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Research Paper

log P Estimation of 1,2-Dithiole-3-thiones and 1,2-Dithiole-3-ones: A Comparison of Experimental and Calculative Approaches

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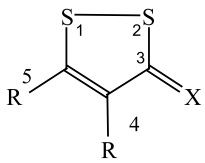
Purpose. To estimate experimental log P values of formerly described 5-formyl- and 5-acyl-dithiole-3-thiones (DTT) and -dithiole-3-ones (DTO) and to check the validity of five log P calculation programs via experimental log P for a database of 68 DTT and DTO.
Methods. Experimental log P values were measured by means of octanol/water partitioning; for determining solute concentrations in water, RP-HPLC with spectrophotometric detection was used. For calculating log P, the fragmental methods ACD/log P, CLOGP, and KOWWIN, the atom-based approach XLOGP, and the whole-molecule approach QLOGP were applied.
Results. Quality of calculations significantly differs depending on the subset under consideration. For database compounds **01**–**48**, comprising alkyl and aryl substitution in 4- and 5-position, the fragmental methods ACD/log P, CLOGP, and KOWWIN perform significantly better than the atom-based approach XLOGP and the whole-molecule method QLOGP. For database compounds **49**–**68**, comprising formyl and acyl substitution in 4- and 5-position, superiority of the whole-molecule method QLOGP over the substructure-based approaches is observed. The strong underestimation of log P for compounds **49**–**68** probably indicates hidden physicochemical phenomena resulting from the juxtaposition of the acyl and dithiole moieties.
Conclusions. All calculation methods included in this study need a thorough refinement to adequately cope with particular solvation behavior suspected to prevail in formyl- or acyl-DTT and DTO, which represent a chemical class of high pharmacological interest.

KEY WORDS: 1,2-dithiole-3-ones; 1,2-dithiole-3-thiones; log P calculation; octanol/water partitioning.

INTRODUCTION

1,2-Dithiole-3-thiones **00** (X = S) are compounds of growing pharmaceutical interest.



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Prevention of cancer through the administration of low-cost, nontoxic molecules such as oltipraz (35972 R.P.) (R^4: methyl; R^5: 2-pyrazinyl) is intensely investigated (1). This molecule, originally developed for its schistosomacidal properties (2), has been the matter of numerous studies on the chemoprevention of cancer (3). Oltipraz is effective in this field because it promotes the induction of phase 2 enzymes that mediate carcinogen detoxification (4); it is also chemoprotective against aflatoxin B1 (5). Anetholtrithione **27**, which is 5-(*p*-methoxyphenyl)-1,2-dithiole-3-thione, has been used in human therapy for about 50 years for its choleretic (6) and sialagogue properties (7) without exhibiting adverse effects; it is also interesting from the standpoint of chemoprevention (8). Anetholtrithione is a free radical scavenger that increases glutathione synthesis and glutathione enzyme activity and inhibits NFκB activation (9). Probably the chemopreventive properties of these two derivatives are also shared by the entire class of dithiolethiones (10). In brief, the family of dithiolethiones is of central interest in the concept of chemoprevention. The pharmacological interest in dithiolones is due to their antirheumatic activity among other properties (11).

Lipophilicity is a major determinant of several aspects of the disposition and biological action of bioactive molecules. Therefore, we were interested in estimating the lipophilicity of dithiolethiones and dithiolones (12–14). In our previous work (12), we determined *n*-octanol/water log P values of 33 DTT **00** (X = S) and 17 DTO **00** (X = 0). From these data, we built a substructure approach for calculating their log P values. For synthetic reasons, however, this approach was only based on experimental log P of 4- and 5-alkyl or -aryl-

