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Thermodynamic investigation of the water/*n*-octanol partition coefficient value of a 5-formyl-1,2-dithiole-3-thione

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Abstract

Thermometric titrations performed in suitable conditions permit the determination of the enthalpic and entropic parts of the standard transfer-free enthalpy of a particular 5-formyl-1,2-dithiole-3-thione from water into *n*-octanol. It may be inferred from this determination that the far too high water/*n*-octanol $\log P$ values of 5-acyl-1,2-dithiole-3-thiones originate in an entropic effect which is in agreement with the hypothesis that these derivatives are more solvated in water than expected and hence with the hypothesis that during partitioning between the two phases, more molecules of water than expected are released from the solvated solute in the aqueous phase. The family of 1,2-dithiole-3-thiones is of growing importance in pharmacology.

Keywords: Thermometric titrimetry; Log P; 1,2-Dithiole-3-thiones; Standard transfer enthalpies

1. Introduction

The knowledge of the water/*n*-octanol partitioning coefficient P of a solute defined by:

$$P = \frac{C_{n\text{-octanol}}}{C_{\text{water}}} \quad \text{(at partition equilibrium)} \qquad (1)$$

is of considerable interest in pharmacochemistry. Actually, only $\log P$ values are considered. The importance of $\log P$ in the field of drug design is such that several methods have been devised to compute it [1–3]. Some of them are based on the fact that the $\log P$ values of the molecular or atomic fragments into which the molecule under consideration may be reduced, may be added to provide an accurate $\log P$ value for the whole molecule.

Fundamentally, from the thermodynamic standpoint, $\log P$ is endowed with the significance of the standard free enthalpy of partitioning $\Delta G^\circ_{\text{T}}$ of the solute from water into the organic solvent. For the water/*n*-octanol system the following relation between $\Delta G^\circ_{\text{T}}$ and $\ln P$ stands:

$$\Delta G^\circ_{\text{T(water}\rightarrow n\text{-octanol)}} = -RT \ln P_{(\text{water}\rightarrow n\text{-octanol})} \qquad (2)$$

It pertains to isobaric and isothermal conditions. Strictly speaking, P must be defined as being the ratio of the activities in both solvents at equilibrium. (Statistical thermodynamic reasoning shows that activities must be related to concentrations expressed in $\text{mol}\,\text{L}^{-1}$ rather than to any other kind of expression of the composition so that $\log P$ corresponds exclusively to the solvation changes accompanying the transfer [4].)

Hence, it is evident that some of the above-mentioned computing methods of $\log P$ 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 bring some interesting insight into the solvation and desolvation processes which occur during the transfer [5]. Some determinations of this kind have already been performed [6–8]. The knowledge of ΔH_{T} and ΔS_{T} may also

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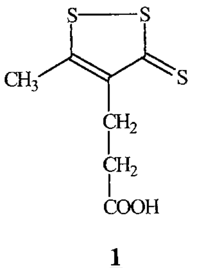
provide an explanation for occasional failure of the additivity of fragmental log *P* values. Reciprocally, failure is evidenced by significant discrepancies between computed and experimental values.

We have devised a calorimetric method which permits the determination of the transfer enthalpy ΔH_T of a solute between two phases. In some favourable cases it permits also the determination of its log *P* and hence its transfer entropy ΔS_T [9]. 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 this work this methodology 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 **1** and **2**



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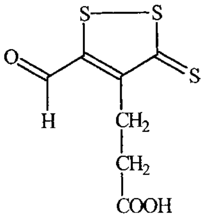

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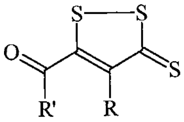
in order to obtain a beginning of explanation for the far too important differences between the experimental and computed log *P* values of 5-acyl-1,2-dithiole-3-thiones **3** [10,11]



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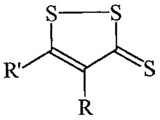

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The family of dithiolethiones **4** is currently of growing pharmacological importance. Among other properties, it is at the center of the pharmacological concept of cancer chemoprevention [12]. 5-Acyldithiolethiones **3** are also endowed with other interesting pharmacological properties [13].

