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Response to “Comment on ‘Structural Determinants of Drug Partitioning in Surrogates of Phosphatidylcholine Bilayer Strata’”

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Abstract

We used the solvatochromic correlation to explain the influence of characteristics of studied compounds on the partition coefficients (P) measured using *n*-hexadecane (C16) and the novel headgroup surrogate (diacetyl phosphatidylcholine - DAcPC), and compare them with those in other systems, including the C16/water (W) system. The comment analyzes, why our correlation for the C16/W system has the standard deviation (SD) higher than that published previously. The main reason is that in our, much smaller, data set the measured P values are complemented by the P values predicted by a reliable, unrelated method. We believe that this approach is acceptable for the aforementioned comparison. We did not use just experimental values, as suggested in the comment, because the solvatochromic correlation, although exhibiting 35 % reduction in the SD, was accompanied by a sign change of one of the regression coefficients. The recommended use of special solvatochromic solute characteristics for a few compounds, and replacement of a predicted $P_{C16/W}$ value by the experimental value resulted in improved correlations. The observed differences between our correlation and those published in the comment and in a previous paper do not affect our main conclusions regarding the solvation of solutes in the surrogates (DAcPC and C16) of intrabilayer strata.

Keywords

transfer energy; partition coefficient; headgroups; core; interface; *n*-hexadecane/water partitioning; bilayer core surrogate; solvatochromic correlation; linear solvation energy relationship (LSER); Abraham solvation model; diacetyl phosphatidylcholine (DAcPC)

This is a response to the comment¹ pertaining to our paper,² which reports and analyzes the partitioning data of compounds between a novel headgroup surrogate phase, hydrated diacetyl phosphatidylcholine (DAcPC) and *n*-hexadecane (C16) as established core surrogate. A partial aim of our study, which is related to the scope of the comment, is described at the bottom of page 3686: “To help with mechanistic understanding of the

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measured [C16/DAcPC partitioning] data and their comparison with those measured in other systems, the values of all used partition coefficients were correlated using the solvatochromic equation” (eq 1). One of the other systems was the C16/W system (W stands for water), and the comment raises several issues with our use of the solvatochromic equation for this system: (1) our selection of a H-bond basicity parameter for a few compounds, and the use of a predicted instead of an experimental value of the partition coefficient for one compound; (2) magnitude of the standard deviation (SD) for our solvatochromic correlation, which is higher than the SD value of a published correlation; and (3) the origin of our data set. We will first highlight the salient features of the solvatochromic approach, to provide the basis for discussing these concerns, and then address the issues in the shown order.

The solvatochromic approach was originally developed to describe effects of solvents on reaction rates and other phenomena using the solute characteristics: overall H-bond acidity (*A*), overall H-bond basicity (*B*), dipolarity/polarizability, (*S*) and the characteristic volume (*V*).³⁻⁷ The approach was modified by replacing the spectral compound characteristics, *A*,⁸ *B*,^{8;9} and *S*,¹⁰⁻¹² by their counterparts derived either directly from H-bonding measurements⁸ or by back-calculation from gas-chromatographic^{10;11} or partitioning^{9;12} data, and re-defining excess molar refraction (*E*).¹³ The dependent variable of the solvatochromic equation can be any suitable solvation-related phenomenon, expressed in the form proportional to the solvation free energy change; shown is the partition coefficient (*P*):

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

The coefficients *a*, *b*, *s*, *e*, *v*, and *c* are quantified by multiple linear regression of experimental data, and reflect the solvent properties or, for *P*, their difference between the two phases. Equation 1, generally applicable to neutral molecules, was recently extended to ionized molecules.¹⁴⁻¹⁷ The approach is also referred to as the (polyparameter) linear solvation (or free) energy relationship (LSER,⁶ LFER,¹⁸ pp-LFER¹⁹), and the Abraham (solvation) model.^{20;21}

With experiment-based solute characteristics *A*, *B*, *S*, *E*, and *V*, eq 1 represents a correlation between different experimental systems, and achieves high quality for proper dependent variables ($r^2 > 0.98$, where *r* is the correlation coefficient).²² To expand eq 1 to a structure-based tool, predicting the solvation-related properties of compounds lacking experiment-based characteristics or even compounds before synthesis, experiment-based solute characteristics were correlated with structure using group-contribution techniques²³ and quantum mechanical calculations.²⁴ While the correlations²³ are excellent for the additive characteristics *E* and *V*, those for *A*, *B*, and *S* explain only 89–92% of experimental variance.²⁵ Consequently, the quality of correlations using eq 1 with predicted solute characteristics is lower than when experiment-based solute characteristics are used and deteriorates with increasing dissimilarity to measured compounds and complexity of solute molecules.

