A critique of Abraham and Acree's correlation for deca-1,9-diene/water partition coefficients

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Supplementary Material

Unless specifically indicated to the contrary, numbers of equations refer to the main text by default. Numbers of supplementary equations and tables presented here begin with the letter "S." Although many references cited here appear in the bibliography of the main text, others do not. To avoid possible confusion regarding reference numbers, citations here refer to the separate self-contained bibliography included at the end of this document.

Calculation of molecular descriptors using partition coefficients

This section furnishes a brief summary of the general procedure employed by Abraham and coworkers.[1-5] To avoid ambiguity we use the symbols P_s and K_s for the quantities they call simply *P* and *K*.

In all that follows we consider a given solute, and regard its molecular descriptors E, V and L to be known. They are relatively easy to come by, as discussed by Abraham and coworkers,[1-5] and typically the challenge is to determine A, B and S. The symbol P_s denotes the solvent s/water partition coefficient defined as the ratio

$$P_s = \frac{\text{solute concentration in solvent s phase}}{\text{solute concentration in aqueous phase}} \qquad \text{(S1)}$$

at equilibrium. The symbol K_s denotes the solvent s/gas partition coefficient defined as the ratio

$$K_s = \frac{\text{solute concentration in solvent s phase}}{\text{solute concentration in gas phase}} \qquad \text{(S2)}$$

at equilibrium. The relation between these two partition coefficients involves a third coefficient K_w defined as the ratio

$$K_w = \frac{\text{solute concentration in aqueous phase}}{\text{solute concentration in gas phase}} \qquad \text{(S3)}$$

at equilibrium. The relation is

$$P_{\rm s} = K_{\rm s}/K_{\rm w}. \tag{S4}$$

With a value of $K_{\rm w}$ in hand, eqn. S4 can be used to determine $K_{\rm s}$ from a measured value of $P_{\rm s}$. This equation can also be written as[1-3]

$$\log K_{\rm s} = \log P_{\rm s} + \log K_{\rm w}. \tag{S5}$$

(The plus (+) sign in Abraham et al.'s[2] eqn 5 is evidently a misprint, and should be a minus (−) sign.) Correlations giving the two partition coefficients $P_{\rm s}$ and $K_{\rm s}$ in terms of the molecular descriptors A, B, S,E, V and L have the forms[1-4, 6, 7]

$$\log P_{\rm s} = c_{\rm s} + a_{\rm s}A + b_{\rm s}B + s_{\rm s}S + e_{s}E + v_{\rm s}V \tag{S6}$$

and

$$\log K_{\rm s} = c'_{\rm s} + a'_{\rm s}A + b'_{\rm s}B + s'_{\rm s}S + e'_{s}E + l'_{\rm s}L. \tag{S7}$$

The molecular descriptor L is not used in eqn S6, and the molecular descriptor V is not used in eqn S7. Equation S6 is a repeat of eqn 1 in the main text. The "prime" ($'$) superscripts appearing in eqn S7 serve as a reminder of the fact that the numerical values of $c_{\rm s}$, $a_{\rm s}$, $b_{\rm s}$, $s_{\rm s}$ and $e_{\rm s}$ are generally different from those of $c'_{\rm s}$, $a'_{\rm s}$, $b'_{\rm s}$, $s'_{\rm s}$ and $e'_{\rm s}$, respectively. Although not strictly necessary, we affix the prime superscript also to the coefficient multiplying L in eqn S7 for consistency of notation; thus all coefficients appearing in this equation carry the prime superscript.

The procedure for calculating A, B and S using solvent/water partition coefficients $P_{\rm s1}$, $P_{\rm s2}$ and $P_{\rm s3}$ measured for three solvents s1, s2 and s3, respectively, is based on the following three equations:[2, 4, 5]

$$\log P_{\rm s1} = c_{\rm s1} + a_{\rm s1}\boldsymbol{A} + b_{\rm s1}\boldsymbol{B} + s_{\rm s1}\boldsymbol{S} + e_{\rm s1}E + v_{\rm s1}V, \tag{S8a}$$
$$\log P_{\rm s2} = c_{\rm s2} + a_{\rm s2}\boldsymbol{A} + b_{\rm s2}\boldsymbol{B} + s_{\rm s2}\boldsymbol{S} + e_{\rm s2}E + v_{\rm s2}V, \tag{S8b}$$
$$\log P_{\rm s3} = c_{\rm s3} + a_{\rm s3}\boldsymbol{A} + b_{\rm s3}\boldsymbol{B} + s_{\rm s3}\boldsymbol{S} + e_{\rm s3}E + v_{\rm s3}V. \tag{S8c}$$

Use of boldface type does not imply vector character, but rather highlights the three unknowns for clarity. All other quantities are known. In particular, the three left-hand sides are base 10 logarithms of the three measured partition coefficients, the 18 coefficients $c_{\rm s1}, \ldots, v_{\rm s3}$, are all known from previously established correlations, and the molecular descriptors E are V have been determined.