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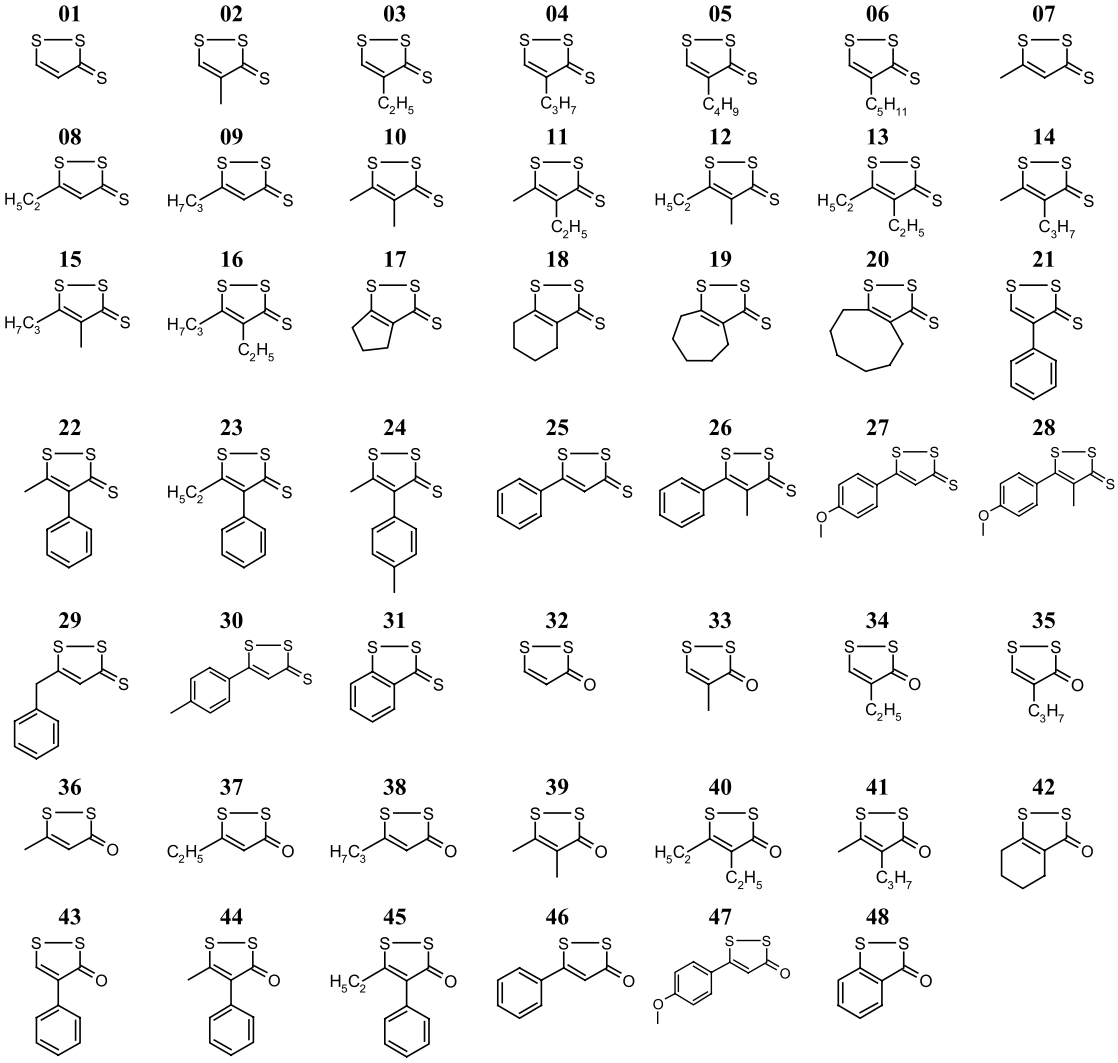
Table I. Structures of 1,2-Dithiole-3-thiones (DTT) and 1,2-Dithiole-3-ones (DTO)



DTT and -DTO, which are not too hard to synthesize (15). The discovery of a rather easy synthetic pathway to 5-formyl- and 5-acyl-DTT (16) allowed us to broaden significantly the number of experimental log P values for our substructure approach.

The aim of the current study is the experimental log P estimation of 5-formyl- and 5-acyl-DTT and -DTO (compounds **49**–**68**) as well as a quality check of substructure and whole-molecule approaches for calculating log P of the entirea database of 68 DTT and DTO (compounds **01**–**68**).

MATERIALS AND METHODS

Database

The database (n = 68) used here comprises 41 DTT and 27 DTO; for structures see Table I. Synthesis is referred to for **01** to **48** in (12), for **49, 50, 52**–**54** in (16), for **61**–**64** in (17), and for **51, 55**–**60, 65**–**68** in (18). 5-acyl-DTT has been patented for its pharmacological properties (19) (Table I).

