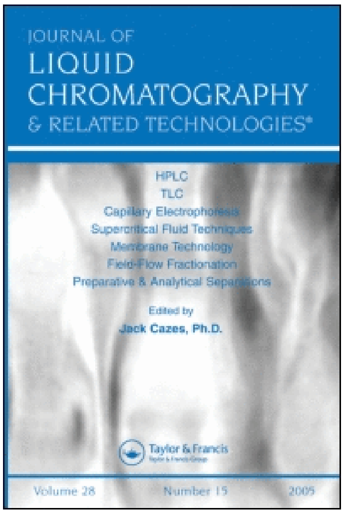

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Evaluation of Chromatographic and Some Physicochemical Properties of Phenolic Compounds using Abraham's Descriptors

Kyung Ho Row[a]
[a] Center for Advanced Bioseparation Technology and Department of Chemical Engineering, Inha University, Incheon, South Korea

To cite this Article Row, Kyung Ho(2008) 'Evaluation of Chromatographic and Some Physicochemical Properties of Phenolic Compounds using Abraham's Descriptors', Journal of Liquid Chromatography & Related Technologies, 31: 10, 1412 — 1421

To link to this Article: DOI: 10.1080/10826070802039341

URL: http://dx.doi.org/10.1080/10826070802039341

Journal of Liquid Chromatography & Related Technologies®, 31: 1412–1421, 2008

ISSN 1082-6076 print/1520-572X online
DOI: 10.1080/10826070802039341

Evaluation of Chromatographic and Some Physicochemical Properties of Phenolic Compounds using Abraham's Descriptors

Kyung Ho Row

Center for Advanced Bioseparation Technology and Department
of Chemical Engineering, Inha University, Incheon, South Korea

Abstract: Abraham's descriptors, as independent variables, were applied to predict the retention factors, k, and acid dissociation constants, pKa, of phenolic compounds for a published collection of data. Other dependent variables (n-octanol-water partition coefficient log P, molar refraction MR, dipole moments μ, energy hydration E_H, and total energy E_{tot}) were calculated by itself and estimated also with these descriptors. Results suggest that chromatographic retention and other properties may be modeled by used independent variables. The Abraham's descriptors based model is an efficient way to study quantitative structure-property relationships (QSPR) and quantitative structure-retention relationships (QSRR) with satisfactory accuracy.

Keywords: Abraham's descriptors, QSPR, QSRR, Phenolic compounds, Retention factor

INTRODUCTION

Quantitative structure–activity relationships (QSAR) and quantitative structure-property relationships (QSPR) approaches are of further growing interest in many areas: biology, medicine, pharmacology, chemistry, and chemical engineering. In chemistry and chemical engineering, they may be applied, for example, to develop methods for selecting conditions for extraction, isolation, and separation processes. The application of such methods

Correspondence: Kyung Ho Row, Center for Advanced Bioseparation Technology and Department of Chemical Engineering, Inha University, Building 2S 335, #253, Yonghyun-Dong, Nam-Ku, Incheon 402-751, South Korea. E-mail: rowkho@inha.ac.kr

requires quantitative information about the characteristic properties of solutes and solvents such as parameters describing the polarity, energy, solubility and its tendency to undergo hydrogen bonding. Such parameters are often determined by solvatochromic experiments, i.e., from the shift of a characteristic wave number of an indicator in that liquid solute/solvent.

Quantitative structure-retention relationships (QSRR) are the statistically derived relationships between the chromatographic parameters determined for a structurally diverse series of analytes in a given separation system and the quantities (descriptors) accounting for the structural differences among the analytes studied.[1,2]

The so-called the linear solvation energy relationship (LSER) method is one of the most successful and known approaches. The LSER is an extension of Hildebrand's[3] and Scatchard's[4] works on the enthalpy related solubility parameters and considers solubility as a function of volume, dipolaritiy, and hydrogen bonding capacity. Consequently, it is generally agreed that one of the most successful applications of QSAR, QSPR, and QSRR is the LSER approach. The QSRR belong to the most often studied manifestations of the LSER.

