the logarithm of the octanol–water partition coefficient log K_{OW} versus the LeBas molar volume and illustrates the trend of increasing log K_{OW} with molar volume. Log-linear behavior is observed for both homologous series. log K_{OW} increases by an average of 0.65 log unit or a factor of 4.5 per chlorine added to anisole and by 0.68 log unit or a factor of 4.8 for the veratroles. The difference in log K_{OW} for isomers with the same degree of chlorine substitution is less than 0.15 log unit. The linear behavior in both Figures 2 and 3 suggests that the data are precise. We prefer not to present regressions for these data in case of misapplication.

Solubility and K_{OW} data for the two homologous series are plotted on a logarithmic scale in Figure 4. This plot demonstrates the expected inverse relationship discussed earlier between the octanol–water partition coefficient and the supercooled liquid solubility. The present data were subjected to linear regression as in eq 7. Figure 4 also contains data for other chlorinated aromatic and phenolic compounds of the types encountered in pulp mill effluents, namely, chlorobenzenes, chloroguaiacols, and chlorophenols (Tam et al., 1994; Mackay et al., 1992; Ma et al., 1993). The slopes (i.e., coefficient B) of 0.96 for chloroanisoles and 0.97 for chloroveratroles are close to 1.0, suggesting that the activity coefficient in octanol γ_O is fairly constant for each series. Figure 4 also suggests that the partitioning behavior of chloroveratroles and chloroanisoles in an octanol–water system is similar to that of chlorobenzenes and thus of nonpolar aromatic chemicals in general. The plot also indicates that chlorinated phenols and guaiacols partition into octanol to a greater extent than is expected from their solubility. It is suggested that solubility–K_{OW} relationships developed from data for largely nonpolar compounds are applicable to the veratroles and anisoles but not to phenols and guaiacols.

Figure 3 also shows that K_{OW} values for chloroguaiacols and chlorophenols are considerably greater than those of chloroveratroles and chloroanisoles of similar molar volume. This is likely a result of a higher affinity of phenolic compounds for the octanol phase, i.e., a lower γ_O. This phenomenon is also demonstrated in Figure 4 which shows that, for species with similar liquid solubilities, the chlorophenols and chloroguaiacols have much higher K_{OW} values than chloroveratroles and chloroanisoles.

There is a need to interpret the values of the octanol–water partition coefficient in terms of the activity coefficients in the aqueous and octanol phases for this and related classes of chemicals in order to better understand the fundamental nature of the bioconcentration and toxicity phenomena of the phenolic compounds and their biotransformation products.

Literature Cited

Brownlee, B. G.; MacInnis, G.; Noton, L. *Environ. Sci. Technol.* **1993**, *12*, 2450–2455.

Dunn, W. J., Block, J. H., Pearlman, R. S., Eds. *Partition Coefficient: Determination and Estimation*; Pergamon Press Inc.: New York, 1986.

Hansch, C.; Quinlan, J. E.; Lawrence, G. L. *J. Org. Chem.* **1968**, *33*, 345–350.

Kringstad, K.; Lindström, K. *Environ. Sci. Technol.* **1984**, *18*, 236–248.

Ma, K. C.; Shiu, W. Y.; Mackay, D. *J. Chem. Eng. Data* **1993**, *3*, 364–366.

Mackay, D. *Multimedia Environmental Models: The Fugacity Approach*: Lewis Publishers: Chelsea, MI, 1991.

Mackay, D.; Bobra, A.; Shiu, W. Y.; Yalkowsky, S. M. *Chemosphere* **1980**, *9*, 701–711.

Mackay, D.; Shiu, W. Y.; Ma, K. C. *The Illustrated Handbook of Physical-Chemical Properties of Environmental Fate of Organic Chemical:* Lewis Publishers: Chelsea, MI, 1992; Vol 1.

Miller, M.; Wasik, S.; Huang, G. L.; Shiu, W. Y.; Mackay, D. *Environ. Sci. Technol.* **1985**, *19*, 522–528.

Neilson, A. H.; Allard, A. S.; Hynning, P. A.; Remberger, M.; Landner, L. *Appl. Environ. Microbiol.* **1983**, *45*, 774–783.

Neilson, A. H.; Allard, A.; Reiland, S.; Remberger, M.; Tärnholm, A.; Viktor, T.; Landner, L. *Can. J. Fish. Aquat. Sci.* **1984**, *41*, 1502–1512.

Neilson, A. H.; Blanck, H.; Förlin, L.; Pärt, P.; Rosemann, A.; Söderstörm, M.; Landner, L. *Chemicals in the Aquatic Environment, Advanced Hazard Assessment*; Springer-Verlag: Berlin, 1989, pp 329–374.

Reid, R. C.; Prausnitz, J. M.; Polling, B. E. *The Properties of Gases and Liquids*, 4th ed.; McGraw-Hill: New York, 1987.

Remberger, M.; Allard, A. S.; Neilson, A. H. *Appl. Environ. Microbiol.* **1986**, *50*, 552–558.

Saarikoski, J.; Lindström, M.; Tyynelä, M.; Viluksela, M. *Ecotox. Environ. Saf.* **1986**, *11*, 158–173.

Suntio, L. R.; Shiu, W. Y.; Mackay, D. *Chemosphere* **1988**, *17*, 1249–1290.

Tam, D.; Varhaníčková, D.; Shiu, W. Y.; Mackay, D. *J. Chem. Eng. Data* **1994**, *39*, 83–86.

Tewari, Y.; Miller, M.; Wasik, S.; Martire, C. *J. Chem. Eng. Data* **1982**, *27*, 451–454.

Yalkowsky, S. H. *Ind. Eng. Chem. Fundam.* **1979**, *18*, 108–111.

Yalkowsky, S. H.; Orr, R. J.; Valvani, S. C. *Ind. Eng. Chem. Fundam.* **1979**, *18*, 351–353.

Yalkowsky, S. H.; Valvani, S. C. *J. Chem. Eng. Data* **1979**, *24*, 127–129.

Received for review January 23, 1995. Accepted March 17, 1995.[⊗] The authors would like to thank the Pulp and Paper Centre at the University of Toronto and NSERC for financial support.

JE950021M

[⊗] Abstract published in *Advance ACS Abstracts*, May 15, 1995.