Quality of the solvatochromic correlation (eq 1) also suffers when dealing with solvation-related phenomena in heterogeneous systems, such as blood,²⁶⁻³⁰ tissues^{26-28;30;31} or more

complex biological systems,³²⁻³⁹ even when experiment-based solvation characteristics are used. Here, several binding (saturable) and partitioning (nonsaturable) processes take place, and each is characterized by its own association constant (K) or partition coefficient (P). To create a conceptual correlation, first the mass balance needs to be used to generate a proper description for the complex partition coefficient as a function of the K s and P s for involved processes,³¹ and eq 1 has to be applied to replace each K and P . The resulting expression is usually nonlinear in the regression coefficients a , b , s , e , v , and c , which are specific for each process. If eq 1 is used directly for the complex partition coefficient of the process in a heterogeneous system, the resulting empirical correlation is usually weaker, and the meaning of regression coefficients a , b , s , e , v , and c as solvent characteristics is lost.

The solvatochromic approach has found wide-spread application in the analysis of solute-solvent interactions and for prediction of solvation-related properties in chromatography, preclinical drug development, and environmental toxicology. The approach has been under extensive development over several decades. Keeping track of the best correlations, experiment-based solute characteristics and their predictions was simplified by creating the commercial Absolv software,²² in close collaboration with M. H. Abraham,²⁵ who significantly contributed to the development of the solute characteristics and their prediction from structure.²⁵

The comment¹ to our paper² is based on the published solvatochromic correlation for the C16/W partition coefficients of 370 compounds.⁴⁰ The published correlation does not contain the errors of regression coefficients, so we recalculated the correlation⁴¹ using the original data, after correcting the typos for the characteristics volumes (V) of two tetrachloroethylenes and three tetrachlorophenols.⁴⁰ The results, summarized in eq 2 (Table 1), are practically identical, considering the rounding errors of the used data, with the original equation.⁴⁰ This is certainly an extraordinary correlation, which can only be obtained using very accurate data. Unfortunately, it is difficult, if not impossible, to assess the errors of the original $P_{C16/W}$ data: the authors state that the used 370 $P_{C16/W}$ values were published previously⁴⁰ but the referenced publication⁴² only reports 270 values. Let us, at least, have a look at general characteristics of the data. The $P_{C16/W}$ values were mostly obtained indirectly as the ratio of the C16/gas (G) and W/G Ostwald (partition) coefficients.⁴⁰

The C16/G values were determined by gas chromatography with C16 as stationary phase.⁴³ The method is very precise but the surface/volume ratio of a stationary phase is much higher than that in a typical two-phase system used in partitioning experiments. Consequently, the undesirable effect of interfacial partitioning, which may be significant for amphiphilic compounds, will be much more pronounced in the former system. Indeed, the differences between the presented $P_{C16/W}$ values and those determined by other techniques are minimal for nonpolar solutes but, for polar solutes, may reach several tenths of log units.⁴⁴

The W/G Ostwald coefficients were taken from previous collections,⁴⁵⁻⁴⁷ and, as the authors state, have much larger experimental errors than their C16/G counterparts.⁴² It is understandable, taking into account inherent problems with sampling the gas phase. Some of the used data were published as early as in the 1930s, before the advent of gas

chromatography and pH-metry.⁴⁸ In these experiments, the amount of a compound in the air bubbling through the aqueous compound solution was determined after trapping in an appropriate solution. The aqueous concentrations needed to be quite high. For some compounds, such as alkanolic acids (0.12–0.28 M)⁴⁸ and alkylpyridines (~2mM),⁴⁹ the high concentrations suppressed ionization, so the ionization correction was not necessary. However, if the correction was still needed, as for alkylamines (25–33 mM),⁴⁸ the pK_a values from diluted solutions might provide a less than perfect representation of real conditions. Unfortunately, the performed ionization corrections are not described, and their impact on the accuracy of the collected data⁴² cannot be assessed. The errors could also be larger for compounds having the Ostwald coefficients calculated from the results of two independent experiments, providing vapor pressures and aqueous solubilities.

We recognize the curating expertise of M. H. Abraham and his coworkers, and believe that most of the C16/W partitioning data for 370 compounds⁴⁰ are of acceptable quality. Our trust in these data is documented by using most of them as a part of the data set for our ClogP-fragmentation based correlation,⁵⁰ and utilizing the respective correlation (eq 2, Table 1)⁴⁰ as a reference in our paper.² However, as indicated in the previous paragraphs, this solid data set probably does not possess extraordinary accuracy that would be required for the especially tight correlations with structure, such as eq 2 (Table 1).⁴⁰ Therefore, we expect that the current SD = 0.124 will increase as more compounds are added to the correlation.

