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Octanol/Water Partition Coefficients of Sulfonamides: Experimental Determination and Calculation Using Physicochemical Descriptors

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1-Octanol/water partition coefficients log K_{ow} of 38 sulfonamides were determined by the isothermal saturation method. These values were used both for direct correlation and as test data for the verification of a regression equation for calculation of log K_{ow} on the basis of two physicochemical descriptors (molecular polarizability, a surrogate for molecular size, and H-bond acceptor ability). Comparison of experimental and calculated K_{ow} values demonstrated the wide applicability of those equations.

Introduction

Sulfonamides are still extensively used for the treatment of certain infections caused by Gram-positive and Gram-negative microorganisms, some fungi, and certain protozoa. Although at present the advent of antibiotics has diminished the usefulness of sulfonamides, they occupy a relatively small but important place in the therapeutic resources of physicians and veterinarians. It should be noted that there were some attempts to correlate different physicochemical parameters of these compounds with their chemotherapeutic activity applying p*K*a, protein binding, and electronic charge distribution.[1−3] An important parameter for the discussion of transport processes of chemicals and drugs between immiscible liquid phases and between aqueous media and biological membranes in living organisms is the 1-octanol/water partition coefficient K_{ow}. There are many publications connected with different approaches of experimental determination and of calculation of this important parameter. Nevertheless, the quality of calculation of K_{ow} for complex organic compounds containing a few chemical functional groups is not always perfect.

This short article presents results of our experimental determination of octanol/water partition coefficients of 38 sulfonamides with wide modification of substituents and also the results of calculation of those values on the basis of regression equations with application of only two physicochemical descriptors.

Experimental Section and Calculation Methods

Chemicals. The chemical synthesis of compounds (**1** to **3**; **1**, *N*-(2-chlorophenyl)-benzene-sulfonamide, CAS 21226-30-2; **2**, *N*-(2,3-dichlorophenyl)-benzene-sulfonamide, CAS 92589-22-5; **3**, *N*-(4-chlorophenyl)-benzene-sulfonamide, CAS 4750-28-1) (see Table 1) has been performed as described before.[4] Sulfonamides (**4** to **9**) have been synthesized by the same procedure, and compounds **10** to **13** have been synthesized analogously using 4-nitro-benzenesulfonyl chloride instead of unsubstituted benzenesulfonyl chloride. Also, the synthesis of sulfanilamide compounds (**19** to **22**; **19**, 4-amino-*N*-(4-chlorophenyl)-benzene-sulfonamide, CAS 16803-92-2; **20**, 4-amino-*N*-(2,3-dichlorophenyl)-benzene-sulfonamide; **21**, 4-amino-*N*-(3,4-dichlorophenyl)-benzene-sulfonamide, CAS 34392-63-7; **22**, 4-amino-*N*-(2,5-dichlorophenyl)-benzene-sulfonamide, CAS 439118-58-8) has been described before.[5] Again sulfonamides (**14** to **18**, **23** to **29**, and **34** to **38**) have been synthesized analogously. The final products have been dried at room temperature under vacuum until the mass was constant. The outlined procedure has been repeated several times and the product checked by NMR after each recrystallization step until the ^{1}H NMR signals corresponded to purity of the compound better than 99 %.

Partitioning Experiments. The experiments for determination of partition coefficients K_{ow} were carried out by the isothermal saturation method. The procedure was as follows: to a defined volume of a water-saturated 1-octanol solution, an identical volume of octanol-saturated water of defined drug concentration was added in an ampule placed in a thermostat. The experiment extended over two days with continuous gentle shaking. After that, the ampules were left alone for 5 h at the defined temperature to allow separation of entrained droplets of the immiscible phases. It should be noted that we also tried to separate the phases by centrifugation. The partition coefficients obtained by the two methods were identical within experimental errors. The drug concentration after partitioning in the octanol-saturated water phase (C_2^{wo}), the initial concentration in the water-saturated octanol phase ($C_2^{\mathrm{ow}}(i)$), and the final concentration of the substance in the water-saturated octanol phase ($C_2^{\mathrm{ow}}(f)$) were determined by UV spectrophotometry. The partition coefficient was calculated by

$$K_{\mathrm{ow}} = C_2^{\mathrm{ow}}(f)/C_2^{\mathrm{wo}} \tag{1}$$

The accuracy of the K_{ow} value was verified by checking the mass balance of the starting amount of the compound compared

