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NONADDITIVE EFFECTS IN THE PARTITIONING BEHAVIOR OF VARIOUS ALIPHATIC AND AROMATIC MOLECULES

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Abstract—Predicting the partition behavior of bifunctional molecules from their molecular structure is a challenge because the combination of two or more functional groups often has nonadditive effects. Data presented here and in the literature reveal that isomers of bifunctional compounds can exhibit partition constants that differ by several orders of magnitude. These effects are not limited to compounds with intramolecular H-bonds. For aliphatic molecules, large effects are found for diones and diesters but not for dioles. For aromatic molecules, large effects are found for compounds with intramolecular H-bonds and also for *p*-isomers with a strong delocalisation of π-electrons over both functional groups as in *p*-nitroaniline and *p*-nitrophenol. Interestingly, these nonadditive effects apply not only to the specific interactions but also to the van der Waals interactions of a molecule. This diversity of possible nonadditive effects makes it difficult to predict partitioning of such polyfunctional molecules. Our results suggest that successful models require either an extensive number of correction factors or a quantum chemical approach. Predicting partitioning of bifunctional molecules to environmental systems might face an additional complication. Unlike with solvents, steric limitations of natural phases may prevent them from forming multiple H-bonds with bifunctional molecules. Our experimental results, however, indicate that this situation does not occur, as the H-bond-interaction behavior of bifunctional molecules in humic matter and on quartz was the same as it was in various solvent systems.

Keywords—Partitioning Quantitative structure–property relationships Multifunctional Sorption

INTRODUCTION

An increasing number of chemicals of environmental concern contain two or more functional groups, such as many pesticides and pharmaceuticals. Many quantitative structure–property relationships (QSPRs) that predict the partitioning properties of chemicals from their molecular structures assume that specific functional groups contribute additively to the partitioning and are not influenced by the presence of other functional groups. However, nonadditive effects are known to occur. Such effects can be due to intramolecular H-bonds and other electronic effects, such as the delocalization of electrons. The extent of such effects should depend on the type of functional groups involved and their position within the molecule. In most QSPRs such nonadditive effects are accounted for by including specific, empirically derived correction factors to better fit experimental partition data. Here, rather than simply identifying new correction factors for bifunctional molecules, we are interested in improving our mechanistic understanding of nonadditive effects. The number of existing bi- and multifunctional chemicals is so high that it would be unrealistic to empirically derive correction factors for all possible functional group combinations. Instead, it would be desirable to systematically investigate the occurrence of nonadditive effects, find generalized patterns, and potentially develop a general empirical correction method for all bi- or multifunctional molecules. In the search for such patterns, we studied the partition behavior of aliphatic bifunctional isomers (diols, diones, and diesters), which have an increasing distance between the functional groups, as well as various isomers of aromatic bifunctional molecules. For a systematic evaluation of the data, we used Abraham's approach (see the next section) of separating out the various interaction energies, such as van der Waals and H-bond interactions, that contribute to partitioning. The underlying reasoning was that any mechanistic or general pattern in nonadditive effects would become visible only on the level of interaction energies and not on the level of partition coefficients themselves that lump the various types of interactions together. What also must be considered when including bifunctional molecules in QSPRs for environmental phases is that, because of steric limitations, more rigid environmental phases may not be able to form multiple H-bonds with bifunctional molecules. Here, we collected experimental data to examine if such steric limitations are significant. Finally, an alternative to QSPRs are quantum-chemical–based approaches. Because of the fundamental mechanistic approaches taken in such models, they are implicitly better equipped to account for how electronic effects and also conformational effects can influence partitioning behavior. Thus, here we also compare the predictive behavior of frequently used QSPRs with a quantum-chemical model.

THEORETICAL APPROACH

To obtain a comprehensive understanding of the partition properties of a particular compound, its partitioning in various systems needs to be looked at and compared, as different systems vary in their sensitivity to the compound's various interaction properties. For example, the octanol–water partitioning system is very sensitive to the H-bond acceptor property of a solute but not to its H-bond donor property [1]. In contrast, the air–water partition system is sensitive to both the H-bond donor and acceptor properties of a solute [2]. Based on em-

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pirical work, Cramer [3] and, later, others [1,2,4] found that the partition properties of a given compound in any partition system can be fully characterized by five molecular descriptors. This is further corroborated by quantum chemical modeling [5]. With these five molecular descriptors at hand, differences in the partition behavior of various compounds in any partition system can be explained with a general equation of the form [6]

$$\log K_{i12} = s_{12}S_i + a_{12}A_i + b_{12}B_i + l_{12}L_i + v_{12}V_i + c_{12} \quad (1)$$

where K_{i12} is the equilibrium partition constant of an organic solute, i, between two bulk phases 1 and 2 at a given temperature. The capital letters in Equation 1 represent the solute descriptors for the various types of interactions that the solute i can undergo: V_i refers to the McGowan volume of the solute and relates to the cavity formation energy; L_i is its logarithmic hexadecane–air partition constant at 25°C, which accounts for the van der Waals interaction energy of the solute; A_i and B_i are measures for the solute's H-bond acidity and H-bond basicity; and S_i denotes other electrostatic interactions and is called the solute's dipolarity/polarizability. Thus, L_i and V_i represent the nonspecific interactions; A_i, B_i, and S_i represent the specific interactions. The small letters in Equation 1 represent the complementary descriptors of the phases 1 and 2 between which the transfer occurs. These phase descriptors have been published for many common solvent–air and solvent–water partition systems, and they can be determined for new systems from a calibration procedure. Note that Abraham and coworkers use two slightly different types of equations, one for air-condensed phase and one for condensed phase–condensed phase partitioning. Here we prefer Equation 1, which is a modification of the Abraham equations that works for all partition systems [6].