Thus, the LSER assumes that solute characteristics are based on various additive properties (P) of molecules that may be isolated as formal descriptors (D) of the solvation process,[5] e.g., as in Eq. (1):

$$\begin{aligned} P = \text{constant} + D_{\text{cavity term(s)}} + D_{\text{polarity term(s)}} \\ + D_{\text{hydrogen bonding terms}} + \dots \end{aligned} \tag{1}$$

Many empirical descriptions of solvation are based on this additive formalism, for example, Kamlett and Taft's original solvatochromic LSER[6] and Hansen's solubility parameters.[7] Abraham's LSER, which is based on the empirical determination of Gibbs energy based descriptors by multiple regression of properties obtained from a variety of processes, is shown in Eq. (2).

$$P = P_0 + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + vV_2 \tag{2}$$

where the some property P, which may be as varied as the extent of solute penetration of membranes, the distribution of solutes between stationary and liquid phases or other physicochemical parameters, is related to the relative influence of the empirically determined solute descriptors.

The first descriptor R_2 is an excess molar refraction of the analyte, whose relative effect on the property P, is given by the magnitude of the coefficient r.[8] The descriptor π_2^H is the analyte dipolarity/polarizability descriptor and its coefficient, s, the relative intensity of these interactions in the two phases.[9] The descriptor α_2^H is the analyte ability to donate a hydrogen bond, and β_2^H is a measure of analyte hydrogen bond accepting potency. Descriptor α_2^H represents the hydrogen bond donor acidity of the solute, and to the coefficient a, representing the relative acceptor strength of the phases. Similar arguments apply to β_2^H, the hydrogen bond basicity of the solute contributed by different hydrogen bonding groups and coefficient *b* represents the relative hydrogen bond donor strength of the two phases.[9] The last descriptor V_2 is its molecular volume according to the McGowan algorithm.[10] The coefficient *v* is thus analogous to the cavity term of Eq. (1) and is related to the Hildebrand solubility parameter and the cohesive energy density.[11] It is worthwhile to say that, often, the descriptors, represented in Eq. (2), called Abraham's descriptors.

Each chemical property *P* is a complex net effect of both atomic composition and steric constitution of a given molecule. There are no precise simple addition rules but, instead, the overall structure affects, simultaneously, the dipolarity/polarizability, hydrogen- bond acidity, hydrogen-bond basicity, and the ability of an analyte molecule to form a cavity in the environment and to interact with it by dispersion forces.

In this paper, Abraham's descriptors were used for evaluation of the retention factors and some others chromatographically significant parameters of phenolic compounds.

THEORETICAL

The data concerning retention of thirteen phenolic compounds were collected from Ref. [12]. The retention factors were measured by reversed-phase liquid chromatography at 40°C in 70% aqueous acetonitrile containing 20 mM sodium phosphate buffer at pH 8.49. Their retention properties are summarized in Table 1. The Abraham's descriptors for the test analytes were taken from West and Lesellier[13] where available (Table 2).

The test analytes of Table 1 were subjected to molecular modeling by the ChemOffice Pro 2006 (CambridgeSoft Corporation, USA) and HyperChem (Hypercube Inc. FL, USA, version 7). The ChemOffice[14] program can perform real-time animation, energy minimization, and molecular dynamic calculations. The *n*-octanol-water partition coefficient (log *P*) and molar refraction (*MR*) were obtained with ChemOffice. The HyperChem program[15] performed geometry optimization by the standard molecular mechanics *MM+* force field procedure for nitrophenol isomers and by the semi empirical *AM1* method in the case of other analytes. Dipole moments (μ), energy hydration (E_H), and total energy (E_{tot}) were calculated with HyperChem. The data of logarithms to base ten of the acid dissociation constant value (*pKa*) were collected from References [12,16–18]. A number of physicochemical descriptors are collected in Table 1.

Chemometric Calculations

The multiple regression equations were derived by employing the Origine package (Microcal Software Inc., MA, USA.)[19] run on a personal computer.

