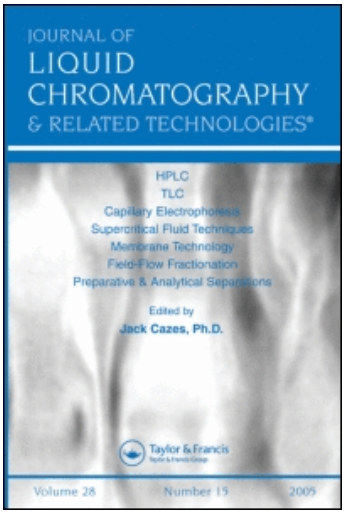

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RETENTION OF SUBSTITUTED BENZALDEHYDES ON RP-HPLC. CORRELATION WITH PARTITION COEFFICIENTS AND MOLECULAR DESCRIPTORS

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ABSTRACT

The RP-HPLC capacity (k') of a series of substituted benzaldehydes were determined on a C_{18} column with methanol/water as the mobile phase. A linear relationship was found between log k' and the volume fraction of methanol (φ) for most tested compounds with the correlation coefficient above 0.96 (except of 2,5-dihydroxybenzaldehyde). High correlation was found between log k'_w and S, which are intercept and slope of plot of log k' vs. φ, respectively.

The values of k', k'_w, and S were quantitatively correlated with

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water solubility (S_w) and octanol-water partition coefficients (log K_{ow}). Additionally, log k'_w and S were highly correlated with various molecular descriptors, and major molecular descriptors governing the retention of these studied compounds in RP-HPLC were determined.

INTRODUCTION

It is widely recognized that knowledge of the environmental fate of pollutants is a basic need for exposure assessment. The lipophilicity character of the chemicals, such as water solubility (S_w) and solvent (usually octanol)-water partition coefficients (log K_{ow}), would play an important role in their environmental transport and fate.[1,2] S_w and log K_{ow} are usually measured by "shake flask", which is time-consuming and requires considerable amounts of pure stable compounds.[3]

It has been proven, that the retention capacity factor (k') of a compound in a reversed-phase high performance liquid chromatography (RP-HPLC) system, is a reliable indirect descriptor of the lipophilicity of a compound.[4-8] Moreover, some studies have shown that log k'_w, the retention capacity factor which is extrapolated from a binary phase to 100% water in a RP-HPLC system, is an even better descriptor of lipophilicity than the isocratic factor.

Substituted benzaldehyde compounds, used extensively as intermediates to synthesize pesticides (e.g., Monsanto's herbicide Lasso and other agricultural chemicals) and medicines (e.g., chloramphenicol, ephedrine, ampicillin, diphenylhydantoin, and other products), are being introduced into the environment. They have also been observed as ozonolysis by-products of water disinfection,[9] as products of incomplete oxidation and combustion,[10] and as products of metabolism.[11]

On the other hand, aldehydes are known to be bioreactive electrophiles, which may cause excess toxicity, by a variety of mechanisms.[12] Few studies on these compounds so far are reported, even though their environmental behavior and ecological effects should be anticipated.

Here, the lipophilicity of these compounds was studied by using a RP-HPLC method. The relationships between HPLC capacity factors (k'), determined on an ODS column, water solubility, and octanol-water partition coefficients were also studied. Finally, we used various molecular descriptors to study the major factors affecting the retention of these studied compounds in RP-HPLC.

EXPERIMENTAL

Instruments

The HPLC system (Shimadzu, Japan) consisted of a SCL-8A system monitor, a LC-8A pump, a C-R4A integrator, and a SPD-6AV ultraviolet spectrophotometer

as the detector. A C_{18} reversed-phase Nucleosil 7 (Dalian Institute of Chemical Physics, Chinese Academy of Sciences) (15 × 4.6 mm i.d.) column was used.

Chemicals

The 16 substituted benzaldehydes (including benzaldehyde) used are listed in Table 1. They were synthesized by the College of Chemistry and Chemical Engineering of Nanjing University. The purity (>96%) was monitored by HPLC to assure that no interference peak had occurred. The water used as a mobile phase component was doubly distilled. Methanol was analytical grade and redistilled before use. Sodium nitrate was also analytical grade.

Determination of Capacity Factors

The mobile phases were made by mixing methanol with water in the proportions 90:10, 85:15, 80:20, 75:25, 70:30, 60:40, and 50:50 (v/v). The flow rate was 0.8 mL/min. All measurements were made, at least, in triplicate. The average reproducibility of each determination was better than 1.0% relative. The capacity factors (k') were determined using $k'=(t_r-t_0)/t_0$, where t_r is the retention time of the compound, and t_0 is the dead time. An aqueous solution of sodium nitrate was used for the measurement of t_0. The capacity factors obtained at different mobile phase composition are shown in Table 2.