The solute descriptors do not only contain comprehensive information on the partition properties of a compound in a concise form, but they also allow for a mechanistically meaningful distinction of the various types of interactions compounds can have with surrounding phases. Therefore, these descriptors are especially appropriate for a systematic study of the influence of functional groups on partitioning behavior, more so than comparing a plethora of partition data. To experimentally derive these descriptors for a given compound, the measurement of several partition constants in various calibrated partition systems is required (e.g., see [7,8]).

EXPERIMENTAL PROCEDURE

The interaction descriptors for many bifunctional aromatic compounds are already tabulated. However, descriptors for the aliphatic molecules as well as L_i values for some aromatic chemicals were not available and had to be determined experimentally. Of the five descriptors needed to describe a molecule, the McGowan volume, V_i, is the only one that can be calculated via a simple, strictly additive incremental method [9]. The L_i value of a compound can be determined from its net retention volume on an Apolane-87 gas chromatographic (GC) column (Alltech, Deerfield, IL, USA) provided that this column has previously been characterized by measuring the net retention volumes of a set of calibration compounds [10,11]. Similarly, a chemical's S_i and A_i value can also be determined from GC-retention measurements if suitable and calibrated columns are used and if the L_i value is known already. While measurements on two different GC columns would be sufficient, adding measurements on a third column helps to check and improve the consistency of the data. For further details on these measurements, the calibration of the GC columns, and the data evaluation, we refer to a previous paper [8]. The measured retention volumes together with information on the calibrated GC columns for the compounds measured in the present study are given in the *Supporting Information* (http://dx.doi.org/10.1897/08-189.S1).

When the V_i, L_i, S_i, and A_i values of a compound are known, the B_i value (H-bond acceptor property) can be derived using at least one additional partition constant for a system that is sensitive to the B_i value and for which a well-established partition equation exists. For example, if the $\log K_{i\mathrm{OW}}$ is known, B_i can be derived using the respective equation [6]:

$$\log K_{i\mathrm{OW}} = -1.41S_i - 0.18A_i - 3.45B_i + 0.43L_i + 2.41V_i + 0.34 \quad (2)$$

Here we have derived B_i values using literature data for the octanol–water partitioning of our compounds of interest. Obviously, any error in the K_{OW} values would directly result in a respective error in the calculated B_i value. Therefore, it would have been desirable to check these B_i values with partition constants from another system that is also sensitive to the B_i value, such as the air–water partition system. Unfortunately, published air–water partitioning data for the compounds studied here either are not available or are inconsistent with other data and were therefore of no use. Thus, to derive the B_i values of most of our compounds, we relied solely on the published K_{OW} values. For 2,3-butanedione, the literature value of $\log K_{\mathrm{OW}} = -1.34$ [12] appeared questionable, and thus we determined a revised value in our lab (for details, see *Supporting Information*, http://dx.doi.org/10.1897/08-189.S1).

Here we also measured sorption constants for bifunctional aliphatic and aromatic compounds from air to a quartz surface at 90% relative humidity and from air to various types of humic and fulvic acids. The partition systems had been previously calibrated according to the general partition Equation 1 given in Niederer, Goss, and Schwarzenbach [13–15]. It should be noted that these natural partition systems were used for validation purposes only. Equation 1 does not fit partitioning in these natural systems well enough to allow an accurate derivation of solute descriptors.

RESULTS AND DISCUSSION

The interaction descriptors for the aliphatic compounds derived from our experimental partition data are listed in Table 1. Before interpreting these data, it is helpful to briefly recapitulate some general features of these descriptors with regard to how their values are typically influenced by functional groups in monofunctional compounds, such as can be seen in tabulated data collections [1,2]. Some typical values for the descriptors extracted for functional groups of monofunctional compounds are shown in Table S3 in the *Supporting Information* (http://dx.doi.org/10.1897/08-189.S1). It appears that in the case of monofunctional molecules, each alcohol, carboxy, or amine group adds a specific increment to each of the interaction descriptors of the total molecule. An additional CH_2 unit adds only to the V_i and the L_i value of a chemical because it does not contribute to the compound's ability for specific interactions. Ketone, aldehyde, ether, and ester groups add not only to the V_i and L_i value but also to the S_i and B_i value of a molecule; however, they do not contribute to the A_i value because these functional groups possess no ability to act as

Table 1. Descriptor values for bifunctional aliphatic compounds based on experimental partition data together with hypothetical values when assuming additive behavior of the functional groups[a]