The authors¹ dispute our use of the H-bond basicity characteristics, B , for some compounds. The Absolv module in the ACD Percepta software²² shows the solvatochromic correlations for most systems, including the C16/W system, with B^0 and not with the B basicity parameter. We assumed that the current version of this software, developed in close collaboration with M. H. Abraham,²⁵ is the best reference for a constantly evolving system of solvatochromic solute characteristics. This led us to use B^0 in all our correlations,² which is a correct approach for all used systems except the C16/W system. (Unaware of the two types of B characteristics, we wanted to keep the symbols simple, and marked B^0 as B everywhere in the article²). The authors¹ correctly suggest that, for three compounds, we should have used the following characteristics: for aniline, $B = 0.41$ instead of $B^0 = 0.50$; for 4-aminoacetophenone, 0.65 instead of 0.77; and for quinolone 0.54 instead of 0.51. The Absolv software²² also suggests the values $B = 0.30$ for both 3- and 4-bromoaniline, while the B^0 values are 0.34 and 0.35, respectively. Although the differences between B and B^0 are small, the corresponding regression coefficient b is the largest in the set (Table 1), and the improvements in the correlations are observable (compare eq 4 with original B^0 coefficients with eq 6 using the three B values suggested in the comment, and with eq 7 using all five B values). The authors¹ also point out that we used a predicted value⁵⁰ of $\log P_{C16/W}$ for N,N-dimethylaniline, although experimental $\log P_{C16/W} = 2.17$ was available.⁴⁰ These objections are valid, and we thank the authors for bringing them to our attention. All C16/W correlations listed in Table 1, except eq 4 that shows our original correlation,² are using the new set of solute characteristics and the experimental $\log P_{C16/W}$ for N,N-dimethylaniline, resulting in improved statistical indices. These amendments also caused minor changes in the correlations for other systems, which are listed in our original Table 3.²

The comment¹ authors analyze why our solvatochromic correlation for 78 C16/W partition coefficients has $SD = 0.412$ (eq 4, Table 1),² which is much higher than eq 2 (Table 1).⁴⁰ We wanted to use the solvatochromic equations for the studied compounds,² rather than the previously published solvatochromic equation for 370 compounds¹ because the regression coefficients depend on the used compounds. First, we tried an obvious choice: the use of all 113 compounds, for which the experimental C16/DAcPC values were measured. For these compounds, only 45 experimental $P_{C16/W}$ values were available, including N,N-dimethylaniline. We added 68 values predicted by our correlation based on the ClogP fragmentation,⁵⁰ mentioned above. The correlation (eq 3, Table 1) was good but coefficients b , v , and c deviated significantly (by 0.5-0.6) from those in the reference eq 2.⁴⁰ As discussed above, better correlations result from the use of the experiment-based solute characteristics, which were available for 78 studied compounds. The correlation improved (eq 4, Table 1), and none of the coefficient deviated more than 0.4 from those of the reference eq 2. The authors¹ suggest that we should have only used 44 compounds with experimental $P_{C16/W}$ values. However, as we needed the common data set also for the O/W system, we could only use 38 compounds (including N,N-dimethylaniline), for which both C16/W and O/W values were available (Table S1).² The correlation (eq 5, Table 1) with new B values for some compounds, as suggested in the comment¹ (see above), improved further ($SD = 0.224$), and the coefficients values became closer to the reference eq 2. However, coefficient c , having a specific meaning for the studied process,²¹ changed sign. In addition, the 38 compounds only represent 34% of our data set. For these reasons, rather than using the correlation for the 38 compounds, we decided to use 78 compounds with calculated and predicted C16/W and O/W values (eq 4, Table 1). After all corrections (eq 7, Table 1), statistical indices improved ($SD = 0.335$) as compared with the original eq 4, although they still did not reach the quality of those in the reference eq 2 ($SD = 0.124$). I believe that for our purpose, stated in the first paragraph, this approach is acceptable.

The comment¹ authors state that we “provided no literature reference for the $\log P_{C16/W}$ correlation or dataset of $\log P_{C16/W}$ values and solute descriptors other than that tabulated in Table S1.” However, a motivated reader will find that the paper² and its Supporting Information do contain all necessary information. As the authors noted, footnote a at the bottom of Table 3 states that 78 compounds with experiment-based solvatochromic parameters were used. Footnote b says that the data are listed in Table S1 in the Supporting Information. Footnote 1 to Table S1 states that “the C16/W partition coefficients were collected or *obtained* [emphasis added] as described in” our paper⁵⁰ reporting a very good correlation of the C16/W partition coefficients using the ClogP-based fragmentation, as mentioned above. The word “obtained” in footnote 1 refers to the $\log P_{C16/W}$ values, calculated using this correlation, and listed in a clearly marked, separate column. The 78 data points used in our solvatochromic correlation are the measured *and calculated* values (if measured values are not available) of the C16/W partition coefficients in Table S1, for compounds for which experiment-based values of solvatochromic solute parameters (shaded blue) are available. It seems that the authors, although discussing several options, also anticipate that this was the case, as shown in the paragraph following the one with eq 4,¹ where they chide us for the use of the 78 data points. The calculated partition coefficients are acceptable for our aim, which is stated in the first paragraph, because they were obtained

from a very good correlation by an approach that is not associated with the solvatochromic correlation.