Experimental Determination of log P

In this study, log P values of compounds **49** to **68** were determined via the same methodology previously used for compounds **01** to **48** (12). Before each determination, the purity of the compounds was checked by TLC using two pairs of eluents. Let us recall only that log P was calculated as the decimal logarithm of the ratio of the solute concentrations in *n*-octanol and in water after partition equilibrium. Actually, the method amounted to determining the concentration of the solute in the aqueous phase at partition equilibrium. Whenever possible, solute concentrations should be determined in both phases after equilibrium. In the current study, however, variations of concentrations in the organic phase were too weak to be determined with some accuracy. In other words, concentration variations in the organic phase fall in the realm of the uncertainty of its determination. Beyond it, degradation of the molecules (identical UV visible spectra of derivative **49** before and after equilibrium partitioning in water) as well as micelle formation (no increase in logP with the total initial concentration of the derivative in the organic phase) could be excluded.

One-phase determination was done by RP-HPLC with spectrophotometric detection, which was the most sensitive method at our disposal. However, for less lipophilic derivatives, direct and pulse polarographies were used and direct spectrophotometric measurements were also performed in the aqueous phase. Both methods permitted, hence, a check and even a double check of the HPLC values. Finally, the whole methodology was validated in this previous work (12) by determining log P values of some derivatives, for which log Ps were already known. In this work, log P was also determined, when possible, by direct spectrophotometric measurements. Material was the same as that used previously (12). For constructing calibration curves, an accurate mole number of the studied product was dissolved in a known volume of methanol. An aliquot of the methanolic solution was taken and diluted with ultrapure water. Finally, the calibration curve was drawn with the help of fine solutions of different concentrations prepared from the preceeding aqueous solution. The methanol percentage in them was below 2 p 100 (v/v). The calibration curve (a straight line according to the Beer's law) was drawn statistically according to the equation $C = aH + b$ where C was the concentration of the solute (mol L^{-1}) and H was the height (cm) at the wavelength of the absorbance maximum. The linear regression coefficient r was systematically over 0.998 and the intercept (in absolute value) less than 0.2 cm for an average deflection of 15 cm. For dithiolethiones λ_{max} was situated in the range 400 to 460 nm and for dithiolones between 300 and 370 nm.

log P Calculation Programs

Methods for calculating log P (20,21) can be divided into two main classes: i) substructure approaches, here the molecules are cut into atoms (atom-based approach) or groups (fragmental approach); the summation of single-atom or fragmental contributions, supplemented by applying correction rules in the latter case, results in the final log P; ii) whole-molecule approaches, these inspect the entire molecule; they use, for example, molecular lipophilicity potentials, topological indices or molecular descriptors to quantify log P and some reflect the impact of the 3D-structure on molecular lipophilicity. In this study, we applied the fragmental approaches ACD/log P (22,23), CLOGP (24–27), and KOWWIN (28), the atom-based approach XLOGP (29,30) and the whole-molecule approach QLOGP (31). For a detailed description see (21).

RESULTS AND DISCUSSION

Experimental log P data obtained in this study for derivatives **49**–**68** are listed in the second column of Table II together with previously published data for compounds **01**–**48** (12, 13). For 10 compounds, experimental values were obtained by both HPLC and spectrophotometry; their close coincidence unequivocally proves the validity of the experimental results.

Most strikingly, the values measured with DTT and DTO **49**–**68** differ considerably from their calculated data (columns 3–8 of Table II), whereas the great majority of the values calculated for compounds **01**–**48** satisfactorily coincide with experimental data.

Compounds **01**–**48** mainly comprise 4-alkyl, 4-aryl, 5-alkyl, 5-aryl, 4,5-dialkyl, and 4,5-alkyl, aryl-DTT and -DTO. From their experimental log P values (12, 13), a fragmental method was devised, which permitted the calculation of accurate log P data for most of the compounds **01**–**48** (Table II, column 3). Before briefly summarizing this method, some particular physicochemical properties of DTT and DTO deserve mentioning: a) the nuclei DTT and to a lesser extent DTO are aromatic; b) the 5-DTT-yl group is a very strongly withdrawing group (as a nitro group); the 5-DTO-yl group is slightly less attractive; and c) aryl groups in position 5 are strongly conjugated with the DTT and DTO nuclei. This is not the case for aromatic 4-substituents which all are twisted relatively to the nucleus plane, as shown by molecular orbital calculations of DTT.