Table 1. Experimental (*k* and *pKa*) and calculated (log *P*, *MR*, μ, E_H, and E_{tot}) parameters

Compound	k[12]	*pKa*	log P^b	MR^b, cm^3mol^{-1}	μ^b, Debay	$E_H{}^c$, kkal mol^1	$E_{tot}{}^c$, kkal mol^{-1}
Phenol	0.661	9.95[16]	1.447	27.752	0.9004	−8.99	− 1419.92(I)
o-Chlorophenol	0.700	8.48[16]	2.096	32.557	−1.5927	−7.54	−1401.23(I)
m-Chlorophenol	0.879	9.02[16]	2.096	32.557	−2.2518	−8.42	−1403.60(I)
p-Chlorophenol	0.889	9.38[16]	2.096	32.557	−1.6330	−8.58	−1403.78(I)
2,3-Dimethylphenol	1.151	10.54[17]	2.307	37.834	−0.5305	−5.21	−1983.33(I)
2,4-Dimethylphenol	1.180	10.6[a]	2.307	37.834	−0.7401	−5.26	−1984.45(I)
2,5-Dimethylphenol	1.169	10.42[16]	2.307	37.834	−0.9190	−5.17	−1984.53(I)
2,6-Dimethylphenol	1.279	10.10[12]	2.307	37.834	−1.0478	−4.95	−1982.92(I)
3,4-Dimethylphenol	1.021	10.10[12]	2.307	37.834	−0.5304	−6.40	−1984.05(I)
3,5-Dimethylphenol	1.074	10.18[18]	2.307	37.834	−0.7681	−6.19	−1985.28(I)
o-Nitrophenol	0.110	7.23[16]	1.437	3.4532	−3.5677	−15.44	0.4586(II)
m-Nitrophenol	0.360	8.35[16]	1.437	3.4532	−6.5731	−18.08	−0.5099(II)
p-Nitrophenol	0.040	7.14[16]	1.437	3.4532	−4.5663	−18.43	−0.5727(II)

[a] An online database of hazardous materials, http://cameochemicals.noaa.gov/.

[b] Obtained with ChemOffice.

[c] Obtained with HyperChem, geometry optimization method MI(II)semi-impirical *AM1*; (II)molecular mechanics MM(+).

Table 2. Abraham's descriptors of phenolic compounds

Compound	R_2	π_2^H	α_2^H	β_2^H	V_2
Phenol	0.805	0.89	0.60	0.30	0.7751
o-Chlorophenol	0.853	0.88	0.32	0.31	0.8975
m-Chlorophenol	0.909	1.06	0.69	0.15	0.8975
p-Chlorophenol	0.915	1.08	0.67	0.20	0.8975
2,3-Dimethylphenol	0.850	0.85	0.52	0.36	1.0569
2,4-Dimethylphenol	0.840	0.80	0.53	0.39	1.0570
2,5-Dimethylphenol	0.840	0.79	0.54	0.37	1.0570
2,6-Dimethylphenol	0.860	0.79	0.39	0.39	1.0570
3,4-Dimethylphenol	0.830	0.86	0.56	0.39	1.0570
3,5-Dimethylphenol	0.820	0.84	0.57	0.36	1.0570
o-Nitrophenol	1.045	1.05	0.05	0.37	0.9490
m-Nitrophenol	1.050	1.57	0.79	0.23	0.9490
p-Nitrophenol	1.070	1.72	0.82	0.26	0.9490

RESULTS AND DISCUSSION

The data set of phenolic compounds was chosen to evaluate the LSER approach to chromatographic retention and some physicochemical properties. We undertook such an attempt here and designed a model series of thirteen phenolic test analytes which we recommend for the LSER-type of QSRR analysis of liquid chromatographic data by the following equation:

$$\log k' = \log P'_0 + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + vV_2 \qquad (3)$$

where log P_0 is a retention parameter corresponding to the hypothetical pure water eluent; *r*, *s*, *a*, *b*, and *v* are regression coefficients, the physical meaning of which is like that of the corresponding coefficients of Eq. (2).

