

Response to “A critique of Abraham and Acree’s correlation for deca-1,9-diene/water partition coefficients”

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

^a Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ (U.K.)

^b Department of Chemistry, 1155 Union Circle # 305070, University of North Texas, Denton, TX 76203-5017 (U.S.A.)

The manuscript responds to the critique of Nitsche and Kasting concerning our published correlation for deca-1,9-diene/water partition coefficients. Several statements made in the critique are refuted, and shown to be misrepresentations of ideas contained in our earlier paper.

In a recent commentary published in this Journal, Nitsche and Kasting¹ provided a highly biased critique of Abraham and Acree’s correlation² for deca-1,9-diene/water partition coefficients. Unfortunately many of the items discussed in the critique were a misrepresentation of ideas contained in the Abraham and Acree paper. We will not go through every one of the misrepresentations, but will focus on a select few.

First, in the abstract Nitsche and Kasting state “Solvation parameters used as independent variables should represent fundamental molecular properties, yet they are assigned revised values apparently based partly on the very data being fitted.” Nowhere in our paper do we state that the experimental deca-1,9-diene/water partition coefficients were used in the computation of solute descriptors. It is fundamentally impossible to use experimental deca-1,9-diene/water partition coefficients to calculate solute descriptors in the absence of an Abraham model for deca-1,9-diene/water partition coefficients, as $\log P(10\text{diene})$, and/or gas-to-deca-1,9-diene, $\log K(10\text{diene})$, partition coefficient correlations. We did have the required linear free energy relationships (LFERs) by the end of our analysis, but not at the start when the solute descriptors were being determined. The same is true for the 1-hexadecene database and correlations. For Nitsche and Kasting to imply otherwise, is a misrepresentation of what was stated in our manuscript.

Second, Nitsche and Kasting state “Fortunately, Anderson et al.[references cited] determined log P values for a number of solutes in solvents other than hex[a]dec-1-ene and [deca-1,9-diene], and so we were able to determine descriptors.” The quoted statement is from our paper; however, the authors have elected not to give the entire passage. The passage in its entirety reads “Fortunately, Anderson et al. [references cited] determined log P values for a number of solutes in solvents other than hexdec-1-ene and dodeca-1,9-diene [typographic error, should be deca-1,9-diene] and so we were able to determine descriptors. For other solutes, we added fragment values for the various descriptors and checked the results by comparison of our calculated values for water-octanol partition, as log $P(\text{octanol})$, with those experimentally determined, or if the latter were not available with ClogP values calculated in the BioLoom software. We also used the Absolv software in the ACD suite to calculate descriptors from structure; this was especially useful in order to obtain an estimate of the L -descriptor.” Had the authors carefully read the paragraph they would have noticed that we stated “Anderson et al. determined log P values for a number of solutes in solvents.” We did not state determined log P values for all solutes in solvents. Moreover they would have learned that some of the solute descriptors were calculated using fragment values for various descriptors and using the Absolv software in the ACD suite³ to calculate some of the descriptors from structure. The calculated solute descriptors were checked by comparison of our calculated log $P(\text{octanol})$ values with either experimental log $P(\text{octanol})$ data⁴ or calculated values based on ClogP method.⁴ Instead the authors did not give the entire passage, and erroneously imply in their critique that we used the deca-1,9-diene/water partition coefficient. As stated above, it was fundamentally impossible to use experimental deca-1,9-diene/water partition coefficient data to calculate solute descriptors because the needed Abraham model log $P(10\text{diene})$ and log $K(10\text{diene})$ equations did not exist when the solute descriptors were being obtained.

As an example of how we use a combination of a log $P(\text{octanol})$ value with calculations of some of the descriptors from structure we cite the solute 3-phenylbenzoic acid, for which log P_{octanol} is 3.75 from the Bioloom data base⁴ but for which there is no log P value in the water-deca-1,9-diene system nor in any other water-solvent system, so that log $P_{\text{octanol}} = 3.75$ is the only partition coefficient to go on. However, we can use a floating value of the gas-water

