



Review article

Descriptors for ions and ion-pairs for use in linear free energy relationships



Michael H. Abraham^{a,*}, William E. Acree Jr.^b

^a Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

^b Department of Chemistry, P.O. Box 305070, University of North Texas, Denton, TX 76203-5070, USA

ARTICLE INFO

Article history:

Received 21 June 2015

Received in revised form 2 July 2015

Accepted 3 July 2015

Available online 10 July 2015

Keywords:

Ions

Ionic species

Ion-pairs

Linear free energy relationship

Physicochemical processes

Biochemical processes

ABSTRACT

The determination of Abraham descriptors for single ions is reviewed, and equations are given for the partition of single ions from water to a number of solvents. These ions include permanent anions and cations and ionic species such as carboxylic acid anions, phenoxide anions and protonated base cations. Descriptors for a large number of ions and ionic species are listed, and equations for the prediction of Abraham descriptors for ionic species are given. The application of descriptors for ions and ionic species to physicochemical processes is given; these are to water–solvent partitions, HPLC retention data, immobilised artificial membranes, the Finkelstein reaction and diffusion in water. Applications to biological processes include brain permeation, microsomal degradation of drugs, skin permeation and human intestinal absorption. The review concludes with a section on the determination of descriptors for ion-pairs.

© 2015 Elsevier B.V. All rights reserved.

Contents

1. Introduction	2
2. Methods	3
2.1. The data to be used	3
2.2. Determination of descriptors	4
3. Results and discussion	5
3.1. The descriptors	5
3.2. Applications of the ionic descriptors	6
4. Ion-pairs	10
5. Conclusions	13
References	13

1. Introduction

A number of important biological and chemical processes proceed at a fixed pH. In some cases, the pH is determined by necessity. For example, intestinal absorption takes place from the intestinal tract where the pH is around 6.5, distribution of compounds from blood across the blood–brain barrier takes place at pH 7.4. In studies on the permeation of compounds from saline across the brain barrier, the pH of the saline is kept at 7.4 in order not to compromise

the blood–brain barrier. Sea water is usually on the alkaline side, with a pH of around 8.0, and so in studies of distribution of compounds from the air into sea water, the pH may have to be taken into account. In other physicochemical systems the pH can be altered but is normally constant in a given series of experiments. Thus water–solvent distributions of a series of compounds will be carried out at some chosen pH, and similarly for various chromatographic separations.

It therefore follows that for many systems, acid and bases will be partially ionised under the conditions of the system. Note that our terms ‘acid’ and ‘base’ refer to proton acids and proton bases. Numerous algorithms, such as linear free energy relationships, LFER, or quantitative structure–activity relationships, QSAR, have

* Corresponding author. Tel.: +44 020 7679 4639; fax: +44 020 7679 7463.
E-mail address: m.h.abraham@ucl.ac.uk (M.H. Abraham).

been devised in order to correlate and then to predict properties of compounds in biological and chemical systems, but invariably these LFERs and QSARs contain descriptors, or independent variables, that refer only to neutral compounds. Even methods that can calculate hundreds of descriptors for a given compound, such as CODESSA [1] or Dragon [2] are restricted to neutral species.

There have been a few studies on descriptors for ions or for ionic species; we refer to protonated base cations and carboxylic anions as ionic species. Marcus et al. [3] obtained descriptors for ions that yielded Gibbs free energies of transfer from water to a variety of organic solvents, but these ion descriptors were not used in any general LFERs or QSARs, and, indeed, seemed to be quite independent of descriptors for neutral molecules. Marenich et al. [4] have developed a new version of the Cramer–Truhlar continuum solvation model that yields solvation energies of a large number of ions and ionic species. Although solvation energies are reproduced very successfully, the errors in the corresponding $\log P$ values for transfer from water to organic solvents are too large for the method to be very useful in the analysis of many of the biological and chemical processes we have mentioned. The mean unsigned errors in $\log P$ across all ions were 3.1 (water to methanol), 4.7 (water to acetonitrile) and 5.5 (water to dimethylsulfoxide). Andersson and Stipp [5] have more recently used the COSMO-RS method to calculate hydration energies of ions. For 13 univalent ions (excluding H_3PO_4^-) their results, transformed into $\log P$ values for transfer from the gas phase to water yield an SD value of 5 log units, again suggesting methods that yield very good results for hydration or solvation energies of ions may not be very useful in transfers between solvents. The results of Lee et al. [6] on hydration energies of ions were considerably better. They used the solvation free energy density model and calculated hydration energies of a series of anions and cations with a mean absolute error of only 1.2 log units, corresponding to $\text{SD} = 1.7$ log units.

Bittermann et al. [7] also obtained excellent results in their calculations of the partition of anionic and cationic species between water and a number of phospholipid membranes, using COSMOmic, with an RMSE of only 0.7 log units between calculated and observed partition coefficients.