Data Analysis and Manipulation

Regression analyses were performed using the STATGRAPHICS Plus version 4.0 (Manugistics, Inc., Rockville, USA, 1999) with a confidence limit of 95%. Equation adequacy was measured as correlation coefficient (r), the square of correlation coefficient (R^2), standard error of estimates (SE), the F value for analysis of variance (F), and the significance level (p).

RESULTS AND DISCUSSION

The capacity factors (k') at different mobile compositions are shown in Table 2. The linear relationship between log k' and methanol concentration in mobile phase given by Snyder et al.[13] was the following:

$$\log k' = \log k'_w - S\varphi \quad (1)$$

where k'_w represented the k' value for a compound if pure water is used as eluent, S is the slope of the regression curve, and φ is the volume percentage of

Table 1. The Physico-Chemical Parameters* of the Studied Substituted Benzaldehydes

No	Chemicals	CAS No.	log K_{ow}	log S_w (mole/L)	$^2X^v$	MW	E
1	2,5-dihydroxybenzaldehyde	1194-98-5	0.54	−1.00	1.861	138.12	0.66
2	3,4-dihydroxybenzaldehyde	139-85-5	1.09	−1.34	1.866	138.12	0.00
3	4-hydroxy-3-methoxybenzaldehyde	121-33-5	1.17	−1.30	2.049	152.15	0.00
4	4-hydroxybenzaldehyde	123-08-0	1.36	−1.16	1.709	122.12	−0.12
5	p-hydroxyacetophenone	99-93-4	1.44	−1.27	2.103	136.15	−0.08
6	Benzaldehyde	100-52-7	1.48	−1.55	1.529	106.12	0.25
7	3-hydroxybenzaldehyde	100-83-4	1.29	−1.23	1.713	122.12	0.37
8	3-bromo-4-hydroxybenzaldehyde	2973-78-6	1.83	−2.18	2.682	201.02	0.27
9	3,4-dimethoxybenzaldehyde	120-14-9	1.20	−1.42	2.232	166.18	0.10
10	3-ethoxy-4-hydroxybenzaldehyde	121-32-4	1.61	−1.77	2.278	166.18	−0.02
11	3,4,5-trimethoxybenzaldehyde	86-81-7	1.39	−2.12	2.577	196.2	0.22
12	4-ethoxy-3-methoxybenzaldehyde	120-25-2	1.63	−2.19	2.461	180.2	0.13
13	2,5-dimethoxybenzaldehyde	93-02-7	1.91	−2.32	2.226	166.18	0.64
14	isopropyl,4-formylphenoxyl actate		1.88	−2.58	3.514	222.13	
15	5-bromo-2-hydroxybenzaldehyde	1761-61-1	2.50	−3.25	2.735	201.02	0.93
16	2,5-dibromobenzaldehyde		3.35	−3.80	3.551	263.92	1.08

* K_{ow} and S_w were octanol/water partition coefficient and water solubility respectively, which were given by Jin, et al.[21]; $^2X^v$ were calculated according to the methods described by Kier and Hall[18, 20]; E was the sum of Hammett σ* values of the substituent groups attached to the carbon of benzene ring, which was calculated according to Hansch and Leo[22].

Table 2. Capacity Factors Obtained at Different Mobile Phase Compositions

No.	k'_{90} φ=90%	k'_{85} φ=85%	k'_{80} φ=80%	k'_{75} φ=75%	k'_{70} φ=70%	k'_{60} φ=60%	k'_{50} φ=50%	S	log k'_{w} φ=0%
1	0.062	0.085	0.071	0.074	0.035	0.024	-		
2	0.500	0.535	0.579	0.596	0.713	0.889	1.104	0.884	0.474
3	0.685	0.712	0.764	0.781	0.795	1.224	1.780	1.026	0.705
4	0.631	0.656	0.672	0.698	0.778	1.216	1.795	1.157	0.774
5	0.653	0.668	0.702	0.698	0.841	1.214	1.975	1.204	0.825
6	0.653	0.676	0.735	0.801	0.932	1.477	1.934	1.261	0.896
7	0.668	0.708	0.719	0.742	0.888	1.460	2.105	1.298	0.922
8	0.504	0.508	0.610	0.628	0.632	1.155	1.889	1.441	0.936
9	0.734	0.772	0.830	0.906	0.974	1.481	2.570	1.330	0.998
10	0.734	0.736	0.814	0.898	1.068	1.798	2.917	1.563	1.188
11	0.784	0.766	0.896	0.934	1.168	2.048	3.454	1.687	1.317
12	0.889	0.901	1.036	1.160	1.469	2.361	4.719	1.832	1.506
13	0.946	1.120	1.347	1.488	2.005	3.537	6.979	2.157	1.860
14	0.790	0.932	1.180	1.379	1.928	4.174	9.458	2.717	2.260
15	1.523	1.566	1.982	2.472	3.345	6.988	14.11	2.529	2.355
16	1.264	1.482	2.384	3.480	4.894	11.432	-	3.274	3.000

methanol in the mobile phase. For each studied chemical (except 2,5-dihydroxybenzaldehyde), a linear correlation was found between log k' and φ, and the correlation coefficients were all above 0.96. The values of S and the extrapolated log k'_w are given in Table 2.