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to the total amount of the compound partitioned between the two phases

$$n_2^{\mathrm{ow}}(i) = n_2^{\mathrm{ow}}(f) + n_2^{\mathrm{wo}} \qquad (2)$$

where $n_2^{\mathrm{ow}}(i) = C_2^{\mathrm{ow}}(i)\cdot V^{\mathrm{ow}}$, $n_2^{\mathrm{ow}}(f) = C_2^{\mathrm{ow}}(f)\cdot V^{\mathrm{ow}}$ are the number of moles of the solute in the initial and in the final octanol phase, respectively. $C_2^{\mathrm{ow}}(i)$ and $C_2^{\mathrm{ow}}(f)$ are the molar concentrations of the solute in the water-saturated octanol, before (i) and after (f) the experiment, respectively. V^{ow} is the volume of the octanol phase. $n_2^{\mathrm{wo}} = C_2^{\mathrm{wo}}\cdot V^{\mathrm{wo}}$ is the number of moles of the solute in the octanol-saturated water.

Each experiment was repeated at least three times. The average observed precision was ± 0.1 units of log K_{ow}.

To the best of our knowledge, the log K_{ow} value of only six of our sulfonamides has been determined before: **14**, CAS 6829-82-9, log $K_{\mathrm{ow}} = 2.14$[19] and log $K_{\mathrm{ow}} = 2.39$;[20] **17**, CAS 19837-74-2, log $K_{\mathrm{ow}} = 1.51$;[19−21] **18**, CAS 25612-07-1, log $K_{\mathrm{ow}} = 1.83$;[19] **19**, CAS 16803-92-2, log $K_{\mathrm{ow}} = 2.71$;[19−21] **32**, CAS 6162-21-6, log $K_{\mathrm{ow}} = 0.76$;[19] **33**, CAS 1709-52-0, log $K_{\mathrm{ow}} = -0.01$.[19] For these chemicals, the literature values log $K_{\mathrm{ow(lit)}}$ are very close to values determined in this work. Their intercorrelation is given by the following equation

$$\log K_{\mathrm{ow(ui)}} = 0.09(\pm 0.08) + 0.87(\pm 0.05)[\log K_{\mathrm{ow(lit)}}]$$
$$n = 6,\ R^2 = 0.989,\ \mathrm{SD} = 0.10,\ F = 347.0 \qquad (3)$$

Calculation Methods. Physicochemical descriptors applied in the calculation of partition coefficients log K_{ow} were estimated by means of the program HYBOT.[6] Statistical analyses were performed by SPSS.[7]

Results and Discussion

Partition Coefficients. Table 1 contains the results of our experimental determination of 1-octanol/water partition coefficients for 38 sulfonamides and corresponding descriptor values. As most of the considered compounds contain an acidic NH group, p*K*a values were determined or calculated for each chemical. The column p*K*a contains data determined by us or taken from the literature or calculated by the ACD program.[8−11] The knowledge of p*K*a and of the drug concentration in the water phase under the conditions of experimental K_{ow} determination (i.e., after establishment of partition equilibrium) provided the possibility to calculate the pH[11] in water (see column pHcalc) and f_{ui}, the fraction of unionized compound (column log $1/f_{\mathrm{ui}}$, where $f_{\mathrm{ui}} = C_{\mathrm{neutral}}/C_{\mathrm{total}}$). Using the relationship[11] log $K_{\mathrm{ow(ui)}}$ = log $K_{\mathrm{ow(exp)}}$ + log $1/f_{\mathrm{ui}}$, the partition coefficient of the unionized

Table 1. Experimental and Calculated 1-Octanol/Water Partition Coefficients (log K_{ow}) and Physicochemical Parameters (Polarizability α; H-Bond Acceptor Ability ∑ C_a; Acidity p*K*a) of Sulfonamides with the General Structure $R_1C_6H_{4(3)}SO_2NR_2R_3$

