Prediction of Abraham Descriptors for Agrochemicals

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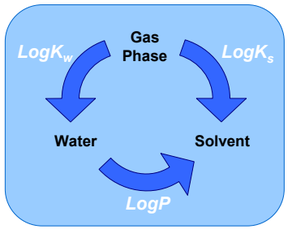
Introduction

The behaviour of an agrochemical in biological and environmental systems depends upon its physical properties[1]. Bioavailability profiles for agrochemicals have been reported by Tice[2,3] and Clarke & Delaney[4] based on whole molecule properties, e.g. molecular weight, octanol/water and alkane/water partition coefficients (*LogP*, *ΔLogP*), aqueous solubility (*Log* S_w), acid-base dissociation constant (pK_a); and simple structure based counts of H-bond donors, H-bond acceptors, heteroatom and aromatic proportions. Clarke & Delaney also used Absolv software by Sirius[5] to profile agrochemicals with respect to Abraham Descriptors for dispersion interactions (*E*), dipolar/polarisability interactions (*S*), hydrogen bond acid (*A*) and hydrogen bond base (*B*) interactions and solute size (*V*). Considerable progress has been made by Prof. M.H. Abraham and co-workers over the past 15 years defining transport related or dependent processes for diverse chemicals in terms of linear solvation energy relationships (*LSERs*) utilising such parameters[6]. Given that *LSERs* exist for many organic/water partition systems the measurement of *LogP* in systems of sufficient diversity can, on regression analysis, yield reliable experimental descriptor values for *S*, *A* & *B*; with the *E* and *V* descriptors readily calculated from structure. For agrochemicals the experimental determination of descriptors was first demonstrated for the phenyl urea herbicide diuron[7], with the most recent example being a set of triazine herbicides, which led to an effective *LSER* for the prediction of Henry's Law constant for this chemical class[8]. In this poster we evaluate the recently released Pharma Algorithms development of Absolv[9] against experimentally derived *S*, *A* & *B* descriptors for a set of ~50 diverse agrochemicals selected to be representative of the Pesticide Manual[10,11]. In addition Abraham descriptors have been predicted for the ~600 agrochemicals in the Pesticide Manual which have measured *LogP* octanol values and compared with Absolv *LogP* octanol predictions.

Absolv

It can be shown that by definition in transport-related properties the partition coefficient between water and any solvent (*LogP*) can be expressed as a difference of the gas phase-solvent and gas phase-water partition coefficients of the solute ($LogK_s$ and $LogK_w$ respectively). This yields the expectation that the solvation of a solute in solvent phase and therefore the transfer of it from one phase to another should only be affected by solute properties that are in general similar for any solvent phase[6]. These considerations resulted in the development of the set of solvation parameters and solvation equations (linear solvation energy relationships - *LSERs*) by Prof. M.H. Abraham[6,12]:



- H-Bonding acidity parameter – *A*
- H-Bonding basicity parameters – *B* and B_o
- Partitioning coefficient between gaseous phase and hexadecane – *L*
- Dipolarity/polarisability parameter – *S*
- Excessive molar refraction – *E*
- McGowan Volume - *V*

$$\log SP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + l \cdot L \qquad (1)$$

$$\log SP = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V \qquad (2)$$

where *SP* is any solvation related property of a series of solutes in a fixed phase (or phases)

The latest version of Absolv software is a product of cooperation between Pharma Algorithms and Prof. M.H. Abraham. It is used for calculating various solvation-associated properties (*SP*) from equations (*LSERs*) involving transfer from the gas phase to a condensed phase (1) or between different condensed phases (2); and structure based prediction of the solvation parameters necessary for those calculations.

Predictive algorithms for every parameter were developed from a data set of more than 5700 compounds with experimental values using a set of Platts-type[13] fragmental descriptors, PLS for statistical analysis and additional optimisation procedures. These additional procedures allow the use of any available experimental data, i.e. partition coefficients between various phases, to enhance the accuracy and robustness of the model. The utilisation of such data is only possible in an analysis based on a fixed fragment set as in this case their contributions (coefficients from the regression) in Abraham solvation parameters can be directly compared to the contributions of the same fragments to the values of various partitioning coefficients. The main assumption behind this method is that Abraham type equations 1 and 2 while intended for whole molecule applications also hold true for the fragments and their coefficients, i.e.:

$$coeff_i(\log SP) = c + e \cdot coeff_i(E) + s \cdot coeff_i(S) + a \cdot coeff_i(A) + b \cdot coeff_i(B) + l \cdot coeff_i(L) \qquad (3)$$

$$coeff_i(\log SP) = c + e \cdot coeff_i(E) + s \cdot coeff_i(S) + a \cdot coeff_i(A) + b \cdot coeff_i(B) + v \cdot coeff_i(V) \qquad (4)$$

where $coeff_i$ denotes the coefficient (contribution) of the i-th fragment of (to) the corresponding whole molecule property