These characteristics indicate that the DTT and DTO nuclei and their respective substituents mutually disturb their

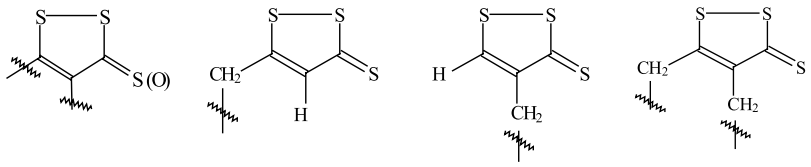
Table II. Experimental *vs.* Calculated log P from Various Approaches[a]

	Exp. data	Calculated data					
	$\log P_{exp}$	Ref. 12	ACD/log P	CLOGP	KOWWIN	XLOGP	QLOGP
01	1.58		1.24	1.60	1.53	0.98	2.63
02	2.18	2.16	1.83	2.10	2.07	1.12	3.06
03	2.67	2.67	2.36	2.63	2.57	1.59	3.51
04	3.18	3.19	2.90	3.16	3.06	2.15	3.96
05	3.70	3.71	3.43	3.69	3.55	2.72	4.40
06	4.06	4.23	3.96	4.22	4.04	3.29	4.85
07	1.85	1.82	1.83	2.10	2.07	0.83	3.07
08	2.31	2.34	2.36	2.63	2.57	1.08	3.51
09	2.83	2.86	2.90	3.16	3.06	1.65	3.96
10	2.45	2.45	2.42	2.55	2.62	0.97	3.50
11	2.94	2.97	2.95	3.08	3.11	1.44	3.95
12	2.95	2.97	2.95	3.08	3.11	1.22	3.94
13	3.51	3.49	3.49	3.61	3.60	1.69	4.34
14	3.39	3.48	3.49	3.61	3.60	2.01	4.40
15	3.42	3.48	3.49	3.61	3.60	1.79	4.39
16	3.76	3.99	4.02	4.14	4.10	2.26	4.82
17	2.53	2.61	2.30	2.62	3.00	0.78	3.70
18	3.10	3.13	2.86	3.18	3.49	1.35	4.15
19	3.27	3.65	3.43	3.74	3.98	1.92	4.59
20	3.75	4.17	3.99	4.29	4.47	2.49	5.04
21	3.2	3.23	3.44	3.14	3.29	2.84	4.52
22	3.17	3.75	4.03	3.34	3.84	2.69	4.96
23	3.52	4.27	4.56	3.87	4.33	2.94	5.40
24	3.78	4.27	4.49	3.84	4.39	3.12	5.41
25	3.67	3.23	3.44	3.70	3.29	2.51	4.52
26	3.95	3.75	4.03	3.90	3.84	2.65	4.95
27	3.82	3.32	3.39	3.62	3.37	2.42	4.45
28	4.10	3.84	3.98	3.82	3.92	2.56	4.89
29	3.43	3.46	3.56	3.67	3.78	2.36	4.95
30	4.26	3.74	3.90	4.20	3.84	2.94	4.97
31	3.57	2.62	3.57	3.20	2.70	1.75	3.79
32	0.82	–	0.60	0.80	0.85	0.73	0.88
33	1.33	1.33	1.19	1.30	1.39	0.87	1.31
34	1.90	1.85	1.72	1.83	1.88	1.33	1.76
35	2.38	2.38	2.25	2.36	2.38	1.90	2.21
36	1.26	1.33	1.19	1.30	1.39	0.58	1.32
37	1.69	1.85	1.72	1.83	1.88	0.83	1.76
38	2.24	2.38	2.25	2.36	2.38	1.40	2.20
39	1.73	1.84	1.78	1.75	1.94	0.72	1.75
40	2.78	2.88	2.84	2.81	2.92	1.44	2.63
41	2.96	2.88	2.84	2.81	2.92	1.75	2.65
42	2.40	2.54	2.22	2.38	2.81	1.10	2.40
43	2.64	2.47	2.80	2.90	2.61	2.58	2.77
44	2.93	2.99	3.39	3.10	3.16	2.43	3.20
45	3.15	3.51	3.92	3.63	3.65	2.69	3.64
46	3.19	2.56	2.80	2.90	2.61	2.25	2.77
47	4.07	4.12	2.74	2.82	2.69	2.17	2.70
48	2.73	1.94	2.73	2.40	2.19	1.50	2.04
Formyl- and acyl derivatives							
49	2.53 (2.55)	1.05	0.96	0.73	1.24	0.26	2.36
50	2.87	1.57	1.46	1.32	1.79	0.41	2.80
51	− (3.15)	2.09	1.99	1.85	2.28	0.87	3.25
52	3.22 (3.43)	2.75	2.50	2.18	3.01	2.12	4.26
53	2.58 (2.56)	1.12	0.89	−0.01	1.33	0.50	2.30
54	3.13 (2.95)	1.78	1.56	0.92	1.89	0.80	2.91
55	1.81	0.29	0.16	0.09	0.93	0.01	0.65
56	2.16 (1.62)	0.81	0.66	0.68	1.47	0.15	1.07
57	2.62 (2.58)	1.32	1.19	1.21	1.97	0.62	1.51
58	2.94	1.99	2.26	1.54	2.69	1.87	2.54
59	1.83 (1.83)	0.36	0.44	−0.65	0.22	0.25	0.58
60	2.18 (2.16)	1.02	0.99	0.28	1.42	0.55	1.18
61	2.18	1.13	1.04	0.78	1.21	0.41	2.08