Besides, the development of predictive QSPR models for thermodynamic properties of mixtures requires the characterization of substances by pure component parameters. For this purpose, we applied Abraham's approach according Eq. (2) for predicting of chromatographic significant and important parameters such as logarithms to base ten of the acid dissociation constant value (*pKa*), the *n*-octanol-water partition coefficient (log *P*), molar refraction (*MR*), dipole moments (μ), energy hydration (E_H), and total energy (E_{tot}).

The results are collected in Table 3, i.e., the QSRR-based, and the QSPR-based models of LSER, respectively. In this table are given the squared regression coefficients (r^2), and the values of the *F*-test of significance, *F*. The fits were all of reasonable quality, r^2 ranging from 0.9011 to 0.9834.

Thus, for the QSRR-based model, if a particular coefficient is numerically large, then any solute having the complimentary property will interact very

Table 3. Coefficients of Eq. (2) and their statistical ability

P	P_0	r	s	a	b	v	r^2	$F_{Statistic}$
log k	-7.187	11.701	-5.774	4.653	1.906	-0.925	0.9011	12.74
pKa	0.771	0.352	-0.329	0.315	0.222	-0.028	0.9576	31.66
log$P$	3.258	-4.684	0.473	-0.989	-4.106	4.407	0.9621	35.49
MR	5.033	-4.495	-0.197	-0.242	-2.748	1.555	0.9723	48.93
μ	10.558	-4.327	-5.295	3.587	8.552	-7.972	0.9092	14.01
E_H	14.468	-30.10	-7.748	-0.884	-19.663	18.458	0.9754	55.46
E_{tot}	-4842.5	5699.5	965.24	-469.58	2197.3	-3126.4	0.9834	82.65

strongly with either the mobile phase (if the coefficient is negative) or the stationary phase (if the coefficient is positive). The dominant contributions to retention are the dispersion interaction term (V_2) and the molar refractivity term (R_2). Generally, for the both approaches (QSRR and QSPR), the coefficients reflect the relative selectivity towards that particular molecular interaction.

QSPR

Self-evidently, wider analytical interest can only be commanded by a QSRR approach employing physicochemical properties of analytes, which can readily be predicted for any compounds. Such are the physicochemical and structural properties of interest for researchers.

Physicochemical properties of the analytes, namely *n*-octanol-water partition coefficient (log P), molar refraction (MR), dipole moment (μ), energy hydration (E_H), total energy (E_{tot}) were calculated by molecular modeling programs which are described in the Experimental section, and are collected in Table 1. Considering the limited and rather arbitrarily selected set of solutes comprising Table 1, chosen to test the Abraham's descriptors, the result may be considered. Using published Abraham solute descriptors and calculated log P for the solutes shown in Table 1, the regression obtained is shown as in Table 3. The probabilities associated with Eq. (2) and given in Table 3 show that only variables relating to volume, and perhaps polarity, make a significant contribution to the regression. Descriptors making little contribution to the regression, e.g., the molar refractivity, and the solute basicity, show little significance.

It is necessary to note that contribution of molar refractivity in the cases of MR, μ, and E_H also are low and coefficients r are quite close in the equations which predicted *n*-octanol-water partition coefficients, dipole moments, and energy hydrations. The molar refraction features in the regression, but it is of low significance.

The QSPR approach was then applied to the same data set using same Abraham's descriptors, but using published values of acid dissociation constant values (pKa) as the dependent variable. Table 3 shows the significance of the parameters of the predictive equation; the regression coefficient, r^2, is 0.9576. It is interesting to note that the weak spread variance in coefficient values is observed. The contributions of molar refraction (0.352) and hydrogen bond donating ability (0.315) are sufficiently close. Two parameters, dipolarity/polarizability and molecular volume, are negative.

The total energy (E_{tot}) of a molecule is the sum of its different energy contributions. Thus, the total energy includes the total electronic energy of the molecule and the nuclear charges of atoms. In Eq. (2), E_{tot} predicted fairly well with the solvatochromic parameters by the term in the LSER model.

The inclusion of E_{tot} in the model indicates there is probably electron-nuclear interactions playing an important role in the solvation process.