Testa et al. [8–10] devised a very interesting method of representing the distribution of ions and ionic species derived from a given acid or base from water to a solvent as a function of pH. This work demonstrates how important it is to consider the distribution of charged species when dealing with ionisable compounds as a function of pH. Some years later, Ingram et al. [11] used the COSMO-RS thermodynamic model to calculate the distribution of the sodium salts of a number of acids, from water to octanol. At the concentrations used, 0.05 M sodium salt in 0.15 M NaCl, Ingram et al. [11] assumed that the ionic species existed only as ion-pairs in both phases, and the COSMO-RS calculations refer specifically to ion-pairs.

As might be expected, there has been considerable interest in the correlation and prediction of HPLC retention times for solutes that are ionised at the experimental pH. The effect of pH on the retention of a given solute is well-known as a function of the pK_a of the solute and the pH of the system [12], but most attempts to include solute ionisation into equations for the correlation of retention data, k' , have been based on the LFER of Abraham [14–23], Eq. (1) where $\text{SP} = \log k'$,

$$\text{SP} = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \quad (1)$$

We shall consider Eq. (1) in detail later, but just note that E, S, A, B and V are descriptors of neutral solutes.

Bolliet et al. [24] introduced into Eq. (1) an additional new descriptor, P , for acidic phenolic solutes defined as,

$$P = (14 - \text{pK}^*)/10 \quad (2)$$

where $P=0$ for neutral solutes, Bolliet et al. [24] also used another descriptor for acidic phenolic solutes, D , defined as

$$D = 1 - 1/[1 + 10^{(\text{pH}^* - \text{pK}^*)}] \quad (3)$$

so that D is the extent of dissociation of the phenol. In Eqs. (2) and (3) pH^* and pK^* refer to the pH of the mobile phase and to the pK_a of the solute in the mobile phase (not in water).

The descriptors P and D were separately used in conjunction with a number of LFER descriptors to successfully analyse the retention of neutral and acidic phenolic solutes with a number of mobile phases at pH^* values between 4 and 12. The P descriptor was used by Rosés et al. [25] to study the retention of acidic phenolic solutes, but these workers also used another descriptor in Eq. (1) based on the previously used D -descriptor,

$$\text{Log}[1 - D(1 - f)] \quad (4)$$

where f is given by $k(\text{X}^-)/k(\text{HX})$; X^- refers to the phenolate anion and HX to the neutral phenol. Espinoza et al. [26] later considerably extended the scope of the use of the $\log[1 - D(1 - f)]$ descriptor to an assembly of solutes that included both acids and bases.

Chirita et al. [27] studied the retention of a very large number of solutes including both acids and bases on two stationary phases. In a very comprehensive analysis, they extended the use of the D -descriptor by defining a D -descriptor for acids (D^-), as in Eq. (3), and another D -descriptor for bases (D^+), and used both D^- and D^+ to give Eq. (5).

$$\text{Log } k' = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V + d^- \cdot D^- + d^+ \cdot D^+ \quad (5)$$

Again, D^- and D^+ are taken as zero for neutral solutes, when Eq. (5) reverts to Eq. (1). At exactly the same time, Stalcup et al. [28,29] used Eq. (5) to correlate HPLC retention, and it seems as though Eq. (5) is a very useful equation to represent HPLC retention data.

All the above work allows the effect of ionisation on HPLC retention to be dealt with in a very satisfactory way. However, neither the P -descriptor nor the D -descriptors are general, in the sense that they cannot be applied to permanent ions such as Me_4N^+ or ClO_4^- . Furthermore, both require a knowledge of pK^* , the pK of a solute in a particular system. For a biological system such as intestinal absorption, the pK of solutes in the intestinal fluid is just not known.

Raevsky [30–33] has listed descriptors for numerous anions and cations, but without any detail as to how these values had been arrived at. The first attempt to obtain an LFER that included properties of ions was that of Marcus et al. [3] but there was no connection with properties of neutral solutes. Cho et al. [34,35] have recently used Eq. (1) with an additional descriptor for anions, but the coefficients in Eq. (1) for neutral compounds were not the same as those the equation for anions. Our intention was therefore to attempt to devise a method for calculating descriptors for ions and ionic species that was quite general, and could, very importantly, be used in the same LFERs as neutral solutes [36–38].

2. Methods

2.1. The data to be used

There are two main sources of data that we used to in order to calculate descriptors for ions and ionic species, first from known transfers of ions from water to other solvents [36–38], and second from studies of the pK_a of acids and bases in water and other solvents [39].

Download English Version:

<https://daneshyari.com/en/article/1198955>

Download Persian Version:

<https://daneshyari.com/article/1198955>

[Daneshyari.com](https://daneshyari.com)