partition coefficient, K_w , to convert $\log P_{\text{octanol}}$ into $\log K_{\text{octanol}}$ for which we have an equation. We also have an equation for $\log K_w$ in terms of eqn (1) and another equation for $\log K_w$ in terms of eqn (2), thus producing four known equations. We take $E = 1.48$ from a calculated refractive index³ and V as 1.5395 by the usual method. Then we have S , A , B , L and $\log K_w$ as unknown descriptors. It is quite easy to estimate $A = 0.59$ by comparison to other compounds (note that since we have 3000 non-zero values of A in our data base of compounds, it is not difficult to find a reasonable analogue) leaving four unknown descriptors. The Absolv calculation³ of L is very reliable because this descriptor simply refers to transfer from the gas phase where there are no solute-solvent interactions to hexadecane where there are only limited solute-solvent interactions. We therefore adjusted the B -descriptor until the solution of the simultaneous equations yielded the Absolv L -value of 7.88. The final descriptors were $E = 1.48$, $S = 1.30$, $A = 0.59$, $B = 0.50$, $V = 1.5395$, $L = 7.88$ and $\log K_w = 6.53$, and the observed and calculated dependent variables in the set of simultaneous equations are in Table 1.

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

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

Table 1. Calculations for descriptors for 3-phenylbenzoic acid

System	Calc	Obs
Water-octanol	3.71	3.75
Gas-water eq in V	6.51	6.53
Gas-octanol	10.28	10.28
Gas-water eq in L	6.54	6.53

Contrary to the suggestion of Nitsche and Kasting,¹ it is therefore quite possible to obtain a set of descriptors using a value for $\log P_{\text{octanol}}$, without the use of any other partition coefficient. The above procedure is absolutely general and can be applied to almost any solute, including several of the solutes in the deca-1,9-diene database.

Third, Nitsche and Kasting further stated that “Abraham and Acree revise the values of A, B, and/or S entering their LFER for 45 of the 61 compounds represented in the decadiene partitioning data set.” This is another misrepresentation of what is stated in our paper. Rather what is stated in our paper is “For a number of solutes the required descriptors in eqn (1) and (2) were available, [cited reference] but for most of the solutes used by Anderson et al.[cited references] descriptors had to be obtained.” We did not have solute descriptors for many of the 61 compounds in the first place, so how could we revise them?

Fourth, the authors imply that one must have a revised Abraham solute descriptor in order to use our log $P(10\text{diene})$ and log $K(10\text{diene})$ correlations. Specifically the authors state “In practical terms, the biggest problem ultimately arises in trying to actually predict $P(10\text{diene})$ for a compound not among the 58 ones fitted. By definition, revised solvation parameters for it do not exist, so one could only get them from Absolv.” Calculated Abraham model solute descriptors now exist for several thousand compounds, and the existing solute descriptors can easily be used to make predictions. Some examples are given in Table 2 where we use eqn (3), below. Descriptors for a number of compounds that have been available since 1994,⁵ and we are constantly obtaining descriptors for new compounds.⁶ As can be seen from Table 2 there is no problem at all in predicting further values of the water-decadiene partition coefficient. We have absolutely no idea how Nitsche and Kasting could have reached their conclusion. One does not have to have a “revised” solute descriptor as Nitsche and Kasting erroneously state.

Table 2. Descriptors for a selection of compounds, and predictions of water-decadiene partition coefficients, as log $P(10\text{diene})$, through eqn (3).

Compound	E	S	A	B	V	log $P(10\text{diene})$
Pentan-1-ol (1994)	0.219	0.42	0.37	0.48	0.8718	0.33
Aniline (1994)	0.955	0.96	0.26	0.41	0.8162	0.01
Oxazole (1994)	0.418	0.70	0.00	0.42	0.4952	-0.44
2-Ethylanthraquinone (2011)	1.410	1.54	0.00	0.56	1.8106	3.65
3-Phenylbenzoic acid (2012)	1.480	1.30	0.59	0.50	1.5395	1.47

Solute descriptors of some compounds have been revised from their initial values as new experimental data becomes available. We have stated this in a number of our publications. The number of revisions in regards to the deca-1,9-diene data set is considerably smaller than the 45 of 61 compounds implied in the recently published critique. Revisions are necessary because a number of the very early numerical solute descriptors were based on a limited number of experimental measurements, and some of the early experimental data have been replaced with more recent and more accurate values. This is also a problem common to group contribution and fragmentation methods in that numerical group values and fragmentation values are periodically adjusted in order to extend the methods to more systems and molecules. Nitsche and Kasting mention the use of the Absolv program to calculate solute descriptors, but here again the numerical values will periodically change as documented by published papers that have used the Absolv program to calculate Abraham solute descriptors. For example the solute descriptors of lamotrigine were $E = 2.79$, $S = 2.81$, $A = 0.50$, $B = 1.09$ and $V = 1.65$ in a 2001 paper⁷ versus $E = 2.40$, $S = 2.13$, $A = 0.45$, $B = 0.93$ and $V = 1.6453$ in a 2009 paper⁸, and of cimetidine were $E = 1.53$, $S = 2.11$, $A = 0.59$, $B = 2.14$ and $V = 1.96$ in a 2001 paper⁷ versus $E = 1.66$, $S = 1.87$, $A = 0.74$, $B = 1.86$ and $V = 1.9563$ in 2009⁸. Many more examples can be found in the published chemical and pharmaceutical literature. Which set of Absolv solute descriptors should one use, the older values or the more recent set of values, and does one need to redo every mathematical correlation derived from the older values when a new set becomes available? Given that Absolv values also change as the fragmentation scheme and group values are revised, many of the comments of Nitsche and Kasting on this matter become meaningless.