	S_i	A_i	B_i	V_i	L_i
Dimethyl oxalate	1.14	0.00	0.65	0.82	3.20
Hypothetical dimethyl oxalate[b]	1.24	0.00	0.90	0.82	3.33
Dimethyl malonate	1.17	0.00	0.75	0.96	3.58
Hypothetical dimethyl malonate[c]	1.22	0.00	0.90	0.96	3.81
Dimethyl succinate	1.13	0.00	0.82	1.10	4.13
Hypothetical dimethyl succinate[d]	1.20	0.00	0.90	1.10	4.17
2,3-Butanedione	0.75	0.00	0.63	0.70	2.27
Hypothetical butanedione[e]	1.40	0.00	1.02	0.70	2.96
2,4-Pentanedione[f]	0.82	0.00	0.64	0.85	3.25
Hypothetical pentanedione[g]	1.36	0.00	1.02	0.85	3.35
2,5-Hexanedione	1.19	0.00	0.84	0.99	3.68
Hypothetical hexanedione[h]	1.40	0.00	1.02	0.99	3.86
1,2-Wthanediol	0.62	0.72	0.90	0.51	2.73
Hypothetical ethanediol[i]	0.84	0.74	0.96	0.51	2.48
1,3-Propanediol	0.74	0.69	0.92	0.65	3.27
Hypothetical propanediol[j]	0.84	0.74	0.96	0.65	3.01
1,4-Butanediol	0.79	0.69	1.01	0.79	3.81
Hypothetical butanediol[k]	0.84	0.74	0.96	0.79	3.58

[a] Values for compounds with hypothetical descriptors result from the assumption of complete additivity (see the main text) by summing descriptor values for the molecules described in the following footnotes.

[b] Methylacetate + methylacetate − ethane.

[c] Methylpropanoate + methylacetate − ethane

[d] Methylbutanoate + methyacetate − ethane.

[e] 2-Butanone + 2-butanone − butane.

[f] The values determined here are almost identical to those reported in Abraham and Leo [28].

[g] 2-Pentanone + 2-pentanone − pentane.

[h] 2-Hexanone + 2-hexanone − hexane.

[i] Ethanol + ethanol − ethane.

[j] 1-Propanol + 1-propanol − propane.

[k] 1-Butanol + 1-butanol − butane.

H-bond donors. Based on these and other published values, it is simple to calculate the descriptor values of many bifunctional molecules under the assumption of *complete additivity.* For example, for 1,3-propanediol, one adds the descriptor values of 1-propanol with 1-propanol and then subtracts the descriptor values of propane. However, it has been long known that descriptors of bifunctional molecules do not always exhibit complete additivity, yet little systematic information can be found on this topic in the literature.

Aliphatic compounds

Table 1 compares experimentally determined descriptor values for various aliphatic compounds with those obtained assuming complete additivity of the functional groups. As can be seen in this table, when two functional groups are direct neighbors or are separated by one CH_2 unit, the specific interactions (S_i and B_i values) are smaller than expected from complete additivity. Note that a difference of 0.25 units in the B_i descriptor results in a difference of 1.2 log units in the air–water partition coefficient. When the functional groups are separated by two CH_2 units, the effects are almost additive. It is interesting to note that not only specific interactions but also nonspecific van der Waals interactions are subject to nonadditive effects. Referring to the tabulated L_i values, it appears that this effect is quite variable: the contributions of two diones to L_i is less than additive, for the diols it is more than additive, and for the diesters it is nearly additive. Also, the effect is more distinct in compounds for which resonance structures can be drawn, such as dimethyl malonate and 2,3-butanedione.

Only a small effect of intramolecular H-bonds on the specific interactions of the diols is observed. The A_i, B_i, and S_i descriptors show an almost additive behavior even for the 1,2-ethanediol. This indicates that it is more favorable for the OH groups to form H-bonds with water molecules than with themselves. This finding is supported elsewhere based on molecular modeling and spectral information [16,17].

Aromatic compounds

Table 2 shows descriptor values for bifunctional aromatic molecules from the literature and partially from the present work and compares them with those values that would be expected assuming complete additivity of the functional groups. The following general trends can be identified: *Meta-* and *para*-substituted compounds have descriptors that are similar to each other and to those expected for additive behavior. Exceptions occur only for compounds with strong resonance effects (compare resonance structures and Hammett sigma values [18]), such as in *p*-nitrophenol and *p*-nitroaniline. The latter compounds have higher S_i and L_i values than those of the *meta*-isomers or based on the additivity assumption.