											log $K_{\mathrm{ow}}(ui)$ (calc)		
	R_1	R_2	R_3	α	∑C_a	p*K*a	pH calc	log $1/f_{\mathrm{ui}}$	log$K_{\mathrm{ow(exp)}}$	log$K_{\mathrm{ow(ui)}}$	eq 5	eq 4	KOWWIN
1	H	H	2-Cl-Phenyl	27.34	3.69	8.18[a]	6.474	0.01	2.72	2.73	2.93	3.61	3.28
2	H	H	2,3-Cl_2-Phenyl	29.27	3.65	7.66[a]	6.668	0.04	3.45	3.49	3.35	4.17	3.92
3	H	H	4-Cl-Phenyl	27.34	3.67	7.96[b]	6.722	0.02	3.44	3.46	2.94	3.63	3.28
4	H	H	4-NO_2-Phenyl	27.25	4.46	6.29[b]	5.364	0.05	2.09	2.14	2.37	2.82	2.45
5	H	H	2,4-Br_2-Phenyl	30.66	3.80	7.86[a]	6.789	0.04	3.75	3.79	3.53	4.39	4.41
6	H	H	2-NO_2-Phenyl	27.25	4.36	6.70[b]	5.837	0.06	2.08	2.14	2.44	2.92	2.45
7	H	H	3-Cl-2-Pyridyl	26.63	5.49	6.09[b]	4.961	0.03	1.54	1.57	1.51	1.62	2.08
8	H	H	2-Cl-3-Pyridyl	26.63	5.17	6.13[b]	5.183	0.05	1.89	1.94	1.74	1.94	2.09
9	H	H	5-C(O)OC_2H_5-2-Pyridyl	30.63	6.17	6.76[a]	6.078	0.08	2.00	2.08	1.84	2.01	1.77
10	4-NO_2	H	4-OC_2H_5-Phenyl	31.19	5.14	8.13[a]	6.452	0.01	2.23	2.24	2.68	3.19	3.02
11	4-NO_2	H	1,3-Thiazol-2-yl	25.75	5.68	6.39[a]	5.985	0.14	1.19	1.33	1.20	1.20	1.45
12	4-NO_2	H	4-NHC(O)CH_3-3-Pyridyl	31.84	8.50	7.41[a]	5.946	0.02	0.71	0.73	0.43	0.00	0.93
13	4-NO_2	H	5-CH_3-2-Pyridyl	28.38	5.74	6.80[a]	5.973	0.06	1.01	1.07	1.69	1.84	1.81
14	4-NH_2	H	4-NO_2-Phenyl	28.73	5.67	6.91[b]	5.585	0.02	1.88	1.90	1.81	2.00	1.53
15	4-NH_2	H	4-C_2H_5-Phenyl	30.56	4.88	9.35[c]	≤ 7.0	0.00	2.62	2.62	2.74	3.28	2.75
16	4-NH_2	H	4-I-Phenyl	31.91	4.95	8.47[b]	≤ 7.0	0.00	2.82	2.82	2.96	3.57	2.88
17	4-NH_2	H	4-OCH_3-Phenyl	29.00	5.50	9.41[b]	≤ 7.0	0.00	1.58	1.58	1.98	2.24	1.80
18	4-NH_2	H	4-CN-Phenyl	28.75	6.11	7.33[b]	6.190	0.03	1.57	1.60	1.50	1.57	1.81
19	4-NH_2	H	4-Cl-Phenyl	28.81	4.88	8.48[b]	6.626	0.01	2.47	2.48	2.38	2.81	2.36
20	4-NH_2	H	2,3-Cl_2-Phenyl	30.74	4.86	8.32[a]	6.735	0.01	2.62	2.63	2.79	3.35	3.00
21	4-NH_2	H	3,4-Cl_2-Phenyl	30.74	4.86	8.08[b]	6.723	0.02	2.64	2.66	2.53	3.35	3.00
22	4-NH_2	H	2,5-Cl_2-Phenyl	30.74	4.94	8.32[a]	6.683	0.01	2.45	2.46	2.73	3.27	3.00
23	4-NH_2	H	2,4,5-Cl_3-Phenyl	30.67	4.94	8.00[a]	6.942	0.04	3.17	3.21	3.12	3.78	3.65
24	4-NH_2	H	2-CH_3-5-Cl-Phenyl	30.65	4.95	9.00[b]	≤ 7.0	0.00	2.73	2.73	2.71	3.23	2.91
25	4-NH_2	H	2-Cl-4-CH_3-Phenyl	30.65	4.94	9.08[a]	≤ 7.0	0.00	2.37	2.37	2.71	3.24	2.91
26	4-NH_2	H	2-CH_3-4-Cl-Phenyl	30.65	4.95	8.68[b]	≤ 7.0	0.00	2.65	2.65	2.71	3.22	2.91
27	4-NH_2	H	3-Cl-4-CH_3-Phenyl	30.65	4.88	8.88[a]	≤ 7.0	0.00	2.92	2.92	2.76	3.30	2.91
28	4-NH_2	H	2-OCH_3-3-Cl-Phenyl	30.92	5.71	9.02[a]	≤ 7.0	0.00	2.43	2.43	2.22	2.55	2.44
29	4-NH_2	H	2-Br-4-NO_2-Phenyl	31.35	5.88	5.60[b]	5.535	0.27	1.87	2.14	2.19	2.49	2.42
30	4-NH_2	H	$CH_2C(O)OC_2H_5$	24.99	6.07	9.95[a]	≤ 7.0	0.00	0.30	0.30	0.76	0.60	−0.05
31	4-NH_2	C_2H_5	C_2H_5	24.57	5.26	1.75[d] ($ArNH_3^+$)	≥ 7.0	0.00	1.52	1.52	1.25	1.30	1.11
32	4-NH_2	CH_3	CH_3	20.90	5.11	1.53[d] ($ArNH_3^+$)	≥ 7.0	0.00	0.72	0.72	0.61	0.47	0.13
33	4-NH_2	H	CH_3	19.06	4.77	10.77[e]	≤ 7.0	0.00	0.07	0.07	0.48	0.32	−0.08
34	2-CH_3-4-NH_2	H	4-Cl-Phenyl	30.65	5.18	8.84[b]	≤ 7.0	0.00	2.73	2.73	2.54	3.99	2.91
35	2-Cl-4-NH_2	H	2-Cl-Phenyl	30.74	4.96	8.15[a]	6.960	0.03	2.98	3.01	2.72	3.25	3.00
36	2-CH_3-4-NH_2	H	2-Cl-Phenyl	30.65	5.20	8.28[b]	6.939	0.02	2.66	2.68	2.53	2.98	2.91
37	2-Cl-4-NH_2	H	4-Cl-Phenyl	30.74	4.94	8.44[b]	6.942	0.01	2.48	2.49	2.73	3.27	3.00
38	2-CH_3-4-NH_2	H	2-NO_2-Phenyl	30.56	5.87	7.47[b]	6.587	0.05	2.19	2.24	2.04	2.29	2.08