A good linear correlation was observed between the slope S and the intercept values (log k'_w):

$$\log k'_w = -0.432(0.052) + 1.045(0.028)\ S \qquad (2)$$
$$n=15 \quad SE=0.073 \quad r=0.995 \quad F=1346 \quad p=0.000$$

S and log k'_w are highly correlated, and this may be a reflection of the suitability of the methanol/water system for estimating the lipophilicity of the compounds.

It has been proven that the retention capacity factor (k') of a compound in a reversed-phase high performance liquid chromatography (RP-HPLC) system is a reliable indirect descriptor of the lipophilicity of a compound.[14, 15] Moreover, it has sometimes been shown that the retention capacity factor (k') is an even better descriptor of lipophilicity than the isocratic factor because it is independent of any organic modifier effects and it reflects polar-non-polar partitioning in a manner similar to shake-flask measurements. For the tested compounds, we found that there were good linear relationships between log k', S and log K_{ow}, log S_w

Table 3. Regression Results of log K_{ow} and log S_w with log k' and S

Y		a	+ b	X	r	F	p
log K_{ow}	=	2.082	+ 3.432	log k'_{90}	0.762	18.1	0.001
		1.987	+ 3.303	log k'_{85}	0.794	22.2	0.000
		1.770	+ 2.855	log k'_{80}	0.879	44.3	0.000
		1.656	+ 2.399	log k'_{75}	0.900	55.1	0.000
		1.495	+ 2.020	log k'_{70}	0.883	46.2	0.000
		1.138	+ 1.686	log k'_{60}	0.905	58.6	0.000
		1.070	+ 1.003	log k'_{50}	0.842	29.1	0.000
		0.692	+ 0.737	log k'_w	0.906	59.5	0.000
		0.375	+ 0.769	S	0.901	55.9	0.000
log S_w	=	−2.533	− 4.798	log k'_{90}	−0.799	22.9	0.000
		−2.394	− 4.548	log k'_{85}	−0.819	26.5	0.000
		−2.096	− 3.924	log k'_{80}	−0.906	59.2	0.000
		−1.939	− 3.260	log k'_{75}	−0.916	67.5	0.000
		−1.718	− 2.773	log k'_{70}	−0.908	61.4	0.000
		−1.227	− 2.316	log k'_{60}	−0.934	88.9	0.000
		−0.986	− 1.751	log k'_{50}	−0.890	45.8	0.000
		−0.597	− 1.026	log k'_w	−0.945	108.0	0.000
		−0.149	− 1.075	S	−0.943	104.0	0.000

(Table 3). Among all the linear relationships between log k' and log K_{ow}, log S_w, the best were between log k'_w and log K_{ow}, log S_w, respectively.

In order to investigate the main factors controlling the retention of these compounds in RP-HPLC, we made a series of regression analysis between log k'_w and various physico-chemical molecular parameters.

Molecular connectivity is a method of describing molecular structure based solely on bonding and branching patterns, rather than physical or chemical characteristics. It has long been shown to be a useful structural parameter for describing diverse physicochemical properties[16] and biological activity.[17] In our work, the indices for inclusion in Quantitative Structure-Property Relationships (QSPR) were selected based on some guidance from past correlations of similar variables,[18, 19] and were introduced into the correlations by stepwise regression analysis to optimize the correlation satisfactorily.

Simple and valence connectivity indices up to third-order path and cluster levels were calculated according to the methods described by Kier and Hall.[18, 20] Only the parameters included in the regression equations were listed in Table 1. The relationship between log k'_w, S and molecular connectivity indices are given by stepwise linear regression analysis. The equations were the following:

$$\log k'_w = -1.024 + 1.004\ {}^2X^v \quad (3)$$
n=15 SE=0.418 r=0.831 F=29.1 p=0.000

$$S = -0.644 + 0.994\ {}^2X^v \quad (4)$$
n=15 SE=0.361 r=0.864 F=38.2 p=0.000

Similar as log K_{ow},[21] log k'_w and S can also be described by molecular weight (MW).