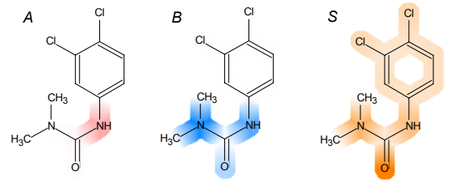
E.g., the contributions of the carboxylic acid fragment to the Abraham solvation parameters should be related to its $LogP_{oct}$ contribution via the corresponding solvation equation (*LSER*). In this manner the fragmental coefficients of the Abraham solvation parameters derived using PLS were further fitted against their independently obtained contributions in a number of partitioning systems. The results of the six models for the Abraham solvation parameters for the training set are presented in the table in the form of R^2 and mean absolute errors (MAE) calculated from plots normalized to give a slope of 1 and intercept of 0.

Absolv software also calculates the contributions of each atom of the molecule to the selected Abraham parameters. This information is colour-coded onto the structure of the compound in single-structure calculation mode, with intensity of the colour indicating the degree of contribution of each atom or substructure to the parameter of interest. An example of such colour-maps of Abraham H-Bonding acidity and basicity parameters (A and B) and dipolarity/polarisability parameter (S) for the diuron molecule are presented below. One can see that H-Bonding donors and acceptors are clearly identified in the case of parameters *A* and *B* with the intensity of the colour correlating with the relative strength of their H-Bonding acidity or basicity. In the case of the parameter *S* the coloured regions can be considered as a representation of the electron density in polar bonds of the molecule and the areas of unrestricted electron movement such as aromatic or other conjugated systems, i.e. the potentially polarisable parts of the molecule.

Model	R^2	MAE
A	0.92	0.03
B	0.91	0.10
B_o	0.91	0.10
L	0.98	0.25
S	0.89	0.14
E	0.98	0.08
V	1.00	0.01

Evaluation Results

The main table presents the first part of the results of this evaluation study, i.e. a detailed comparison of the experimentally determined and predicted values using Absolv[9] of the Abraham dipolarity/polarisability, H-Bonding acidity and H-Bonding basicity parameters (S, A and B respectively) for a set of 46 agrochemicals grouped into similar chemical types to clarify trends within chemical classes. The predictions are categorised relative to the absolute error values as explained in the legend of the table.



Indicates prediction within 0.25 of the experimental value
Indicates prediction > 0.25 & < 0.50 from the experimental value
Indicates prediction > 0.50 & < 1.00 from the experimental value
Indicates prediction > 1.00 & < 2.00 from the experimental value
Indicates prediction > 2.00 & < 3.00 from the experimental value
Indicates prediction > 3.00 from the experimental value

