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## Estimation of descriptors for hydrogen-bonding compounds from chromatographic and liquid-liquid partition measurements

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## ABSTRACT

Retention factors obtained by gas chromatography and reversed-phase liquid chromatography on varied columns and partition constants in different liquid-liquid partition systems are used to estimate WSU descriptor values for 36 anilines and N-heterocyclic compounds, 13 amides and related compounds, and 45 phenols and alcohols. These compounds are suitable for use as calibration compounds to characterize separation systems covering the descriptor space  $E = 0.2-3$ ,  $S = 0.4-2.1$ ,  $A = 0-1.5$ ,  $B = 0.1-1.5$ ,  $L = 2.5-10.0$  and  $V = 0.5-2.2$ . Hydrogen-bonding properties are discussed in terms of structure, the possibility of induction effects, intramolecular hydrogen bonding and steric factors for anilines, amides, phenols and alcohols. The relationship between these parameters and observed descriptor values are difficult to predict from structure but facilitate improving the general occupancy of the descriptor space by creating incremental changes in hydrogen-bonding properties. It is verified that the compounds included in this study can be merged with an existing database of compounds recommended for characterizing separation systems.

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## 1. Introduction

The solvation parameter model is a linear free energy model used for quantitative structure-property relationship studies including the elucidation of retention mechanisms in gas [1-3], reversed-phase liquid [4-6], supercritical fluid [7] and micellar electrokinetic chromatography [8,9], the distribution of compounds between immiscible solvents [10-12], the solubility of compounds in different solvents [13-15], and to study the distribution and fate of organic compounds in environmental and biological systems [16-19] as well as other distribution properties that can be described by a free energy-related model. For neutral compounds two forms of the model are used to describe transfer between a gas and a condensed phase, for example as in gas-liquid chromatography.

$$\log SP = c + eE + sS + aA + bB + lL \quad (1)$$

or between two condensed phases, for example as in reversed-phase liquid chromatography, liquid-liquid partition, and micellar electrokinetic chromatography

$$\log SP = c + eE + sS + aA + bB + vV \quad (2)$$

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The experimental free energy-related property ( $\log SP$ ) is typically the retention factor or partition constant for chromatographic or liquid-liquid partition systems. The characteristic properties of the compounds are encoded by the numerical values for six descriptors indicated by the upper case letters in Eqs. (1) and (2) [1,5,16,20]. These values describe the capability of the compound to participate in interactions due to the presence of loosely bound  $n$ - and  $\pi$ -electrons defined by an excess molar refraction (E) [21], interactions of a dipole-type resulting from the dipolarity/polarizability of the compound (S) [22], and the effective overall capability of the compound to enter into hydrogen-bonding interactions in which the compound acts as a hydrogen-bond acid (or donor) (A) or hydrogen-bond base (or acceptor) (B) [23,24]. In the case of the B descriptor for compounds such as anilines, amines and sulfoxides, an alternative descriptor  $B^\circ$  is required to describe the transfer of solutes from aqueous solutions to systems containing solvents (or phases) that can absorb an appreciable amount of water [24]. For example, the  $B^\circ$  descriptor is used to model retention in reversed-phase liquid chromatography and micellar electrokinetic chromatography and partition constants in  $n$ -octanol-water and chloroform-water distribution systems, while the B descriptor is used for gas-liquid chromatography and partition constants in totally organic biphasic systems and aqueous biphasic systems in which water is effectively insoluble in the counter solvent, such as hexadecane-water. The L descriptor describes the change in free energy arising from dispersion interactions formed by transfer of a compound from the gas phase to a condensed phase opposed by

the disruption of solvent-solvent interactions required to create a cavity in the condensed phase of the same size as the compound [25–27]. The L descriptor is encoded as the gas-hexadecane partition constant for the compound at 298 K. The V descriptor is the McGowan characteristic volume [28] and describes the relative molecular volume of the compounds. It accounts for the difference in the contribution from cavity formation when a compound is transferred between two condensed phases as well as any dispersion interactions that are not self-cancelling after the transfer.

The lower case letters on the right-hand side of Eqs. (1) and (2) are the system constants that describe the complementary interactions of the system with the compound descriptors. The system constants are determined by multiple linear regression analysis with the experimental free energy-related property ( $\log SP$ ) as the dependent variable for a number of varied compounds selected to meet criteria for the variation of the experimental property ( $\log SP$ ) and the descriptor values (E, S, A, B, L or V) to obtain a chemically and statistically valid model [29–34]. Once determined the system constants provide a valid description of the interaction of the system with further compounds provided these compounds occupy a portion of the descriptor space covered by the calibration compounds used to construct the model of the system. This enables the calibrated system to be used with other calibrated systems to estimate descriptor values for compounds not used for the initial calibration.