2. Experimental

2.1. Materials

UV spectra were recorded on a UVIKON 922 apparatus. pH-metric titrations for pK_a determinations of derivatives **1** and **2** were recorded on a Metrohm ion analysis Ltd CH 9101 piloted by the software Tinet. Thermometric titrations were performed with the apparatus already described [14]. Dithiolethiones **1** and **2** had been designed for the purpose of this work (see Section 3). Their synthesis is described elsewhere [15]. It must be noticed that synthesis of dithiolethione **2** offered some difficulties.

Prior to each determination, the purity of each derivative was checked by determination of its melting point and also by TLC using two pairs of solvents. *p*-Methyl- and *p*-formylbenzoic acids, the partitionings of which were also studied for the sake of comparison, were commercial products (Acros) and used as they were purchased. Hydrochloric acid ($1\,\mathrm{mol\,L^{-1}}$) and *n*-octanol were of analytical grade. Water and *n*-octanol were mutually saturated before experiments.

2.2. Calorimetric determinations

Calorimetric measurements involved thermometric titrations of the carboxylate salts of dithiolethiones **1** and **2** by an aqueous hydrochloric acid solution in a biphasic medium containing a known ratio *r* of water and *n*-octanol volumes [9]. The overall physico-chemical processes which occur may be schematized according to:

$$\mathrm{RCOO_w^{\ominus}} + \mathrm{H_w^{\oplus}} \rightarrow \mathrm{RCOOH_w} \rightleftharpoons \mathrm{RCOOH_{oct}}$$

We demonstrated that slope *A* of the titration curve: thermal effects versus volumes *v* of added titrant solution is given by relation:

$$A = C_T\left[\Delta H_P + \frac{\Delta H_T}{1 + (r/P)}\right] \quad (3)$$

where ΔH_P is the protonation enthalpy of the carboxylate salt and C_T the titrant molarity. Thermal effects which are taken into account are, of course, those corrected for inevitable parasitic thermal effects accompanying a thermometric titration [16]. Let us recall that for this relation to apply, the following assumption was admitted: the only species to partition is the acid and the concentrations $[\mathrm{OH^-}]$ and $[\mathrm{H^+}]$ in the aqueous phase are negligible in the electroneutrality relation. Furthermore, thermal effects resulting from the possible salting out of *n*-octanol from water or conversely during the titration were neglected. In the current work, ratios *r*/*P* were negligible in relation (3) and hence the independent determination of ΔH_P was necessary.

The following procedure was validated in a previous work [9]. The total volume of both the aqueous and organic phases in the calorimeter was $92\,\mathrm{cm^3}$. Different volumes were chosen for the organic phase (0.5–1–2–5–$10\,\mathrm{cm^3}$) to obtain different ratios *r* of *n*-octanol and water volumes ($r = V_{aq}/V_{oct}$). The volume of the aqueous phase necessary to complete that of the organic phase (to obtain the required total volume) was introduced into the calorimeter and followed by the introduction of the organic phase. The aqueous phase contained 5×10^{-4} mol of titrand. The titrant ($1\,\mathrm{mol\,L^{-1}}$) was delivered at the constant rate of 0.0085 ($\pm 6 \times 10^{-5}$) $\mathrm{cm^3\,s^{-1}}$. Titration vessel and titrant delivery tip were enclosed in a bath at constant temperature. Care was taken to exactly match the temperatures of titrand and titrant solutions at the beginning of the titrant addition in order to minimize non-chemical thermal effects. Protonation enthalpies ΔH_P were obtained in the same manner as above except for the fact that no *n*-octanol was added into the calorimeter. For all calorimetric measurements, only initial slopes of the thermograms were retained. It has, indeed, been demonstrated that working with them minimize parasitic thermal effects [17]. There was a further reason to work with the initial slope in the case of the determination of protonation enthalpies for which no octanol was added: the precipitation of the carboxylic acid formed by protonation during the titration gives a supplementary parasitic thermal effect. At the very beginning of the titration corresponding to the initial slope of the thermogram no precipitation had occurred yet. Finally, working with the initial slope is interesting because at the beginning of the titration, the curvature of the thermogram which possibly would result from the protonation equilibrium:

$$\mathrm{RCOO}^{\ominus} + \mathrm{H}^{\oplus} \rightleftharpoons \mathrm{RCOOH}$$

is negligible [18]. Hence the protonation enthalpy cannot be underestimated because of an incomplete reaction. The initial slope values retained for calculations were the average of four measurements for each ratio *r*.

2.3. Determination of log P values

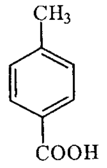
This work required determining $\log P$ values of dithiolethiones **1** and **2**. Partition coefficients P were calculated as ratios of concentrations in $\mathrm{mol\,L^{-1}}$ in octanol and in water according to relation (1). Our methodology, previously validated [9], consisted in determining the concentration of the solute in the aqueous phase once the partition equilibrium had been achieved by shaking both solvents. The aqueous concentration of dithiolethiones **1** and **2** were, respectively, determined by HPLC (with a UV–visible detector) and directly by UV spectrophotometry at 410 nm. In both cases the sample concentration was determined by comparison to a calibration curve constructed with five points chosen in the same range of concentrations as the measured one (from 0.5 to 1.5 times the sample concentration). Owing to the low water solubility of solutes, the solutions used to build up the calibration curve were prepared by dissolving a known amount of solute in methanol; this solution was first diluted with methanol/water (50/50, v/v). Then the latter solution was diluted with pure water. The resulting precision of the $\log P$ determination was estimated to be ±0.1 $\log P$ unit.

2.4. pK_a determinations

They were performed at 298 K according to our methodology which consists in finding the best-fit between calculated and experimental pH-curves obtained during titration of the acids [19]. Owing to the poor solubility of acids in water, working solutions were filtered before they were studied in order to eliminate the undissolved solute. Hence, the concentration of compounds was unknown. As a result, the fitting process of the calculated titration curve to the experimental one required taking into account both pK_a and concentration parameters as unknowns.

3. Results and discussion

Table 1 mentions the average slope values. Table 2 gives the thermodynamic parameters of water/*n*-octanol transfer of dithiolethiones **1**, **2** and of *p*-methylbenzoic acid **5** and *p*-formylbenzoic acid **6**



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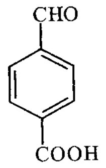

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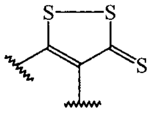
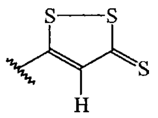
The goal of this work was to provide a thermodynamic explanation for the very abnormal $\log P$ values of 5-acyl (or 5-formyl) dithiolethiones **3**. A comparison of experimental $\log P$ values with calculated ones evidenced this phenomenon, $\log P$ values were calculated with the help of fragmental constants f(o) and f(I) (chosen according to the substituent in position 4) and with the help of the fragmental aromatic constant f(CHO) for the position 5 together with the convenient Rekker fragmental constant for the substituent in 4 [10,11]



f(o)



f(I)

It must be noticed that when the fragmental f(CHO) aliphatic value was used, the discrepancy between the experimental and the calculated $\log P$ was still higher than with the fragmental f(CHO) aromatic one. The mean of the discrepancy $A \log P$ between the experimental and the calculated $\log P$ established starting from 14 derivatives was 1.08 and, thus, was well above the limit ±0.2 retained by Rekker [20] to consider some derivatives as being outliers (from the standpoint of $\log P$ values) in a chemically homogeneous series.

In a first step the hypothesis of the formation of some kind of dimer of derivatives **3** in octanol (which would explain the abnormal $\log P$ values [21]) was ruled out by determination of $\log P$ starting with different initial concentrations of solute. After that, we thought of an abnormal entropic or enthalpic effect occurring during the partitioning.