Table II. Continued

	Exp. data	Calculated data					
	log P_{exp}	Ref. 12	ACD/log P	CLOGP	KOWWIN	XLOGP	QLOGP
62	2.79	1.65	1.54	1.37	1.76	0.55	2.52
63	3.21 (2.11)	2.17	2.07	1.90	2.25	1.01	2.94
64	3.31	2.83	2.58	2.23	2.97	2.26	3.97
65	1.14	0.37	0.24	0.14	1.15	0.15	0.36
66	1.58	0.89	0.74	0.73	1.69	0.30	0.79
67	2.12	1.41	1.27	1.26	2.19	0.76	1.22
68	2.50	2.07	2.34	1.59	2.91	2.01	2.24

[a] In column 2, log P data based on spectrophotometric determination are given in parentheses.



I **II** **III** **IV**

Scheme 1. Basic fragments for log P calculations (Ref. 12).

physicochemical behavior including partitioning. Correspondingly, anomalous log P values are to be suspected.

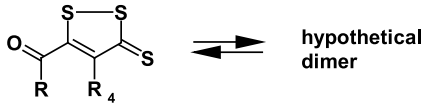
On the basis of the above considerations, a fragmental method was developed using different basic fragments I to IV depending on the respective substitution pattern (Scheme 1). Calculations of compounds **01**–**48** obtained with this fragmental method are listed in the third column of Table II. The great majority of these calculations are quite close to the experimental data. Differences between experiment and calculation (Δ log P) exceeding ±0.50 are observed for compounds **22**–**24**, **27**, **28**, **46**, and **48**. Interestingly enough, all of them exhibit phenyl substitution in 4- or 5-position.

In sharp contrast, application of the same fragmental method to derivatives **49**–**68** yielded rather disappointing results. For this subgroup almost all Δ log P values exceed ±0.50 with the exception of compound **68** (Table III).

The possibility of dimer or polymer formation in the organic phase according to the equilibrium, shown in Scheme 2, is a specific physicochemical hypothesis why these compounds might have higher log P values than expected. Such a case is easily evidenced by log P values that increase with the initial concentration of the derivatives put into either of the two phases.