The most widely used methods for estimating descriptor values are based on chromatographic and liquid-liquid partition methods [10,16,35–39]. To improve the predictive properties of existing systems and to facilitate the evolution of new methods to estimate descriptor values, calibration compounds with a range of descriptor values are needed. These have to simultaneously meet the selection criteria for the dependent variable (e.g., suitable retention in the chromatographic system) and provide a wide range of descriptor values with low cross-correlation for robust multiple linear regression analysis. We have gone some way to achieving this goal for compounds suitable for describing the retention properties of chromatographic systems with the current WSU compound descriptor database [36,40,41]. However, the current coverage by compounds with hydrogen-bonding properties is inadequate, especially for compounds with varied hydrogen-bond acidity, since many compounds lack functional groups with hydrogen-bond acid properties for which  $A = 0$ . The purpose of this report is to collate data for suitable compounds (anilines, amides, phenols, alcohols and related compounds) with hydrogen-bonding properties determined in calibrated separation systems which can be seamlessly merged with the WSU compound descriptor database previously suggested for the evaluation of the retention properties of chromatographic systems [34,36,40,41]. The same descriptors have been shown to be suitable for estimating environmental, biological and physicochemical properties that can be described by the solvation parameter model [16].

## 2. Experimental

### 2.1. Data sources

Except as noted in Section 2.2 for V and E, the descriptor values were estimated from experimental retention factors and partition constants determined in calibrated chromatographic and liquid-liquid partition systems. Isothermal gas chromatographic retention factors were determined on up to 45 poly(siloxane) and poly(ethylene glycol) stationary phases [2,40] at appropriate temperatures for each compound but more commonly for the eleven column chemistries indicated in [41] together with gas-liquid partition constants for a poly(siloxane) hydrogen-bond acidic sta-

tionary phase [42]. Also, retention factors were determined on four ionic liquid stationary phases (SLB-IL60, SLB-IL61, SLB-IL76, and SLB-IL100) in this study to assist in the estimation of the B descriptor [3,34,43–45]. Retention factors on up to 20 columns were measured by reversed-phase liquid chromatography for binary mobile phases consisting of at least two different organic solvents for compositions providing accessible retention factors [4,6]. These values were scrutinized for contributions to the retention mechanism from steric repulsion [46–48] and electrostatic interactions for silica-based column packings [4,46,49] and excluded from the consolidated data set if found to be significant. For anilines and pyridines (weak bases) the retention factors determined with acetonitrile-water mobile phase compositions were mostly removed due to contributions from electrostatic interactions. No new measurements by micellar electrokinetic chromatography were performed but retention factors for compounds studied previously in up to eleven surfactant-buffer systems were included when available [8,36]. Partition constants in up to 25 liquid-liquid aqueous or totally organic biphasic systems were used [10,35,37]. The partition constants for aqueous systems were taken from the literature for hexadecane-water and cyclohexane-water [25,50], chloroform-water [51], 1,2-dichloroethane-water [51,52], and *n*-octanol-water [15,50,51–56]. ChemSpider (Royal Society of Chemistry, Cambridge, UK) on-line database ([www.chemspider.com](http://www.chemspider.com)) was used to identify further values for the *n*-octanol-water partition constants and the values validated by consulting the cited source. Only values measured directly in the *n*-octanol-water partition system were used and estimated values by either calculation or indirect experimental measurements were excluded. The partition constants for water-based systems are summarized in Table S-1. The models for water-based partition systems were updated, Table 1, by adding partition constants for additional compounds with descriptors determined since the earlier publications. Partition constants for totally organic biphasic systems were taken from the WSU partition constant database and can be found in Ref. [57] together with the updated models used for descriptor calculations.

### 2.2. Calculations

Multiple linear regression analysis and statistical calculations were performed on a Dell Optiflex 9020 computer (Austin, TX, USA) using the program PASW Statistics 24 (SPSS, Chicago, IL, USA). Descriptor values were optimized using the Solver algorithm, an add-in module for Excel (Microsoft Corporation, Redmond, WA) [35–38]. The Solver method varies the values of selected changing cells (descriptors) to minimize the value in a target cell (standard deviation of the residuals) for a series of equations set up as for Eqs. (1) and (2) with the experimental values of  $\log SP$  as the dependent variable. The V descriptor was always calculated from the structural formula by summing atom constants and correcting for the number of bonds using the relationship [20,28,35,36]

$$V = [\Sigma(\text{allatomcontributions}) - 6.56(N-1 + Rg)]/100 \quad (3)$$

where N is the total number of atoms and Rg the total number of ring structures. V is scaled to have similar values to the other descriptors by division by 100 and has units of ( $\text{cm}^3 \text{mol}^{-1}/100$ ). For compounds that are liquid at room temperature with an available value for the refractive index (sodium D-line at 20°C) the E descriptor was calculated using the relationship [16,20,21,36]

$$E = 10V(\eta^2 - 1/\eta^2 + 2) - 2.832V + 0.526 \quad (4)$$

where  $\eta$  is the refractive index. E is scaled to have similar values to the other descriptors by division by 10 and has units of ( $\text{cm}^3 \text{mol}^{-1}/10$ ). For solid compounds the E descriptor was esti-

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