In all cases when *ortho*-substituted isomers are capable of forming intramolecular H-bonds, their descriptor values differ significantly from the *meta-* and *para*-isomers. The most prominent example of this can be seen for 2-nitrophenol. Note that these effects for the *ortho*-substituted aromatics can also be quite strong in cases when chlorine is positioned next to an H-bond-donating functional group, such as with the chlorophenols and chloroanilines. No descriptors are available for such *ortho*-isomers that cannot form intramolecular H-bonds, such as 1,2-dinitrobenzene, though there are partition data for such compounds that indicate that they behave similar to the *meta-* and *para*-isomers (see Table 3). General rules as to which of the descriptors are affected by intramolecular H-bonds in ar-

Table 2. Descriptor values for bifunctional aromatic compounds from the literature together with hypothetical values when assuming completely additive behavior of the functional groups[a]

	S_i	A_i	B_i	V_i	L_i	Reference
2-Nitrophenol	1.05	0.05	0.37	0.95	4.76	[2]
3-Nitrophenol	1.57	0.79	0.23	0.95	5.69	[2]
4-Nitrophenol	1.72	0.82	0.26	0.95	5.88	[2]
Hypothetical nitrophenol[b]	1.48	0.60	0.45	0.95	5.54	
2-Chlorophenol	0.88	0.32	0.31	0.90	4.18	[2]
3-Chlorophenol	1.06	0.69	0.15	0.90	4.77	[2]
4-Chlorophenol	1.08	0.67	0.21	0.90	4.78	[2]
Hypothetical chlorophenol[c]	1.02	0.60	0.24	0.90	4.64	
2-Chloroaniline	0.92	0.25	0.31	0.94	4.67	[2]
3-Chloroaniline	1.10	0.30	0.30	0.94	4.91	[2]
4-Chloroaniline	1.13	0.30	0.32	0.94	4.89	[2]
Hypothetical chloroaniline[d]	1.09	0.26	0.34	0.94	4.80	
2-Nitroaniline	1.37	0.30	0.36	0.99	5.63	[2]
3-Nitroaniline	1.71	0.40	0.35	0.99	5.88	[2]
4-Nitroaniline	1.91	0.42	0.38	0.99	6.34	[2]
Hypothetical nitroaniline[e]	1.55	0.26	0.55	0.99	5.70	
2-Methoxyphenol	0.91	0.22	0.52	0.97	4.45	[2]
4-Methoxyphenol	1.17	0.59	0.38	0.97	4.80	[2]
3-Methoxyphenol	1.17	0.57	0.48	0.97	4.77	[29,30]
Hypothetical methoxyphenol[f]	1.11	0.60	0.46	0.97	4.87	
2-Methoxyaniline	1.03	0.23	0.50	1.02	4.82	[2]
3-Methoxyaniline	1.22	0.25	0.55	1.02	5.02	[2]
4-Methoxyaniline	1.19	0.23	0.61	1.02	4.95	[2]
Hypothetical methoxyaniline[g]	1.18	0.26	0.56	1.02	5.03	
2-Cyanophenol	1.33	0.78	0.34	0.93	4.53	[29,30]
3-Cyanophenol	1.55	0.77	0.28	0.93	5.18	[2]
4-Cyanophenol	1.63	0.79	0.30	0.93	5.42	[2]
Hypothetical cyanophenol[h]	1.48	0.60	0.50	0.93	5.02	
1,2-Dihydroxybenzene	1.07	0.85	0.52	0.83	5.06	[29,30]
1,3-Dihydroxybenzene	1.11	1.09	0.52	0.83		[31]
1,4-Dihydroxybenzene	1.27	1.06	0.57	0.83		[30,31]
Hypothetical dihydroxybenzene[i]	1.26	1.20	0.48	0.83	4.75	
Dimethylphatalate	1.41	0.00	0.88	1.43	6.05	[32]
Hypothetical dimethylphtalate[j]	1.49	0.00	0.93	1.43	5.98	
1,3-Dimethoxybenzene	1.01	0.00	0.45	1.12	5.02	[1,30]
1,4-Dimethoxybenzene	1.00	0.00	0.50	1.12	5.04	[1,33]
Hypothetical dimethoxybenzene[k]	0.96	0.00	0.44	1.12	4.99	
1,3-Dinitrobenzene	1.600	0.00	0.47	1.06	5.84	[34], this work
1,4-Dinitrobenzene	1.630	0.00	0.41	1.06	5.79	[34], this work
Hypothetical dinitrobenzene[l]	1.700	0.00	0.42	1.06	6.33	
4-Nitroanisol	1.29	0.00	0.40	1.09	5.85	[34], this work
Hypothetical nitroanisol[m]	1.33	0.00	0.43	1.09	5.66	

[a] Values for compounds with hypothetical descriptors result from the assumption of complete additivity (see the main text) by summing descriptor values for the molecules described in the following footnotes.

[b] Nitrobenzene + phenol − benzene.

[c] Phenol + chlorobenzene − benzene.

[d] Aniline + chlorobenzene − benzene.

[e] Aniline + nitrobenzene − benzene.

[f] Anisol + phenol − benzene.

[g] Anisol + aniline − benzene.

[h] Benzonitrile + phenol − benzene.

[i] Phenol + phenol − benzene.

[j] Methylbenzoat + methylformat.

[k] Anisol + anisol − benzene.

[l] Nitrobenzene + nitrobenzene − benzene.

[m] Anisol+nitrobenzene − benzene.

omatic molecules and to which extent do not seem to be discernable.