[a] Calculated by ACD, ref 8. [b] Experimental p*K*a (Schaper, K.-J., Seydel, J. K., 22 °C, pH-dependent UV & nonlinear regression analysis). [c] Ref 9. [d] Experimental p*K*a listed by ACD, ref 8. [e] Ref 10.

drug can be calculated. Under our conditions, the correction term log $1/f_{ui}$ in most cases is below 0.1.

log K_{ow} Calculations on the Basis of Physicochemical Descriptors. It has been proposed that the partition coefficients of chemicals in the system 1-octanol/water encode two major structural contributions: a molecular size term (describing steric bulk effects) and a term which reflects such interactions as dipole−dipole and hydrogen bonding.[12,13] This idea has been tested by us first using a small log K_{ow} data set of 38 chemicals containing carbonyl and hydroxyl groups.[14] In that study, we used molecular weight as a surrogate of the molecular size term and H-bond factors and obtained favorable results. Later we investigated different descriptors connected with the molecular size term (such as molecular weight, surface area, molecular volume, molecular refractivity, molecular polarizability) and H-bond descriptors for a data set containing 234 diverse chemicals (nitriles, amines, carbonyls, ethers, esters, alcohols, phenols, acids, chemicals with phenyl, nitro, halogen groups).[15] An equation based on molecular polarizability (α, mainly acting as a surrogate for molecular size) and H-bond acceptor factor ($\sum C_a$) showed the best statistics. Then, 2850 chemicals containing one functional group were selected for correlation of log K_{ow} with those descriptors[16]

$$\log K_{ow} = 0.266(\pm 0.030)\alpha - 1.00(\pm 0.10)\sum C_a$$
$$n = 2850,\ R^2 = 0.941,\ \text{SD} = 0.23 \qquad (4)$$

Finally, for log K_{ow} calculation of complex compounds containing several functional groups, an approach was proposed and tested using a large data set. This approach is based on the application of experimental values of nearest structurally similar compounds (nssc) and estimation of additional contributions due to differences in α and $\sum C_a$ in a given chemical of interest (i) and its nssc.[17,18]

In the present work, our own experimentally determined log K_{ow} data were available for 38 sulfonamides with wide modification of substituents. So the possibility arises to confirm the applicability of α and $\sum C_a$ for estimation of log $K_{ow(ui)}$ by direct correlation with those descriptors and to use the data for validation of eq 4.