To compare the impact of the discussed suggestions on the conclusions of our paper,² the solvatochromic correlation of the C16/DACPC data is listed in Table 1 as eq 8, and the relations between the regression coefficients and those obtained in solvatochromic correlations for various data sets, as formulated in the paper,² are shown as eq 9. Obviously, our conclusions would not change, if any of the discussed data sets was used. This is the most important outcome of our response to the comment.¹ We are grateful to the comment¹ authors for the opportunity to better explain the origin of our data and for correction of both the *B* factors for the three or five compounds as well as the $P_{C16/W}$ value for *N,N*-dimethylaniline, regardless of the lack of impact these changes had on the final conclusions of our paper.²

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Table 1

Solvatochromic Correlations for the C16/W Partitioning Using Different Data Sets and for the C16/DAcPC Partitioning.

eq. no.	number of log P values ^a			solute characteristics		regression coefficients $\pm$ errors							statistical indices		
	total	exptl	pred	exptl	pred	a	b	s	e	ν	c	r^2	SD	F	
2 ^b	370	370	0	370	0	-3.568 $\pm$ 0.038	-4.870 $\pm$ 0.037	-1.616 $\pm$ 0.032	0.665 $\pm$ 0.028	4.434 $\pm$ 0.025	0.087 $\pm$ 0.023	0.996	0.125	20111	
3 ^c	113	45	68	78	35	-3.540 $\pm$ 0.274	-4.290 $\pm$ 0.290	-1.914 $\pm$ 0.274	0.915 $\pm$ 0.204	3.755 $\pm$ 0.242	0.635 $\pm$ 0.211	0.961	0.517	524	
4 ^d	78	44	34	78	0	-3.300 $\pm$ 0.242	-4.568 $\pm$ 0.298	-1.982 $\pm$ 0.245	0.855 $\pm$ 0.202	4.197 $\pm$ 0.232	0.342 $\pm$ 0.201	0.971	0.412	489	
5 ^e	38	38	0	38	0	-3.497 $\pm$ 0.175	-4.894 $\pm$ 0.219	-1.554 $\pm$ 0.269	0.491 $\pm$ 0.188	4.682 $\pm$ 0.273	-0.055 $\pm$ 0.200	0.989	0.224	602	
6 ^f	78	45	33	78	0	-3.161 $\pm$ 0.199	-4.886 $\pm$ 0.249	-1.877 $\pm$ 0.201	0.754 $\pm$ 0.166	4.300 $\pm$ 0.192	0.276 $\pm$ 0.166	0.981	0.339	725	
7 ^g	78	45	33	78	0	-3.168 $\pm$ 0.197	-4.884 $\pm$ 0.246	-1.891 $\pm$ 0.198	0.749 $\pm$ 0.165	4.322 $\pm$ 0.190	0.266 $\pm$ 0.164	0.981	0.335	742	
8 ^h	78	78	0	78	0	-3.735 $\pm$ 0.263	-4.033 $\pm$ 0.328	-1.575 $\pm$ 0.265	-0.149 $\pm$ 0.220	4.748 $\pm$ 0.254	-0.470 $\pm$ 0.219	0.963	0.451	375	
9 ⁱ						$a_8 < a$	$b_8 \gg b$	$s_8 > s^j$	$e_8 \ll e$	$\nu_8 > \nu$	$c_8 \ll c$				

^aFor N,N-dimethylaniline, experimentally determined log*P*C16/W = 2.17 used except eq 4.

^bMagnitudes of some coefficients and statistical indices exhibit very small deviations from the original correlation, probably because of the rounding in solvation characteristics.

^cFive new *B* values for the compounds suggested in the comment (aniline, 4-aminoacetophenone, and quinolone) plus 3- and 4-bromoaniline.

^dOriginal correlation for comparison.

^eNew *B* values for the suggested compounds plus 3-bromoaniline (4-bromoaniline absent in this data set).

^fThree new *B* values for the suggested compounds shown in footnote c.

^gFive new *B* values as in footnote c.

^hCorrelation for the C16/DAcPC data.

ⁱComparison of the regression coefficients of eq 8 (subscript 8) with those in eqs 2-7 (no subscript).

^jExcept eq 5.