The descriptor values discussed previously provide a good systematic overview of the effects of two functional groups at various positions in a molecule. However, the descriptors themselves are too abstract to provide any direct impression on their corresponding impact on actual partition constants (as they must be seen in the context of their corresponding system-specific descriptors [Eqn. 1]). We have therefore collected some representative data for air–water, octanol–water, and humic acid–air partitioning (calculated and measured data from this work and the literature) in Table 3. The data reveal that the maximum difference in partition constant between various isomers of a bifunctional aromatic molecule can amount to several orders of magnitude as in the nitrophenols. Similarly, measured partition constants can also differ by orders of magnitude from their value predicted based on the assumption of additivity. In general, these effects are much more pronounced for air–water partitioning than for octanol–water partitioning. This may be due to the fact that the latter process does not respond to the H-bond donor property of the solute. For aliphatic molecules, more than one log unit difference in the *K*

Table 3. Predicted and experimental octanol–water, air–water, and humic acid–air partition constants for bifunctional molecules and predicted values assuming additive behavior of the functional groups.[a] Superscripts in the reference columns refer to calculated values (see footnotes)

	Log K_{OW}	Reference	Log K_{AW}	Reference	Log $K_{HA/air}$	Reference
1,2-Ethanediol	−1.36	[35]	−7.73	[b]		
Hypothetical ethanediol	−2.00	[c]	−8.44	[b]		
1,3-Propanediol	−1.04	[35]	−7.87	[b]		
Hypothetical propanediol	−1.73	[c]	−8.32	[b]		
1,4-Butanediol	−0.83	[35]	−8.31	[b]		
Hypothetical butanediol	−1.18	[c]	−8.19	[b]		
Dimethyl oxalate	−0.17	[35]	−4.38	[b]		
Hypothetical dimethyl oxalate	−1.10	[c]	−5.86	[b]		
Dimethyl malonate	−0.05	[35]	−4.75	[b]		
Hypothetical dimethyl malonate	−0.53	[c]	−5.69	[b]		
Dimethyl succinate	0.35	[35]	−4.91	[b]		
Hypothetical dimethyl succinate	−0.01	[c]	−5.47	[b]		
2,3-Butanedione	−0.21	[d]	−3.33	[b]		
Hypothetical butanedione	−2.18	[c]	−6.90	[b]		
2,4-Pentanedione	0.4	[35]	−3.63	[b]		
Hypothetical pentanedione	−1.62	[c]	−6.65	[b]		
2,5-Hexanedione	−0.27	[35]	−5.22	[b]		
Hypothetical hexanedione	−1.12	[c]	−6.62	[b]		
2-Nitrophenol	1.85	[1]	−3.36	[2]	4.63 (60°C)	[d]
3-Nitrophenol	2.00	[1]	−7.06	[2]	7.15 (60°C)	[d]
4-Nitrophenol	1.91	[1]	−7.81	[2]	7.71 (60°C)	[d]
Hypothetical nitrophenol	1.26	[c]	−7.10	[b]		
2-Chlorophenol	2.29	[c]	−3.34	[2]	4.05 (60°C)	[d]
3-Chlorophenol	2.64	[c]	−4.85	[2]	5.91 (60°C)	[d]
4-Chlorophenol	2.53	[c]	−5.16	[2]	6.02 (60°C)	[d]
Hypothetical chlorophenol	2.12	[c]	−4.83	[b]		
2-Chloroaniline			−3.60	[2]		
3-Chloroaniline			−4.27	[2]		
4-Chloroaniline			−4.33	[2]		
Hypothetical chloroaniline			−4.19	[b]		
2-Nitroaniline	1.85	[1]	−5.41	[36]	5.41 (60°C)	[d]
3-Nitroaniline	1.37	[1]	−6.49	[2]	6.59 (60°C)	[d]
4-Nitroaniline	1.39	[1]	−7.54	[2]	7.44 (60°C)	[d]
Hypothetical nitroaniline	1.05	[c]	−6.46	[b]		
2-Methoxyphenol	1.32	[1]	−4.09	[2]		
4-Methoxyphenol	1.58	[1]	−5.62	[2]		
3-Methoxyphenol	1.34	[c]				
Hypothetical methoxyphenol	1.52	[c]	−6.00	[b]		
2-Methoxyaniline			−4.49	[2]		
3-Methoxyaniline			−5.35	[2]		
4-Methoxyaniline			−5.49	[2]		
Hypothetical methoxyaniline			−5.36	[b]		
2-Cyanophenol			−6.48	[b]		
3-Cyanophenol	1.70	[1]	−6.92	[b]		
4-Cyanophenol	1.60	[1]	−7.38	[b]		
Hypothetical cyanophenol	0.82	[c]	−7.15	[b]		
1,2-Dihydroxybenzene	0.88	[1]	−7.58	[b]	6.14 (60°C)	[d]
1,3-Dihydroxybenzene	0.80	[1]			7.08 (60°C)	[d]
1,4-Dihydroxybenzene	0.59	[1]			7.26 (60°C)	[d]
Hypothetical dihydroxybenzene	0.74	[c]	−8.91	[b]		
2-Nitroanisole					6.30 (15°C)	[d]
3-Nitroanisole					5.88 (15°C)	[d]
4-Nitroanisole					6.55 (15°C)	[d]
1,2-Dinitrobenzene					5.79 (60°C)	[d]
1,3-Dinitrobenzene	1.54	[c]	−5.10	[b]	5.82 (60°C)	[d]
1,4-Dinitrobenzene	1.68	[c]	−4.84	[b]	5.75 (60°C)	[d]
Hypothetical dinitrobenzene	1.78	[c]	−5.30	[b]		
2,4-Dinitrotoluene					6.54 (60°C)	[d]
2,3-Dinitrotoluene					6.24 (60°C)	[d]
2,6-Dinitrotoluene					6.38 (60°C)	[d]
1,3-Dimethoxybenzene	2.22	[c]	−3.25	[b]		
1,4-Dimethoxybenzene	2.07	[c]	−3.48	[b]		
Hypothetical dimethoxybenzene	2.30	[c]	−3.09	[b]		