The procedure for calculating A, B and S using solvent/water partition coefficients $P_{\rm s1}$ and $P_{\rm s2}$ measured for two solvents s1 and s2, respectively, is based on the following four equations:[1, 3]

$$\log P_{\rm s1} = c_{\rm s1} + a_{\rm s1}\boldsymbol{A} + b_{\rm s1}\boldsymbol{B} + s_{\rm s1}\boldsymbol{S} + e_{\rm s1}E + v_{\rm s1}V, \tag{S9a}$$
$$\log P_{\rm s1} + \log \boldsymbol{K}_{\rm w} = c'_{\rm s1} + a'_{\rm s1}\boldsymbol{A} + b'_{\rm s1}\boldsymbol{B} + s'_{\rm s1}\boldsymbol{S} + e'_{\rm s1}E + l'_{\rm s1}L, \tag{S9b}$$
$$\log P_{\rm s2} = c_{\rm s2} + a_{\rm s2}\boldsymbol{A} + b_{\rm s2}\boldsymbol{B} + s_{\rm s2}\boldsymbol{S} + e_{\rm s2}E + v_{\rm s2}V, \tag{S9c}$$
$$\log P_{\rm s2} + \log \boldsymbol{K}_{\rm w} = c'_{\rm s2} + a'_{\rm s2}\boldsymbol{A} + b'_{\rm s2}\boldsymbol{B} + s'_{\rm s2}\boldsymbol{S} + e'_{\rm s2}E + l'_{\rm s2}L. \tag{S9d}$$

Again, use of boldface type highlights the unknowns for clarity. The parameter $\log K_{\rm w}$ is considered as an unknown to be determined along with A, B and S. The value found for it can be ignored subsequently if there is interest only in A, B and S. Equation S5 has effectively been used on the left-hand sides of eqns S9b and S9d to express $K_{\rm s}$ in terms of $P_{\rm s}$ and $\log K_{\rm w}$ for

solvents s1 and s2, respectively. These two equations (statements of eqn S7 for solvents s1 and s2) encode information additional to P_{s1} and P_{s2} needed to determine four unknowns — and the two-solvent scheme is valid — insofar as only experimentally determined solvent/gas partition coefficients K_{s1} and K_{s2} entered the correlation analysis underlying eqn S7.

The determination of molecular descriptors is strengthened by the inclusion of more than three and two measured solvent/water partition coefficients, respectively, in the schemes of eqns S8a–c and S9a–d . If more data are available, correspondingly more equations are added to these schemes, and they are solved as over-determined systems for the values of the molecular descriptors that best satisfy all the equations, based on some overall error criterion.[1-5] For present purposes we emphasize the equations as written in order to indicate the minimum number of solvent/water partition coefficients needed to determine A, B and S. By the first scheme as written (eqns S9a–c) measured values of P_s for three different solvents s are required. By the second scheme (eqns S9a–d) only two are required.

Summary of partition coefficients reported by Xiang, Anderson and coworkers

Table S1 lists the 18 compounds referred to in the main text for which only the deca-1,9-diene/water partition coefficient is reported by Xiang, Anderson and coworkers in their series of papers relating to phospholipid bilayer permeability.[8-17] Table S2 catalogs all solvent/water partition coefficients reported by these investigators. The compounds listed in Table S1 are distinguished by grey highlights in Table S2 to show their place within the overall dataset.

Numerical oversights in Abraham and Acree's dataset

Table S3 lists the numerical oversights in Abraham and Acree's[1] Table 2 referred to in the main text.

Sources of octanol/water partition coefficients

Database matches are indicated for four of the 18 compounds listed in Table S1 (*N*,*N*-dimethylacetamide, methyl acetate, phenylethylamine, 4-ethylphenol) in the Estimation Program Interface (EPI) Suite, US Environmental Protection Agency,[18] accessed through ChemSpider.[19] For the remaining 14, calculated estimates can be obtained using ACD/Labs' log *P* calculator accessed through the ChemSketch interface,[20] which utilizes the recommended "A" algorithm of the ACD/LogP DB program (Vers. 12).