Direct correlation of HYBOT descriptors with log K_{ow} of the 38 sulfonamides results in

$$\log K_{ow(ui)} = -0.40(\pm 0.49) + 0.214(\pm 0.015)\alpha - 0.70(\pm 0.05)\sum C_a$$
$$n = 38,\ R^2 = 0.906,\ \text{SD} = 0.27,\ F = 165.7 \qquad (5)$$

A plot of experimental log $K_{ow(ui)}$ against log K_{ow} calculated by eq 5 leads to $R^2 = 0.906$, an intercept value close to zero (−0.05 ± 0.13) and slope value close to one (1.01 ± 0.05). These parameters indicate that the two physicochemical descriptors completely describe the considered property and can be applied to successfully calculate log K_{ow} values of complex organic compounds. log K_{ow} values calculated on the basis of eq 5 are listed in column log $K_{ow(ui)}$ calc, eq 5, of Table 1. log K_{ow} values predicted on the basis of eq 4 are shown in column log $K_{ow(ui)}$ calc, eq 4. Equation 6 presents a comparison of experimental log K_{ow} and log K_{ow} predicted by means of eq 5

$$\log K_{ow(ui)} = 0.31(\pm 0.12) + 0.73(\pm 0.04)[\log K_{ow(ui)}\ (\text{calc by eq 4})]$$
$$n = 38,\ R^2 = 0.893,\ \text{SD} = 0.28,\ F = 303.3 \qquad (6)$$

The 95 % confidence intervals of the regression coefficients of eq 6 are ± 0.24 (intercept) and ± 0.09 (slope). In the case of a correlation with fixed zero intercept (as in eq 4), the slope is equal to 0.83 ± 0.02. It is obvious that eq 6 also has rather good statistic parameters. Nevertheless the intercept and gradient values are not ideal for this kind of correlation. The result certainly reflects the character of training sets. Equation 5 was obtained for a rather narrow set of structurally similar sulfonamides, whereas eq 4 is based on a vast data set of diverse chemicals of different chemical classes with slightly different subset correlations. Nevertheless, eqs 4 and 5 contain the same two physicochemical descriptors with approximately the same regression coefficients. This demonstrates the possibility to calculate log K_{ow} values for rather simple chemicals containing one functional chemical group as well as for complex organic compounds with few functional groups on the basis of only two physicochemical descriptors (i.e., molecular polarizability and H-bond acceptor factor).

The last column of Table 1 contains log K_{ow} values calculated by the program KOWWIN V1.67. A correlation of those values with the previously mentioned literature data of six sulfonamides provided the following equation

$$\log K_{ow(lit)} = 0.33(\pm 0.28) + 0.92(\pm 0.18)[\log K_{ow}\ \text{KOWWIN}]$$
$$n = 6,\ R^2 = 0.870,\ \text{SD} = 0.40,\ F = 26.7 \qquad (7)$$

The correlation of the same values with log K_{ow} calculated by eq 4 resulted in

$$\log K_{ow(lit)} = 0.07(\pm 0.35) + 0.91(\pm 0.19)[\log K_{ow}\ (\text{eq 4})]$$
$$n = 6,\ R^2 = 0.845,\ \text{SD} = 0.43,\ F = 21.9 \qquad (8)$$

Conclusion

1-Octanol/water partition coefficients log K_{ow} of 38 sulfonamides were determined by the isothermal saturation method. Two approaches were applied to calculate log K_{ow} values: (i) direct correlation with molecular polarizability and H-bond acceptor ability and (ii) application of an analogous equation obtained for simple chemicals containing one functional group. Both methods ensure good estimation of octanol/water partition coefficients with statistic parameters close to program KOWWIN and demonstrate the possibility to predict log K_{ow} values of complex organic compounds with few functional groups on the basis of only two physicochemical descriptors (molecular polarizability and H-bond acceptor factor).

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