Unfortunately, we did miscalculate the numerical solute descriptors for a few compounds. The molecular structures of five molecules in the 58 compound data set of Nitsche and Kasting⁹ were incorrectly drawn by us in performing the atom counts and fragment sums. The molecules and corrected solute descriptors are in Table 3. In order to make a direct comparison between correlations that use calculated Absolv descriptors, as set out by Nitsche and Kasting,⁹ and correlations that use ‘experimental’ Absolv descriptors, as set out by Abraham and Acree, we use the $\log P(10\text{diene})$ and $\log P(\text{octanol})$ values in the 58-compound data set of Nitsche and Kasting⁹ and apply our ‘experimental’ Absolv descriptors. We leave out only the

new entry 'DB-67 Lactone'. For the 57 remaining compounds we obtain eqn (3) and eqn (4). For comparison we give the Nitsche and Kasting equations that use the calculated Absolv descriptors, eqn (5) and eqn (6).⁹ It is quite clear that eqn (3), using the experimental Absolv descriptors is significantly better than eqn (5) that uses the calculated descriptors.

Table 3. Corrected values of descriptors

Compound	<i>E</i>	<i>S</i>	<i>A</i>	<i>B</i>	<i>V</i>
p-Toluyldialanine	1.600	2.80	1.39	1.50	2.1490
4-Methylcarbamoylmethyl-phenyl)acetic acid	1.120	1.94	1.10	1.35	1.6108
{4-[2-(Dimethylamino)-2-oxoethyl]phenyl}acetic acid	1.120	2.00	0.68	1.45	1.7517
[4-(2-{[2-(Dimethylamino)-2-oxoethyl]-amino}-2-oxoethyl)phenyl]acetic acid	1.650	3.30	1.14	1.60	2.1490
α-Carboxy-p-methylhippuric acid	1.400	2.85	1.80	1.28	1.6852

$$\text{Log } P(10\text{diene}) = 0.185 + 0.468 E - 1.888 S - 2.911 A - 3.972 B + 4.382 V \quad (3)$$

$$N = 57, \text{SD} = 0.282, R^2 = 0.986, F = 730.05$$

$$\text{PRESS} = 5.575, Q^2 = 0.981, \text{PSD} = 0.331$$

$$\text{Log } P(10\text{diene}) = -0.035 + 1.022 \log P_{\text{octanol}} - 0.153 E - 1.049 S - 2.801 A + 0.547 V \quad (4)$$

$$N = 57, S = 0.337, R^2 = 0.980, F = 505.97$$

$$\text{PRESS} = 7.110, Q^2 = 0.976, \text{PSD} = 0.373$$

$$\text{Log } P(10\text{diene}) = 0.068 + 0.656 E - 2.598 S - 3.367 A - 3.204 B + 4.447 V \quad (5)$$

$$N = 58, \text{SD} = 0.653, R^2 = 0.926, F = 130.49$$

$$\text{PRESS} = 27.95, Q^2 = 0.907, \text{PSD} = 0.733$$

$$\text{Log } P(10\text{diene}) = 0.284 + 1.113 \log P_{\text{octanol}} - 0.608 E - 1.109 S - 3.564 A + 0.745 V \quad (6)$$

N = 58, S = 0.419, R² = 0.970, F = 331.54
 PRESS = 12.432, Q² = 0.959, PSD = 0.489

Both of the log *P*plus equations, eqn (4) and eqn (6), are quite reasonable. However, there are serious disadvantages in the use of the log *P*plus equations by comparison to the general equation, eqn (1). The small number of experimental values in the deca-1,9-diene dataset limits our testing of the derived correlations using an external data set. A validation based on an external data set would require 20 or more data points to give meaningful statistics,¹⁰ which would give us a small number of data points in the training set.