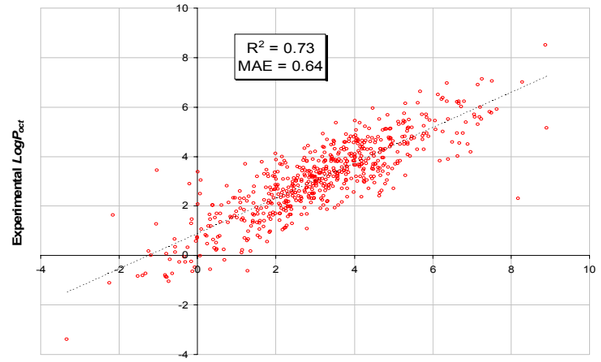
CAS number	Compound Name	*S* (exp.)	*S* (pred.)	Abs. Error	*A* (exp.)	*A* (pred.)	Abs. Error	*B* (exp.)	*B* (pred.)	Abs. Error
Strobilurins										
131860-33-8	azoxystrobin	1.68	3.01	1.33	0.00	0.00	0.00	2.46	1.86	0.60
143390-89-0	kresoxim methyl	0.98	1.58	0.60	0.00	0.00	0.00	1.55	1.15	0.40
117428-22-5	picoxystrobin	1.19	1.71	0.52	0.00	0.00	0.00	1.42	1.24	0.18
Chloroacetamides										
34256-82-1	acetochlor	1.04	1.63	0.59	0.31	0.00	0.31	1.36	1.01	0.35
1918-16-7	propachlor	0.72	1.57	0.85	0.00	0.00	0.00	1.16	0.80	0.36
61213-25-0	flurochloridone	0.92	1.37	0.45	0.32	0.00	0.32	1.01	0.81	0.20
S-triazines										
21725-46-2	cyanazine	2.24	1.74	0.50	0.45	0.36	0.09	0.97	1.05	0.08
122-34-9	simazine	1.71	1.25	0.46	0.37	0.36	0.01	0.79	0.84	0.05
1912-24-9	atrazine	1.24	1.24	0.00	0.33	0.36	0.03	0.94	0.88	0.06
5915-41-3	terbuthylazine	1.37	1.19	0.18	0.18	0.36	0.18	0.88	0.90	0.02
Pyrimidines										
5221-53-4	dimethirimol	0.28	1.11	0.83	0.00	0.50	0.50	1.53	0.97	0.56
23947-60-6	ethirimol	0.86	1.10	0.24	0.36	0.63	0.27	1.25	0.92	0.33
41483-43-6	bupirimate	0.86	1.83	0.97	0.92	0.13	0.79	1.66	1.64	0.02
53112-28-0	pyrimethanil	1.00	1.39	0.39	0.05	0.13	0.08	0.96	0.68	0.28
121552-61-2	cyprodinil	0.97	1.47	0.50	0.10	0.13	0.03	0.90	0.70	0.20
Amides										
57837-19-1	metalaxyl	0.98	1.87	0.89	0.00	0.00	0.00	1.85	1.37	0.48
57646-30-7	furalaxyl	1.14	2.05	0.91	0.00	0.00	0.00	1.71	1.27	0.44
15299-99-7	napropamide	0.87	2.00	1.13	0.00	0.00	0.00	1.52	1.08	0.44
82558-50-7	isoxaben	0.86	2.04	1.18	0.31	0.41	0.10	1.74	1.42	0.32
957-51-7	diphenamid	0.13	1.97	1.84	0.07	0.00	0.07	1.75	0.87	0.88
Azoles										
76674-21-0	flutriafol	1.51	2.03	0.52	0.20	0.31	0.11	1.22	1.20	0.02
107534-96-3	tebuconazole	1.59	1.76	0.17	0.31	0.31	0.00	1.20	1.00	0.20
79983-71-4	hexaconazole	0.91	1.82	0.91	0.15	0.31	0.16	1.59	1.02	0.57
76738-62-0	paclobutrazol	1.49	1.79	0.30	0.23	0.31	0.08	1.42	1.02	0.40
Carbamates										
63-25-2	carbaryl	1.93	1.66	0.27	0.32	0.21	0.11	0.75	0.72	0.03
23103-98-2	pirimicarb	1.31	1.54	0.23	0.00	0.00	0.00	1.41	1.26	0.15
72490-01-8	fenoxycarb	1.95	2.11	0.16	0.78	0.23	0.55	1.03	1.19	0.16
16118-49-3	carbetamide	1.86	2.12	0.26	0.62	0.62	0.00	1.23	1.28	0.05
Thiocarbamates										
52888-80-9	prosulfocarb	0.40	1.69	1.29	0.03	0.00	0.03	1.23	0.92	0.31
Phenylureas										
2164-17-2	fluometuron	1.33	1.25	0.08	0.47	0.38	0.09	0.77	0.77	0.00
15545-48-9	chlorotoluron	1.64	1.49	0.15	0.33	0.38	0.05	0.86	0.82	0.04
330-54-1	diuron	1.86	1.66	0.20	0.52	0.44	0.08	0.71	0.79	0.08
101-42-8	fenuron	1.92	1.48	0.44	0.38	0.31	0.07	0.78	0.87	0.09
Sulfonylureas										
64902-72-3	chlorsulfuron	-0.10	2.89	2.99	0.00	0.75	0.75	2.28	1.74	0.54
94125-34-5	prosulfuron	2.56	2.59	0.03	0.07	0.75	0.68	1.82	1.68	0.14

(continued)