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[a] Experimental data or calculated data (based on the descriptor values in Table 1 and 2) are shown depending on data availability. Calculated values for K_{OW} and K_{AW} are expected to be quite accurate with a standard deviation of 0.15 log units. This accuracy and the fact that the calculation method is based on experimental molecular descriptors let us suggest that these values are suitable for an independent validation of the models tested here. Only experimental data are shown for $K_{HA/air}$, as calculations based on the descriptors have a standard deviation of 0.3 log units, which is too high to allow a meaningful comparison.

[b] Calculated with descriptors from Table 1 and 2 according to $\log K_i \mathrm{AW} = -2.07\ S_i - 3.67\ A_i - 4.87\ B_i - 0.48\ L_i + 2.55\ V_i + 0.59$ from Goss [6].

[c] Calculated with descriptors from Table 1 and 2 in combination with Equation 2.

[d] Experimental values from the present work.

values is found for the diones and diesters but not for the dioles. This is despite the fact that only the latter can form intramolecular H-bonds. For aromatic molecules, large effects are found for compounds with intramolecular H-bonds (i.e., *ortho*-substituted isomers with a H-bond donor and a H-bond acceptor function) and for *para*-isomers with a strong delocalisation of π-electrons over both functional groups (as with *p*-nitroaniline and *p*-nitrophenol). All other isomers that cannot form mutual H-bonds (i.e., *meta*- and *para*-substituted compounds as well as *ortho*-substituted compounds with two H-bond acceptor groups) behave similarly to each other and additive.

Predicting partitioning of bifunctional molecules

Three existing models were evaluated for their ability to estimate the log K_{OW} and air–water partitioning (log K_{AW}) for the bifunctional molecules gathered in Table 3: The U.S. Environmental Protection Agency's EPI Suite (KowWin v1.67 and HenryWin v3.10, http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm), SPARC v4.0 (http://ibmlc2.chem.uga.edu/sparc), and the quantum-chemical software COSMOtherm (Ver C2.1, COSMOlogic, Leverkusen, Germany; some additional details are given in the *Supporting Information*, http://dx.doi.org/10.1897/08-189.S1) [19–21]. The results are displayed in Figure 1 and in Tables S4 and S5.

Octanol–water partitioning. The overall agreement between predicted values for log K_{OW} from these three models and experimental values is quite good (root-mean-square errors: KowWin: 0.33, SPARC 0.33, COSMOtherm 0.54). In some cases, though, COSMOtherm and KowWin deviate by more than one order of magnitude from the experimental value and unfortunately there is no way of predicting which compounds can be expected to generate such a weak performance. The program KowWin calculates K_{OW} values by adding contributions from molecular increments and includes various correction factors for nonadditive effects. Interestingly, we observed several compounds with a nonadditive behavior of functional groups, for which KowWin applied no corrective term at all. Further, in several cases, KowWin applied a correction factor, although additive behavior was observed experimentally (see Table S4). This discrepancy is especially notable for nitrophenols. As mentioned previously, the *ortho*- and the *para*-isomer behave nonadditively to different extents (because of internal H-bonding and delocalization of π-electrons, respectively), but the *meta*-isomer behaves additively. However, KowWin applies one and the same correction factor to all three nitrophenol isomers. All in all, it appears that the correction factors in KowWin do not reflect any mechanistic reasoning but are based only on a statistical routine to make the predicted values agree with experimental ones in the calibration data set while using as little correction as necessary. Despite this, KowWin predictions are generally good for the compounds studied here; however, it must be noted that this may be because these compounds were included in the large calibration data set used for KowWin (2351 compounds [22]). Despite this large calibration data set, however, errors can still occur when erroneous data are included for compound classes that are not well represented. An example can be found from the data used here: When two adjacent keto groups are present, KowWin uses a correction factor that is apparently derived from the published log K_{OW} value of 2,3-butadione of −1.4 [12]. As a consequence, KowWin calculates a K_{OW} for 2,3-butadione that is identical to this published value. However, in our lab we experimentally determined this log K_{OW} value to be −0.21, which is much more consistent with the values for the other diones. The good performance of SPARC for predicting K_{OW} values may also be partly due to an overlap with its calibration data set. The COSMOtherm results for K_{OW} are somewhat inferior but are still acceptable for most purposes, and they are at the accuracy level that one would generally expect for this software. Note that COSMOtherm is not calibrated with the K_{OW} values used here for validation purposes, and thus the validation is not biased by them.