Having excluded the possibility of dimer formation, we decided to try systematically other methods of calculating log P. In detail, we applied the substructure-based programs ACD/log P (22, 23), CLOGP (24–27), KOWWIN (28), and XLOGP (30, 31) and the whole-molecule approach QLOGP (31). In Table II (columns 4-8), log P data obtained with these five software packages are confronted with experimental partition coefficients (column 2) as well as calculated data (column 3) based on the fragmental system outlined above and in detail described in Ref. 12. Validity of the calculations was compared as follows: as a first statistical criterion, the averaged absolute residual sums (AARS) for the differences between experiment and calculation are given. AARS represent the mean of the summed absolute differences between measured and calculated data. Second, the differences (Δ log P) between log P_{exp} and calculated data in the range of 0.00 to ±0.49 are qualified as acceptable, Δ log P values of ±0.50 to ±0.99 are viewed as disputable and differences exceeding ±0.99 are classified as unacceptable. In addition, the numbers of calculations exhibiting higher or lower values than experimental log P are counted. These data are given in Table IV for the database compounds **01**–**48** and for the subset of formyl and acyl derivatives **49**–**68**. Before inspecting the observed differences, it should be admitted that the rather small number of test molecules confines a generalization of such validity comparisons.

Comparing the results for database compounds **01**–**48** with those for the subset of formyl and acyl derivatives **49**–**68** immediately shows profound differences. On the basis of the averaged absolute residual sums (AARS) the fragmental



Scheme 2. Hypothetical dimer formation.

Table III. log P Values Found with Different Initial Concentrations of Dithiolethione

Initial concentrations[a] (mol $L^{-1} \times 10^{-3}$)	log P_{HPLC}
1.05	2.47
1.12	2.58
1.12	2.53
1.64	2.68
1.71	2.65
5.15	2.35
5.19	2.56
6.68	2.37
5.01	2.55[b]

[a] In octanol.
[b] Value found by spectrophotometry.

Table IV. Comparative Validity Check of Calculation Programs

	Ref. 12	ACD/log P	CLOGP	LOGKOW	XLOGP	QLOGP
Compounds 01–48						
AARS	0.20	0.24	**0.19**	0.30	1.08	0.75
Acceptable	39	43	46	38	7	17
Disputable	7	3	1	9	11	13
Unacceptable	0	2	1	1	30	18
>log P obs.	28	20	30	29	0	41
<log P obs.	14	25	18	18	48	6
Compounds 49–68						
AARS	1.06	1.44	1.15	0.73	1.62	**0.62**
Acceptable	3	0	1	7	1	9
Disputable	4	3	5	6	1	4
Unacceptable	12	16	12	6	17	6
>log P obs.	0	0	0	4	0	2
<log P obs.	19	19	19	15	19	17

AARS (averaged absolute residual sum) values show that substructure approaches perform better for the alkyl- and aryl-substituted DTT and DTO **01**–**48**, whereas the whole-molecule approach QLOGP performs better in the case of the formyl- and acyl-substituted DTT and DTO **49**–**68**.

methods ACD/log P (AARS = 0.24), CLOGP (0.19), and KOWWIN (0.30) perform significantly better than the atom-based approach XLOGP (1.08) and the whole-molecule method QLOGP (0.75), when inspecting the database compounds **01**–**48**. The classification into acceptable, disputable and unacceptable calculations nicely mirrors this view. Counting the negative and positive deviations of calculations from experimental log P demonstrates a rather equilibrated pattern for ACD/log P. A trend to overestimate log P is observed for CLOGP, KOWWIN, and QLOGP, whereas XLOGP underestimates all 48 structures.

Inspecting the subset of formyl and acyl derivatives **49**–**68** on the basis of the AARS values demonstrates that the whole-molecule method QLOGP (0.62) is superior to the four substructure-based approaches KOWWIN (0.73), CLOGP (1.15), ACD/log P (1.44), and XLOGP (1.62). This finding might reflect the well-known obstacle of substructure-based approaches to fail in coping with extended intramolecular interactions and explain the better performance of QLOGP. Regarding negative and positive deviations of calculations from log P_{exp}, all aproaches preferentially (KOWWIN, QLOGP) or exclusively (ACD/log P, CLOGP, XLOGP) underestimate log P.