First, it is difficult to interpret the log *P*plus equation. Nitsche and Kasting,⁹ comment on their eqn (6), above, “interestingly the hydrogen bond acidity *A*, but not the basicity *B* seems to be essential to predicting the decadiene/water partition coefficient”. Nitsche and Kasting,⁹ have misinterpreted eqn (6). The log *P*octanol term itself includes the influence of the various solute properties as described through eqn (7).⁹ Then the overall effect of solute hydrogen bond basicity on log *P*(10diene) is given by 1.113*(-3.460) = - 4.573, a very large effect indeed. But a much simpler interpretation is given by eqn (3), where the effect of solute hydrogen bond basicity (*B* = -3.972) is found just by inspection.

$$\text{Log } P(\text{octanol}) = 0.088 + 0.562 E - 1.054 S - 0.034 A - 3.460 B + 3.814 V \quad (7)$$

Second, it has been shown by Abraham and Acree¹¹⁻¹⁶ that eqn (1) can be extended to include both ionic species and neutral species. This is a very important development which allows the permeation of ionic species across membranes to be investigated, see for example the work of Zhang et al.¹⁷ on permeation through human skin. The log *P*plus method as used by Nitsche and Kasting⁹ simply cannot be extended to ionic species because neither the EPI suite¹⁸ nor the ACD software³ can calculate log *P*(octanol) for ionic species.

We conclude that although the log *P*plus method can lead to quite good correlations for systems such as water-solvent partitions, it has no great advantage over correlations through eqn (1), and at least two particular disadvantages. The use of calculated Absolv descriptors appears to

lead to poorer correlations than the experimental Absolv descriptors, and so we recommend the use of eqn (1) together with experimental Absolv descriptors where available. If experimental descriptors are not available, then calculated Absolv descriptors could be used.

Notes and References

- 1 J. M. Nitsche and G. B Kasting, *New J. Chem.*, 2012, DOI: 10.1039/c2nj40622e.
- 2 M. H. Abraham and W. E. Acree, Jr., *New J. Chem.*, 2012, 36, 1798-1806.
- 3 Advanced Chemistry Development, 110 Yonge Street, 14th Floor, Toronto, Ontario, M5C 1T4, Canada.
- 4 Biolum, 2011; BioByte Corp, 201 W. 4th Street, #204 Claremont, CA 91711-4707.
- 5 M. H. Abraham, H. S. Chadha, G. S. Whiting and R. C. Mitchell, *J. Pharm. Sci.*, 1994, 83, 1085-1100.
- 6 K. Holley, W. E. Acree, Jr. and M. H. Abraham, *Phys. Chem. Liquids*, 2011, 49, 355-365.
- 7 Y. H. Zhao, J. Le, M. H. Abraham, A. Hersey, P. J. Eddershaw, C. N. Luscombe, D. Boutina, G. Beck, B. Sherborne, I. Cooper and J. A. Platts, *J. Pharm. Sci.*, 2002, 90, 749-xxx.
- 8 M. H. Abraham, J. Gil-Lostes and M. Fatemi, *Eur. J. Med. Chem.*, 2009, 44, 2452-2458.
- 9 J.M. Nitsche and G. B Kasting, *J. Pharm. Sci.*, 2013, 105, 136-144.
- 10 D. M. Hawkins, *J. Chem. Inf. Comput. Sci.*, 2004, 44, 1-12.
- 11 M. H. Abraham and W. E. Acree, Jr., *J. Org. Chem.*, 2010, 75, 1006-1015.
- 12 M. H. Abraham and W. E. Acree, Jr., *J. Org. Chem.*, 2010, 75, 3021-3026.
- 13 M. H. Abraham and W. E. Acree, Jr., *New J. Chem.*, 2010, 34, 2298-2305.
- 14 M. H. Abraham and W. E. Acree, Jr., *Phys. Chem. Chem. Phys.*, 2010, 12, 13182-13188.
- 15 M. H. Abraham and W. E. Acree, Jr., *Thermochimica Acta*, 2011, 526, 22-28.
- 16 M. Saifullah, S. Ye, L. M. Grubbs, N. E. De La Rosa, W. E. Acree, Jr. and M. H. Abraham, *J. Soln. Chem.*, 2011, 40, 2082-2094.
- 17 K. Zhang, M. Chen, G. K. E. Scriba, M. H. Abraham, A. Fahr and X. Lui, *J. Pharm. Sci.*, 2012, 101, 2034-2044.
- 18 ChemSpider, <http://www.chemspider.com>, includes the EPI suite of calculations.