Although the main text emphasizes the 18 compounds listed in Table S1, the sources just stated are what we consider to provide the most reliable values of *P*(oct). They were used to obtain *P*(oct) in Ref. [21] for all compounds for which a measured value was not reported by Xiang, Anderson and coworkers, according to the following procedure. Where available, values of *P*(oct) were obtained from the EPI Suite accessed through ChemSpider. In the absence of a database match within the EPI Suite, we used ACD/Labs' log *P* calculator.

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Table S1. Eighteen compounds referred to in the main text for which only the deca-1,9-diene/water partition coefficient is reported by Xiang, Anderson and coworkers in their series of papers relating to phospholipid bilayer permeability.[8-17] Specific references for the reported values of *P*(10diene) are indicated by footnote letters matching those in the more detailed Table S2 below, namely h denotes Cao et al.[15] and j denotes Tejwani et al.[17]

Compound name	Designation in Ref. h (Cao et al.[15])	Compound name/formula and place in numerical order of Abraham and Acree's[1] Table 2		Reference for *P*(10diene)
N,*N*-dimethylacetamide	Ac-NMe_2	N,N-Dimethylacetamide	9	h
methyl acetate	Ac-OMe	Methyl acetate	10	h
2-(acetylamino)-*N*,*N*-dimethylacetamide	Ac-G-NMe_2	CH3CONHCH2CONMe2	11	h
methyl (acetylamino)acetate	Ac-G-OMe	CH3CONHCH2CO2Me	12	h
p-toluoylalanine	Tol-A	MeC6H4CONHCH(Me)CO2H	26	h
p-toluoyldialanine	Tol-A-A	MeC6H4CONHCH(Me)CONHCH(Me)CO2H	27	h
p-toluoylsarcosine	Tol-Sar	MeC6H4CON(Me)CH2CO2H	29	h
p-toluoylglycylsarcosine	Tol-G-Sar	MeC6H4CONHCH2CON(Me)CH2CO2H	31	h
4-methylcarbamoylmethyl-phenyl)acetic acid	CMPA-NHMe	CO2HCH2C6H4CH2CONHMe	44	h
{4-[2-(dimethylamino)-2-oxoethyl]phenyl}acetic acid	CMPA-NMe_2	CO2HCH2C6H4CH2CONMe2	45	h
[4-(2-{[2-(dimethylamino)-2-oxoethyl]-amino}-2-oxoethyl)phenyl]acetic acid	CMPA-G-NMe_2	CO2HCH2C6H4CH2NHCH2CONMe2	46	h
phenylethylamine		2-Phenylethylamine	56	j
p-hydroxyphenylethylamine		*p*-Hydroxy-2-phenylethylamine	57	j
N-methyltyramine		*p*-Hydroxy-*N*-methyl-2-phenylethylamine	58	j
N,*N*-dimethyltyramine		*p*-Hydroxy-*N*,*N*-dimethyl-2-phenylethylamine	59	j
p-methoxyphenylethylamine		*p*-Methoxy-2-phenylethylamine	60	j
N-methyl-*O*-methyltyramine		*p*-Methoxy-*N*-methyl-2-phenylethylamine	61	j
4-ethylphenol		4-Ethylphenol	62	j

Table S2. Catalog all solvent/water partition coefficients reported in a series of papers by Xiang, Anderson and coworkers.[8-17] The 18 compounds listed in Table S1 are distinguished by grey highlighting. Footnotes a–h here correspond exactly to footnotes a–h in Nitsche and Kasting's[21] Table 1.