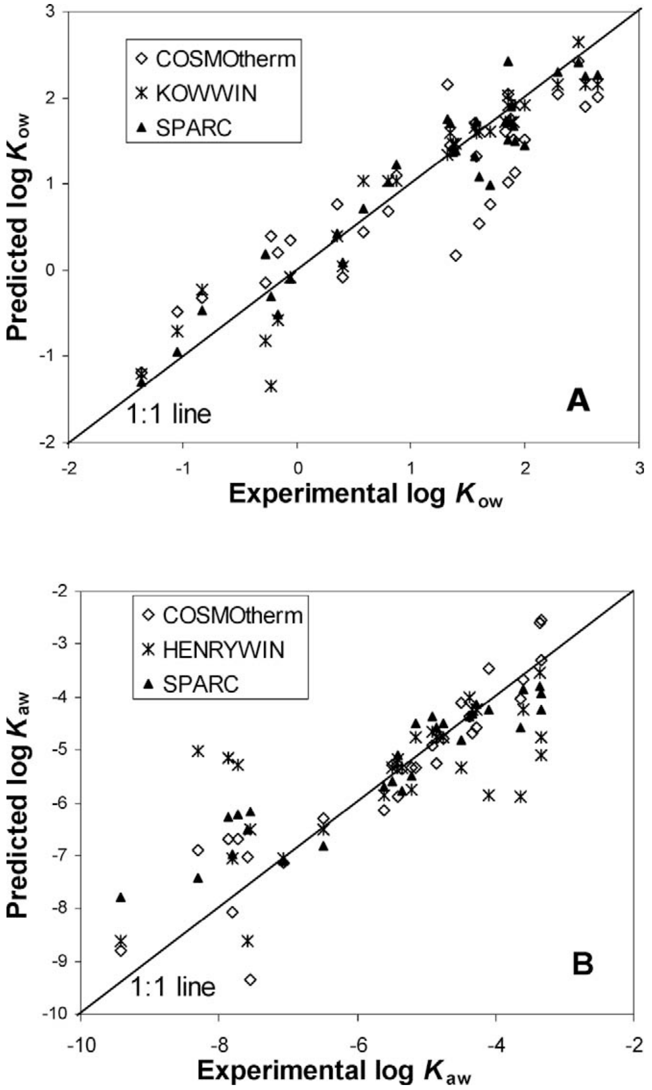

Fig. 1. Experimental log K_{OW} and K_{AW} values (from Table 3) for bifunctional molecules compared to predicted values from KowWin, HenryWin (Bond method), SPARC, and COSMOtherm.

Air–water partitioning. The root-mean-square error from the comparison between experimental and predicted log K_{AW} values are as follows: HenryWin (Bond method) 1.26, SPARC 0.77, and COSMOtherm 0.65. Similar to KowWin, HenryWin (Bond method) also uses correction factors when they are not needed and does not use correction factors where they are needed (Table S5; http://dx.doi.org/10.1897/08-189.S1) in various cases. In addition to this problem, HenryWin is based on a very small calibration data set (345 compounds [23]), which accounts for the large disagreement with the experimental data reported here. Another inconvenience with HenryWin arises from the fact that for each compound, two different calculated

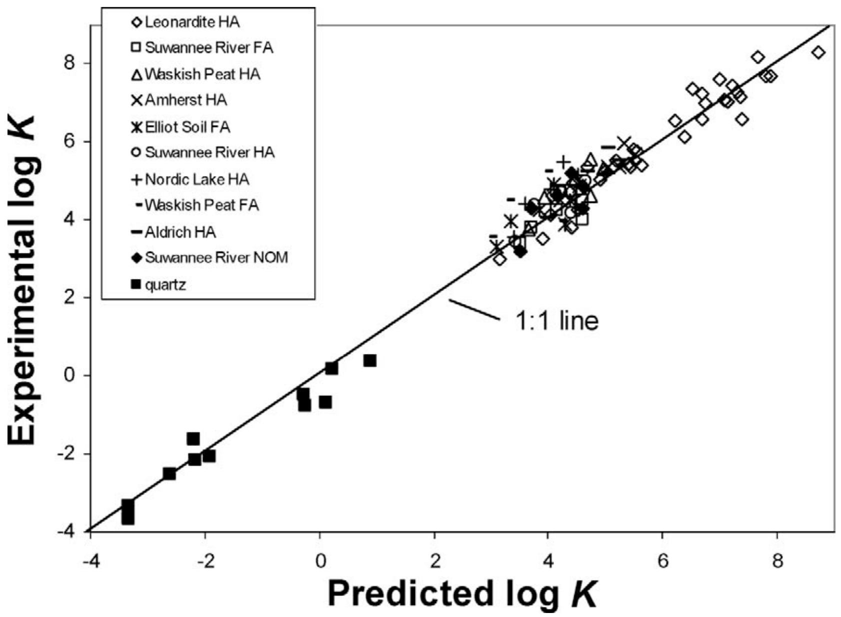

Fig. 2. Comparison of experimental and predicted sorption coefficients of bifunctional molecules to humic acids, fulvic acids, and a quartz surface (data are shown in Table S6, *Supporting Information*, http://dx.doi.org/10.1897/08-189.S1).

values are offered: one from a bond contribution method and one from a group contribution method. Often these values deviate by more than one log unit from each other (in some cases up to three log units; see Table S5). Predictions from SPARC and COSMOtherm for K_{AW} are typically within one order of magnitude of the real value, which is acceptable for most practical purposes.