CAS number	Compound Name	*S* (exp.)	*S* (pred.)	Abs. Error	*A* (exp.)	*A* (pred.)	Abs. Error	*B* (exp.)	*B* (pred.)	Abs. Error
Benzoylureas										
35367-38-5	diflubenzuron	1.09	2.15	1.06	0.04	0.65	0.61	1.11	0.99	0.12
86479-06-3	hexaflumuron	1.12	2.10	0.98	1.08	0.79	0.29	1.16	1.03	0.13
71422-67-8	chlorfluazuron	2.29	2.74	0.45	0.38	0.70	0.32	1.39	1.28	0.11
Pyrethroids										
79538-32-2	tefluthrin	1.18	0.93	0.25	0.00	0.00	0.00	0.55	0.44	0.11
Diphenyl ethers										
12680-11-4	bifenox	2.46	2.34	0.12	0.00	0.00	0.00	0.55	0.77	0.22
72178-02-0	fomesafen	2.12	3.19	1.07	0.06	0.49	0.43	1.60	1.29	0.31
42874-03-3	oxyfluorfen	1.87	1.76	0.11	0.00	0.00	0.00	0.30	0.58	0.28
69806-50-4	fluazifop-butyl	2.03	1.69	0.34	0.00	0.00	0.00	1.18	1.21	0.03
2,6-dinitroanilines										
79622-59-6	fluazinam	2.74	1.97	0.77	0.00	0.22	0.22	0.65	0.40	0.25
1582-09-8	trifluralin	2.03	1.84	0.19	0.34	0.00	0.34	0.53	0.61	0.08
62924-70-3	flumetralin	2.71	2.33	0.38	0.00	0.00	0.00	0.58	0.63	0.05

As can be seen from the main table ~90% of the H-Bonding acidity *A* descriptor and the H-Bonding basicity *B* descriptor predictions are good, i.e. lie within 0.5 units of the experimentally determined values for most of the chemical classes. In the case of the dipolarity/polarisability descriptor (*S*) ~60% of predictions have this high level of reliability, with ~85% giving acceptable predictions within 1 unit of experimental values. Whilst there appears to be some degree of variation in predictive performance across and within some chemical classes only the S value for chlorsulfuron is judged unacceptable.

An indirect evaluation of the Absolv predicted Abraham descriptors was also performed using a larger set of ~600 agrochemicals with measured *LogP* octanol values reported in the Pesticide Manual[11]. Descriptors and *LogP* octanol values using the corresponding *LSER* were calculated via the Pharma Algorithms ADME Boxes Absolv module[9] with a plot of measured vs. predicted *LogP* values resulting in respectable R^2 and MAE values of 0.73 and 0.64 respectively.



We conclude that the current implementation of Absolv can lead to acceptable prediction of Abraham descriptors for effective profiling of transport related processes through *LSERs* for agrochemicals.

References

1. *Handbook of Property Estimation Methods for Chemicals: Environmental and Health Sciences*. Eds.: Boethling, R. S., Mackay, D., 2000, CRC Press, Boca Raton, USA.
2. Tice, C. M., *Pest. Manag. Sci.*, 2001, 57, 3-16.
3. Tice, C. M., *Pest. Manag. Sci.*, 2002, 58, 219-233.
4. Clarke, E. D., Delaney, J. S., *Chimia*, 2003, 57, 731-734.
5. Absolv v1.4. Sirius Analytical Instruments, Forest Row, East Sussex, UK.
6. Abraham, M. H., Ibrahim, A., Zissimos, A. M., *Journal of Chromatography A*, 2004, 1037, 29-47.
7. Green, C. E., Abraham, M. H., Acree Jr., W. E., De Fina, K. M., Sharp, T.L., *Pest. Manag. Sci.*, 2000, 56, 1043-1053.
8. Abraham, M. H., Enomoto, K., Clarke, E. D., Roses, M., Rafols, C., Fuguet, E., *J. Environ. Monit.*, 2007, 9, 234-239.
9. ADME Boxes v3.5. Pharma Algorithms, Inc., *www.ap-algorithms.com*
10. Enomoto, K., *Application of linear solvation energy relationships to the prediction of important physico-chemical properties of agrochemicals*, 2003, PhD thesis University College London.
11. *The Pesticide Manual (12th Edition)*. Ed. Tomlin, T. D. S., 2000, British Crop Protection Council, Farnham, Surrey, UK.
12. Abraham, M. H., *Chem. Soc. Rev.*, 1993, 22, 73-83.
13. Platts, J. A., Butina, D., Abraham, M. H., Hersey, A., *J. Chem. Inf. Comput. Sci.*, 1999, 39, 835-845.