Compound name	Designation in Refs. a, d, e, h	No. in Ref. b	Compound name/formula and place in numerical order of Abraham and Acree's[i] Table 2		Reference(s) identified by footnote letter(s) for reports of partition coefficient in various solvents								
					octanol	isoamyl alcohol	decane	hexadecane	hexadecene	carbon tetrachloride	chlorobutane	butyl ether	1,9-decadiene
p-toluic acid	a [a,d] or 1a [e]	8	MeC6H4CO2H	17	a,d		b	a,d	a,b,d		d	d	a,b,d,f,g,h
α-chloro-*p*-toluic acid	b [a,d] or 1b [e]	10	ClCH2C6H4CO2H	18	a,d		b	a,d	a,b,d		d	d	a,b,d,f,h
α-methoxy-*p*-toluic acid	c [a,d] or 1c [e]	12	MeOCH2C6H4CO2H	19	a,d		b	a,d	a,b,d		d	d	a,b,d,f
α-cyano-*p*-toluic acid	d [a,d] or 1d [e]	11	CNCH2C6H4CO2H	20	a,d		b	a,d	a,b,d		d	d	a,b,d,f
α-hydroxy-*p*-toluic acid	e [a,d] or 1e [e]	9	HOCH2C6H4CO2H	21	a,d		b	a,d	a,b,d		d	d	a,b,d,f
α-carboxy-*p*-toluic acid	f [a,d] or 1f [e]	15	CO2H.CH2C6H4CO2H	22	a,d		b	a,d	a,b,d		d	d	a,b,d,f
α-carbamoyl-*p*-toluic acid	g [a,d] or 1g [e]	16	NH2OC.CH2C6H4CO2H	23	a,d		b	a,d	a,b,d		d	d	a,b,d,f
p-methylhippuric acid	2a		CH3C6H4CONHCH2CO2H	49	e			e	e				e,f,g,h
α–chloro-*p*-methylhippuric acid	2b		ClCH2C6H4CONHCH2CO2H	50	e			e	e				e,f
α-methoxy-*p*-methylhippuric acid	2c		MeOCH2C6H4CONHCH2CO2H	51	e			e	e				e,f
α-cyano-*p*-methylhippuric acid	2d		CNCH2C6H4CONHCH2CO2H	52	e			e	e				e,f
α-hydroxy-*p*-methylhippuric acid	2e		HOCH2C6H4CONHCH2CO2H	53	e			e	e				e,f
α-carboxy-*p*-methylhippuric acid	2f		CO2HCH2C6H4CH2NHCH2CO2H [i]	54	e			e	e				e
α-carbamoyl-*p*-methylhippuric acid	2g		CONH2CH2C6H4CH2NHCH2CO2H [i]	55	e			e	e				e
water		1	Water	5			b		b				b
formic acid		2	Formic acid	6			b		b				b,h
acetic acid		3	Acetic acid	7			b		b				b,h
acetamide		4	Acetamide	8			b		b				b
butyric acid		5	Butanoic acid	14			b		b				b
adenine		6	Adenine	67			b		b				b
benzoic acid		7	Benzoic acid	16			b		b				b
α-naphthoic acid		13	1-Naphthoic acid	63			b		b				b
β-naphthoic acid		14	2-Naphthoic acid	64			b		b				b
9-anthroic acid		17	9-Anthroic acid (not used)	70			b		b				b
2′-3′-dideoxyadenosine		18	2,3-Dideoxyadenosine	68			b		b				b
2′-deoxyadenosine		19	2-Deoxyadenosine	69			b		b				b
prednisolone		20	Prednisolone (not used)	71			b		b				b
hydrocortisone		21	Hydrocortisone	65			b		b				b
hydrocortisone-21-pimelamide		22	Hydrocortisone-21-pimelamide	66			b		b				b
N,*N*-dimethylacetamide	Ac-NMe_2 [h]		N,N-Dimethylacetamide	9									h

methyl acetate	Ac-OMe[h]		Methyl acetate	10									h
2-(acetylamino)-*N*,*N*-dimethylacetamide	Ac-G-NMe_2[h]		CH3CONHCH2CONMe2	11									h
methyl (acetylamino)acetate	Ac-G-OMe[h]		CH3CONHCH2CO2Me	12									h
p-toluoylalanine	Tol-A[h]		MeC6H4CONHCH(Me)CO2H	26									g,h
p-toluoyldialanine	Tol-A-A[h]		MeC6H4CONHCH(Me)CONHCH(Me)CO2H	27									g,h
p-toluoylsarcosine	Tol-Sar[h]		MeC6H4CON(Me)CH2CO2H	29									g,h
p-toluoylglycylsarcosine	Tol-G-Sar[h]		MeC6H4CONHCH2CON(Me)CH2CO2H	31									g,h
p-tolylacetic acid	MPA-OH[h]		MeC6H4CH2CO2H	36						h			g,h
N-methyl-2-*p*-tolylacetamide	MPA-NHMe[h]		MeC6H4CH2CONHMe	37						h			h
N,*N*-dimethyl-2-*p*-tolylacetamide	MPA-NMe_2[h]		MeC6H4CH2CONMe2	38	h					h			h
p-tolylacetic acid methyl ester	MPA-OMe[h]		MeC6H4CH2CO2Me	39	h					h			h
(2-*p*-tolylacetylamino)acetic acid	MPA-G-OH[h]		MeC6H4CH2CONHCH2CO2H	40						h			h
N-methylcarbamoylmethyl-2-*p*-tolylacetamide	MPA-G-NHMe[h]		MeC6H4CH2CONHCH2CONHMe	41						h			h
N,*N*-dimethylcarbamoylmethyl-2-*p*-tolylacetamide	MPA-G-NMe_2		MeC6H4CH2CONHCH2CONMe2	42	h					h			h
(2-*p*-tolylacetylamino)acetic acid methyl ester	MPA-G-OMe		MeC6H4CH2CONHCH2CO2Me	43	h					h			h
4-methylcarbamoylmethyl-phenyl)acetic acid	CMPA-NHMe[h]		CO2HCH2C6H4CH2CONHMe	44									g,h
{4-[2-(dimethylamino)-2-oxoethyl]phenyl}acetic acid	CMPA-NMe_2[h]		CO2HCH2C6H4CH2CONMe2	45									g,h
[4-(2-{[2-(dimethylamino)-2-oxoethyl]-amino}-2-oxoethyl)phenyl]acetic acid	CMPA-G-NMe_2[h]		CO2HCH2C6H4CH2NHCH2CONMe2[i]	46									h
phenylacetic acid			Phenylacetic acid	47		c	c						c
D-(–)-mandelic acid			Mandelic acid	48		c	c						c
DB-67 lactone[j]													i
phenylethylamine			2-Phenylethylamine	56									j
p-hydroxyphenylethylamine			*p*-Hydroxy-2-phenylethylamine	57									j
N-methyltyramine			*p*-Hydroxy-*N*-methyl-2-phenylethylamine	58									j
N,*N*-dimethyltyramine			*p*-Hydroxy-*N*,*N*-dimethyl-2-phenylethylamine	59									j
p-methoxyphenylethylamine			*p*-Methoxy-2-phenylethylamine	60									j
N-methyl-*O*-methyltyramine			*p*-Methoxy-*N*-methyl-2-phenylethylamine	61									j
4-ethylphenol			4-Ethylphenol	62									j
Ethane[k]			Ethane	4									
helium[k]			Helium	1									
neon[k]			Neon	2									
hydrogen[k]			Hydrogen	3									