General performance of predictive models

We conclude that COSMOtherm and SPARC are to be preferred over HenryWin when predicting K_{AW} values. This agrees with our earlier experience with these models [24,25]. With respect to K_{OW} values, KowWin, at first sight, appears to perform well, but one has to keep in mind that this model lacks a sound mechanistical background that jeopardizes its applicability to polyfunctional molecules not included in the calibration data set. This and the missing information about any applicability range of KowWin lead us to suggest that the use of this model should be avoided. In comparison, SPARC and COSMOtherm have a much more mechanistic background. While SPARC still has to extract empirical correction factors from experimental data, it is not limited to data from a given partition process, such as octanol–water, but can use all available partition data to derive this information because of its much more fundamental modeling approach. Hence, one can expect SPARC to have a wider range of applicability with respect to multifunctional molecules than models that are restricted to a single partition process.

The data collected here suggest that no simple pattern would allow for a derivation of general correction factors that work for all multifunctional compounds. Thus, all predictive methods that rely on empirical correction factors to account for nonadditive effects will always be much limited in the applicability domain by the underlying calibration data set. In contrast, a quantum-chemical approach such as COSMOtherm does not require calibration with any structural information. We therefore expect COSMOtherm to have by far the widest applicability when it comes to new compounds and structures (especially multifunctional molecules).

Sorption to complex environmental media

The data analysis presented here has shown that most molecules with two H-bonding sites that cannot engage in intramolecular H-bonds do indeed form two H-bonds with the surrounding phase in simple partition media such as octanol. However, this is possible only if the partition phase is able to provide complementary H-bond partners at a distance that is preset by the distance of the functional groups of the bifunctional molecule. In solvents like octanol or water, this is not a problem because separate solvent molecules can arrange themselves to maximize the H-bond formation with the bifunctional molecule. However, in a complex macromolecular structure like humic matter, this is not necessarily the case; that is, complementary H-bond partners may not exist at the distance required to form two or more H-bonds with a bifunctional molecule. In order to check this, we measured sorption of a number of bifunctional molecules from air to 10 different humic and fulvic acids and also sorption onto a quartz surface. In Figure 2, these values are compared with predicted values based on the respective interaction descriptors of the compounds from Tables 1 and 2 and sorption equations that were calibrated with monofunctional molecules in earlier works [14,15,26]. If the bifunctional molecules realize their full interaction capacity (like in a solvent), then the measured values should agree with the predicted ones. If the measured values were systematically smaller than predicted values, then this would indicate restrictions in the ability of the bifunctional molecules to form H-bonds with these phases. As is evident from Figure 1, no such systematic deviation appears to be present, and the scatter around the 1:1 line is not substantially larger than expected from that given by calibration compounds. The standard deviation for the calibration compounds for each single equation had been approximately 0.3 log units, while for the bifunctional molecules tested here the standard deviation is only 0.4 log units. Thus, modeling following the Abraham approach gives adequate predictions for sorption to complex environmental phases even though the sorbent descriptors were derived from partitioning to simple solvents.

Application of QSPRs to large data sets

Within the new chemical legislation in the European Union (Registration Evaluation Authorization and Restriction of Chemicals), there is a need to assess large numbers of chemicals for their partition behavior based on predictions from their molecular structure. This can be done in one of two ways: using a quantum chemical approach like COSMOtherm or a QSPR approach that accounts for nonadditive effects by empirically calibrated correction factors. Although the presented work is quite limited with respect to the number of bifunctional molecules looked at, it demonstrates that nonadditive effects occur quite often, can be substantial, and affect various types of intermolecular interactions in a complex way. Thus, deriving an empirical approach for systematically accounting for all possible nonadditive effects of multifunctional molecules appears unrealistic. The wide applicability range and the satisfying performance of COSMOtherm in the evaluation for bifunctional molecules presented here lets us conclude that this software may be much more promising for assessing the large diversity of existing structures. This is also supported by another study that we have published recently [27].

SUPPORTING INFORMATION

Table S1. System descriptors for various stationary phases and sorbents that were used in determining the solute descriptors of bifunctional molecules.

Table S2. Experimental partition constants for aliphatic bifunctional molecules.

Table S3. Solute interaction descriptors for monofunctional molecules.

Table S4. Experimental and predicted log $K_{i\mathrm{OW}}$ values for bifunctional molecules at 25°C.

Table S5. Experimental and predicted log $K_{i\mathrm{AW}}$ values for bifunctional molecules at 25°C.

Table S6. Experimental sorption data of bifunctional molecules from air to various humic materials and quartz.

All found at DOI: 10.1897/08-189.S1 (227 KB PDF).

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