$$\log k'_w = -1.033 + 0.014\ MW \quad (5)$$
n=15 SE=0.427 r=0.823 F=27.2 p=0.000

$$S = -0.624 + 0.014\ MW \quad (6)$$
n=15 SE=0.383 r=0.845 F=32.4 p=0.000

E values for substituted benzaldehydes are the sum of Hammett σ^* values of the substituent groups attached to the carbon of benzene ring.[22] They relate to a lot of physicochemical properties and biological activity. The relationships between E and log k'_w, S were the following:

$$\log k'_w = 0.809 + 1.705\ E \quad (7)$$
n=14 SE=0.317 r=0.901 F=51.8 p=0.000

$$S = 1.192 + 1.578\ E \quad (8)$$
n=14 SE=0.298 r=0.899 F=50.3 p=0.000

It has been suggested that an adequate model should include as many descriptors as possible to increase the probability of good characterization of

compounds. Multiple regression analysis of the log k'_w, S of the chemicals under study versus molecular connectivity indices, MW and E, resulted in the following equations:

$$\log k'_w = -0.216 + 1.224\,E + 0.510\,{}^2X^v \quad (9)$$
n=14 SE=0.25 R^2=0.892 F=45.2 p=0.000

$$S = -0.129 + 1.078\,E + 0.529\,{}^2X^v \quad (10)$$
n=14 SE=0.22 R^2=0.907 F=53.7 p=0.000

The F and p values of equations (9) and (10) showed the correlations were significant. The equations had a large correlation coefficient and low SE, and the experimental values were close to the predicted values. So, it could be used to predict the log k'_w and S of similar series of chemicals.

From the above correlation equations, we found that the most effective coefficients of log k'_w and S are E (the sum of Hammett σ^* values of the substituent groups attached to the carbon of benzene ring) and ${}^2X^v$. Log k'_w and S both increased as E and ${}^2X^v$ increased. This showed HPLC capacity factors of tested chemicals mainly related to their electronic effect.

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REFERENCES

1. Yalkowsky, S.H.; Valvani, S.C. J. Chem. Eng. Data **1979**, *24*, 127–129.
2. Abraham, M.H.; Weathersby, P.K. J. Pharm. Sci. **1994**, *83*, 1450–1456.
3. Kaliszan, R. *Quantitative-Structure Chromatographic Retention Relationships*; John Wiley & Sons: New York, 1987.
4. Braumann, T. J. Chromatogr. **1986**, *373*, 191–225.
5. Pereira, L.; Barreiro, E.J.L.; Freitas, A.C.C.; Correa, C.J.C.; Gomes, L.N.L.F. J. Liq. Chromatogr. **1991**, *14*, 1161–1171.
6. Kumar, K.; Sukumaran, K.; Taylor, S.; Chang, C.A.; Nunn, A.D.; Tweedle, M.F. J. Liq. Chromatogr. **1994**, *17*, 3735–3746.
7. Valvino, R.; Fruttero, R.; Gasco, A. J. Chromatogr. **1991**, *547*, 167–173.
8. Benito, I.; Saz, J.M.; Marina, M.L. J. Liq. Chromatogr. & Rel. Technol. **1998**, *21*, 331–347.
9. Koga, M.; Akiyama, T.; Glaze, W.H. Toxicol. Ind. Health **1991**, *7*, 423–432.

10. Manaha, S.E. *Environmental Chemistry*, 4th Ed; Lewis: Boca Raton, FL, 1990.
11. Que Hee, S.S. *Biological Monitoring: An Introduction*; Van Nostrand Reinhold: New York, 1993.
12. Hermans, M. Environ. Health Persp. **1990**, *87*, 219–225.
13. Snyder, R.; Dolan, J.W.; Gant, J.R. J. Chromatogr. **1979**, *165*, 3–30.
14. Dai, J.; Yao, S.; Ding, Y.; Wang, L. J. Liq. Chromatogr. & Rel. Technol. **1999**, *22*, 2271–2282.
15. Jenke, D.R. J. Liq. Chromatogr. & Rel. Technol. **1996**, *19*, 2227–2245.
16. Nirmalakhandan, Speece, R.E. Environ. Sci. Technol. **1988**, *22*, 328–338.
17. Blum, D.J.W.; Speece, R.E. Ecotoxicol. Environ. Safety **1991**, *22*, 198–203.
18. Kier, L.B.; Hall, L.H. *Molecular Connectivity in Chemistry and Drug Research;* Academic Press: New York, 1976.
19. Blum, D.J.W.; Speece, R.E. Environ. Sci. Technol. **1990**, *24*, 284–291.
20. Kier, L.B.; Hall, L.H. J. Pharm. Sci. **1981**, *70*, 583–589.
21. Jin, L.; Wei, Z.; Dai, J.; Guo, P.; Wang, L. Bull. Environ. Contam. Toxicol. **1998**, *61*, 1–7.
22. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; John Wiley & Sons: New York, 1979.

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