QSRR

Previous studies in our laboratory[20–24] resulted in a QSRR model employing the following analyte descriptors: the polarizability, molar refractivity, lipophilicity, dipole moment, total energy, heat of formation, molecular surface area, binding energy, molecular connectivity indexes, Wiener index, Kier flexibility index, Harary index, Balaban indexes, and Zagreb indexes. The corresponding QSRR equations had the linear and multiple linear forms. Below, we discuss the QSRR models based on LSER descriptors served to predict retention times for a set of test analytes.

In Eq. (3), the P_0 is a constant. In the case of QSRR, this constant is related to the phase ratio contribution to retention. In our case, the low value of the P_0 constant indicates that the phase ratio V_s/V_m is also small, that is to say, V_s (the volume of stationary phase) increases more than V_m (the volume of mobile phase).

The molar refraction term (R_2) is related to charge transfer, reflecting interactions caused by the electronic excess of the solutes (π and n electrons). It is not too difficult to see that the r coefficient obtained by Eq. (3) is 11.107. With the QSRR approach, this coefficient being positive indicates that the stationary phase is dominant over the mobile phase towards this particular type of interaction.

The dipolarity/polarizability term (π_2^H) represents the polarity or polarizability of the solutes and its coefficient, s, reflects the contribution of the relative intensity of these interactions in the two phases.

The α_2^H term is related to the hydrogen bond donating ability of the molecules. In case of QSRR, the coefficient a describes the contribution, which will be determined by the difference in hydrogen bonds accepting ability between the mobile and stationary phases. The a, obtained with Eq. (3), showed lower values than r, but higher than the values of other descriptors' coefficients. The positive value of coefficient also testifies about the fact that the Lewis basicity of the C_{18} surface remains higher than the one of the mobile phase (70% aqueous acetonitrile containing 20 mM sodium phosphate buffer at pH 8.49), possibly due to the high adsorption of the mobile phase modifier at the surface.

The β_2^H term is related to the overall hydrogen bond basicity of the molecules. For the QSRR-based equation, as confirmed by its quite low descriptor coefficient (1.906), acetonitrile is known to be a relatively weak eluent toward the solutes used.

The V_2 term is related to molecular volume calculated according to the McGowan algorithm. For the QSRR-based equation, the coefficient v represents the contribution of dispersion interactions between the tested solutes and the stationary phase. The fact that it is a negative value of the contribution indicates that the mobile phase is dominant over the stationary phase with respect to this property.

All of these encouraging results have been achieved with LSER methodology; correlations based on parameters from experimental investigations are still often applied as, up to now, they mostly result in a better agreement between predicted and measured properties.

CONCLUSION

In this report, Abraham's descriptors were applied for evaluation of the chromatographic retention and some physicochemical properties of phenolic compounds. It is established that the Abraham's descriptors based model is an efficient way to study quantitative structure-property relationships (QSPR) and quantitative structure-retention relationships (QSRR) with suitable accuracy. These parameters, as ordinary descriptors, showed satisfactory predictive ability.

ACKNOWLEDGMENTS

The author is grateful for financial support from the Center for Advanced Bioseparation Technology, Inha University. This work was supported by INHA University Grant (INHA-2008).

REFERENCES

1. Kaliszan, R. *Quantitative Structure-Chromatographic Retention Relationships*; Wiley: New York, 1987.
2. Polyakova, Y.L.; Row, K.H. Quantitative structure-retention relationships applied to reversed-phase high-performance liquid chromatography. Med. Chem. Res. **2006**, *14* (8/9), 488–522.
3. Hildebrand, J.; Solubility. XII Regular solutions. J. Am. Chem. Soc. **1929**, *51*, 66–80.
4. Scartchard, G. Equlilibria in non electrolyte solutions in relation to the vapor pressures and densities of the components. Chem. Rev. **1931**, *8*, 321–333.
5. Famini, G.R.; Marquez, B.C.; Wilson, L.Y. Using theoretical descriptors in quantitative structure activity relationships: gas-phase acidity. J. Chem. Soc. **1993**, *2*, 773–782.
6. Kamlet, M.J.; Abboud, J.L.; Abraham, M.H.; Taft, R.W. Linear solvation energy relationships. 23. A comprehensive collection of the solvatochromic parameters, ð*, R, and *â* and some methods for simplifying the generalized solvatochromic equation. J. Org. Chem. **1983**, *48*, 2877–2887.
7. Hansen, C.M. *Hansen Solubility Parameters: A User's Handbook*; CRC Press: Boca Raton, FL, 2000.