[a]Xiang and Anderson (1994a).[8]
[b]Xiang and Anderson (1994b).[9]
[c]Xiang and Anderson (1995).[10]

[d]Xiang, Xu and Anderson (1998).[11]
[e]Mayer, Xiang and Anderson (2000).[12]
[f]Mayer and Anderson (2002).[13]
[g]Mayer et al. (2003).[14]
[h]Cao et al. (2008).[15]
[i]Joguparthy et al. (2008).[16]
[j]Tejwani et al. (2009).[17]
[i]Chemical formula seems to be incorrect.
[j]Compound not considered by Abraham and Acree (2012).[1]
[k]Compound considered by Abraham and Acree (2012),[1] but not by Xiang, Anderson and coworkers.[8-17]

Table S3. List of numerical oversights in Abraham and Acree's[1] Table 2.

Compound name	Compound name or formula and place in numerical order of Abraham and Acree's Table 2		Quantity	Value listed by Abraham and Acree	Correct value
water	Water	5	log *P*(10diene)	−3.82	−3.92 [a]
p-toluoyldialanine	MeC6H4CONHCH(Me)CONHCH(Me)CO2H	27	V	2.2146	2.1490 [b]
4-methylcarbamoylmethyl-phenyl)acetic acid	CO2HCH2C6H4CH2CONHMe [c]	44	V	1.4699	1.6108 [b]
{4-[2-(dimethylamino)-2-oxoethyl]phenyl}acetic acid	CO2HCH2C6H4CH2CONMe2	45	V	1.6108	1.7517 [b]
[4-(2-{[2-(dimethylamino)-2-oxoethyl]-amino}-2-oxoethyl)phenyl]acetic acid	CO2HCH2C6H4CH2NHCH2CONMe2	46	V	1.9924	2.1490 [b]
α-carboxy-*p*-methylhippuric acid	CO2HCH2C6H4CH2NHCH2CO2H	54	V	1.6695 [d]	1.6852 [b]
α-methoxy-*p*-toluic acid	MeOCH2C6H4CO2H	19	V	1.2720 [d]	1.2722 [b]
α-cyano-*p*-toluic acid	CNCH2C6H4CO2H	20	V	1.2270 [d]	1.2273 [b]
α-hydroxy-*p*-toluic acid	HOCH2C6H4CO2H	21	V	1.1310 [d]	1.1313 [b]

[a]Value given by Xiang and Anderson[9] is $(1.2 \pm 0.1) \times 10^{-4}$; $\log_{10}(1.2 \times 10^{-4}) = -3.92$.
[b]Value given by Absolv program from ACD/Labs' ADME Suite (Vers. 5.0).[20]
[c]Chemical formula seems to be incorrect.
[d]The slight difference from the correct value is flagged for completeness, but we regard it as numerically inconsequential.