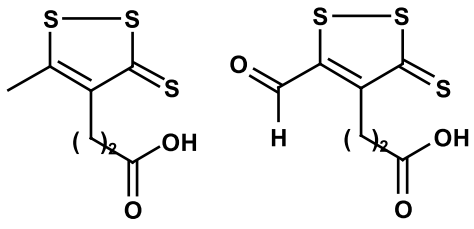
The failure of the calculation programs to correctly predict their log P probably indicates the occurrence of some hidden physicochemical phenomenon resulting from the juxtaposition of the acyl and dithiole moieties. From the thermodynamic standpoint, log P is endowed with the significance of the standard free enthalpy of partitioning ΔG°_{T} of the solute from water into the organic solvent. For the water/n-octanol system the following relation between ΔG°_{T} and ln P stands:

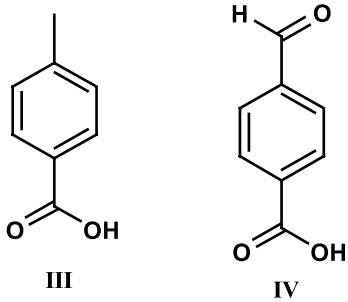
$$\Delta G^{\circ}_{T_{(\text{water}\rightarrow n-\text{octanol})}} = -RT \ln P_{(\text{water}\rightarrow n-\text{octanol})} \qquad (1)$$

Strictly speaking, P must be defined as being the ratio of the activities in both solvents at equilibrium. It is evident that some of the fragmental methods for log P are based on the additivity of the partitioning free enthalpies of the different constitutive fragments of the molecule and the thermodynamic significance of log P induces immediately the search for its enthalpic ΔH_T and entropic ΔS_T components. Their knowledge may allow some insight into the solvation and desolvation processes which occur during the transfer. The knowledge of ΔH_T and ΔS_T may also provide an explanation for occasional failure of the additivity of fragmental log P values.

We have devised a calorimetric method that permits the determination of the transfer enthalpy ΔH_T of a solute between two phases. In some favorable cases it permits also the determination of its log P and hence its transfer entropy ΔS_T (33). It involves isoperibol thermometric titrations. The advantage of this methodology is to provide a direct calorimetric measurement of ΔH_T. However, it requires the solute to be an acid or a base.

In Ref. 34, this method was applied to the determination of the water/*n*-octanol partitioning parameters ΔH°_{T}, ΔG°_{T}, and ΔS°_{T} of 1,2-dithiole-3-thiones **I** and **II** in order to explain the extreme differences between experimental and computed log P of 5-acyl-1,2-dithiole-3-thiones.





The following conclusions may be drawn from the consideration of the transfer thermodynamic functions of derivatives **I** and **II** on the one hand and of derivatives **III** and **IV** on the other: transfer entropy is greatly enhanced when the methyl group is replaced by the formyl one. A possible explanation is that there exists a strong solvation in water of 5-acyl-DTT by several water molecules which are released during the partitioning. From the structural standpoint, the particular solvation may involve the two ends of the electric dipole of water which interact with the positive charge brought by the sulfur atom (or even the whole dithiole nucleus) and the negative one of the oxygen atom. The occurrence of a positive electrical charge on the nucleus of dithiolethiones is a characteristic of this heterocycle and has been well-known for many years (35). In the particular case of 5-acyl-DTT the polarization of the dithiole nucleus and of the carbonyl group are confirmed by theoretical calculations (36).

There exists in literature another case of particular behavior of heteroatomic ketones with a thioatom in the heterocycle. Proton equilibria and the corresponding proton affinities concerning 2-thienylketones differ markedly from those concerning other aryl or heteroalkylmethylketones (37). In this case, the hypothesis of a particular solvation in relation with the proximity of the sulphur atom of the thiophene nucleus and of the carbonyl group may also be retained. Thus, the unexpectedly high log P values of 5-acyl-DTT demonstrate once more that the physico-chemical properties of the substituting moieties are strongly disturbed by the dithiole nucleus (38, 39).

CONCLUSIONS

Validity of the calculation approaches used here strictly depends on the subset under consideration. For compounds, comprising formyl and acyl substitution in 4- and 5-position, a strong underestimation of log P is observed. Thus, calculation methods need refinement to adequately treat particular solvation behavior suspected to prevail in these compounds. The comparably better performance of QLOGP in this subgroup might favor attempts to combine substructure- and whole molecule-based methodology in forthcoming log P calculation software.

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