8. Abraham, M.H.; Whiting, G.S.; Doherty, R.M.; Shualy, W.J. Hydrogen bonding. part 14. The characterisation of some N substituted amides as solvents: comparison with gas-liquid chromatography stationary phases. J. Chem. Soc. **1990**, *2*, 1851–1857.
9. Abraham, M.H.; Chadha, H.S.; Whiting, G.S. Hydrogen bonding. 32. An Analysis of water-octanol and water-alkane partitioning and the delta log *P* parameter of seiler. J. Pharm. Sci. **1994**, *83*, 1085–1100.
10. McGowan, J.C.; Abraham, M.H. Chromatographia **1987**, *23*, 243–246.
11. Hildebrand, J.H.; Scot, R.L. *The Solubility of Non-Electrolytes*; Reinhold: New York, 1950.
12. Hanai, T.; Koizumi, K.; Kinoshita, T. Prediction of retention factors of phenolic and nitrogen-containing compounds in reversed-phase liquid chromatography based on Log *P* and pKa ontained by computational chemical calculation. J. Liq. Chrom. & Rel. Technol. **2000**, *23* (3), 363–385.
13. West, C.; Lesellier, E. Characterization of stationary phases in subcritical fluid chromatography by the solvation parameter model I. Alkylsiloxane-bonded stationary phases. J. Chromatogr. A **2006**, *1110*, 181–190.
14. Seyhan, N. *Organic Chemistry: Structure and Reactivity* (Paperback); Houghton Mifflin College, 1999.
15. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. A new general purpose quantum mechanical molecular model. J. Am. Chem. Soc. **1985**, *107*, 3902–3909.
16. Williams, R. pKa Data Compiled. http://research.chem.psu.edu/brpgroup /pKa_-compilation.pdf. Sep. 2004.
17. Jover, J.; Bosque, R.; Sales, J. Neural network based QSPR study for predicting pKa of phenols in different solvents. QSAR Comb. Sci. **2007**, *26* (3), 385–397.
18. Hauptmann, S. *Reaktion und Mechanismus in der organischen Chemie* (Broschiert); Thieme Georg Verlag, 1997.
19. Smith, T.J.; Stevenson, K.J. Origin 7.0 originlab corporation, one roundhouse plaza, northampton, MA 01060. 1-800-969-7720. www.OriginLab.com. J. Am. Chem. Soc. **2003**, *125*, 3669–3669.
20. Lee, S.K.; Polyakova, Y.; Row, K.H. Evaluation of predictive retention factors for phenolic compounds with QSPR equations. J. Liq. Chrom. & Rel. Technol. **2004**, *4* (27), 629–639.
21. Lee, S.K.; Polyakova, Y.; Row, K.H. Interrelation of retention factor of amino acids by QSPR and linear regression. Bull. Korean Chem. Soc. **2003**, *12* (24), 1757–1762.
22. Polyakova, Y.; Jin, L.M.; Row, K.H. QSPR models for chromatographic retention of some azoles with physicochemical properties. Bull. Korean Chem. Soc. **2006**, *27* (2), 211–218.
23. Polyakova, Y.; Jin, L.M.; Row, K.H. Linear regression based QSPR models for the prediction of the retention mechanism of some nitrogen containing heterocycles. J. Liq. Chrom. & Rel. Technol. **2006**, *29* (4), 533–552.
24. Zheng, J.; Polyakova, Y.; Row, K.H. Prediction of chromatographic retention of nucleic acids based on QSPR model. Chromatographia **2006**, *64*, 129–137.

Received October 1, 2007
Accepted January 10, 2008
Manuscript 6219