To check this hypothesis we addressed ourselves to the study of the derivative **2** to obtain the partitioning enthalpy and entropy of a derivative bearing a formyl group in position 5. Compound **2** was designed according to the following requirements:

- first of all our calorimetric methodology requires that the molecule under study must be a protolyte. Hence, the presence of the carboxylic group is justified;
- secondly the occurrence of the carboxylic group must not change the solvations of 5-formyl and 5-acyl groups of

Table 1
Average slope values ($J\,mol^{-1}$) at each ratio r for derivatives **1**, **2**, **5**, **6** at $T = 298\,K$

	$r = 5.13$	$r = 8.20$	$r = 17.40$	$r = 45$	$r = 91$	$r = 183$	$r = 305.7$
5-Methyldithiolethione (**1**)	–	−2483	−2165	−1921	−1407	−924	–
5-Formyldithiolethione (**2**)	–	−2989	−2644	−2034	−1468	–	–
p-methylbenzoic acid (**5**)	–	–	−2596	−2269	−1926	−1592	−1217
p-Formylbenzoic acid (**6**)	−2163	−1965	−1763	−1333	−999	−707	–

> derivatives **3** in both solvents. It seemed to us that this may be the case with derivative **2** in which a bridge of two methylene groups separates the dithiole nucleus from the carboxylic group.

In another respect, we also decided to compare results obtained with derivatives **1** and **2** on the one hand with those obtained with the *p*-methyl- and *p*-formylbenzoic acid **5** and **6** on the other hand in order to detect an abnormal entropic or enthalpic effect during the transfer of **2**. At first glance, indeed, it may be thought that for physico-chemical reasons given below, the same trends in the variation of partitioning parameters exist when *p*-methylbenzoic acid is replaced by *p*-formylbenzoic acid on the one hand and when dithiolethione **1** is replaced by dithiolethione **2** on the other hand.

Hence, the discussion of the results follows three lines. Firstly, we bring some experimental arguments which show that there exists no noticeable interaction between the dithiole nucleus and the carboxylic group in compound **3** and, thus, this justifies the attribution of some results obtained with **2** to derivatives **3**. Secondly, we give the reason of the choice of the pair **5** and **6** for the sake of comparison with the pair **1** and **2**. Finally, we draw inferences from the results.

pK_a values of derivatives **1** and **2** determined in this work are, respectively, 4.65 and 4.70. These values are those of acetic acid (4.75 at 298 K) [22]. This result precludes any strong interaction between the dithiole nucleus and the carboxylic group in both derivatives. Moreover, the nearly identical values 4.65 and 4.70 precludes also any interaction between the formyl and carboxylic groups. The protonation enthalpies of **1** and **2** ($\Delta H = -1.46$ and $-1.59\,kJ\,mol^{-1}$, respectively) are normal (for comparison see [23]). As a result the carboxylic group is not in a strong electronic or steric interaction with the dithiole nucleus. We recall by the way that the dithiolethione nucleus is a group which modifies very strongly the physico-chemical properties of groups which are adjacent to it or which are even separated by one methylene bridge [24].

The choice of *p*-methylbenzoic acid **5** and *p*-formylbenzoic **6** acid was justified by the fact that it may permit finding some trends in the evolution of the partitioning thermodynamic parameters when a methyl on an aromatic nucleus is replaced by a formyl group. This is the case with dithiolethiones **1** and **2**. The chemistry of 1,2-dithiole-3-thiones is, indeed, characterized by two main physico-chemical properties which may be born in mind:

- they are aromatic compounds [25,26],
- the 3-thioxo-1,2-dithiole-5-yl group is a very strong electron-withdrawing one [19].

These features are also exhibited by compound **6** in which the formyl group is brought by a withdrawing aromatic group.

The following conclusions may be drawn from the consideration of the transfer thermodynamic functions of derivatives **1**, **2**, **5** and **6** (Table 2):

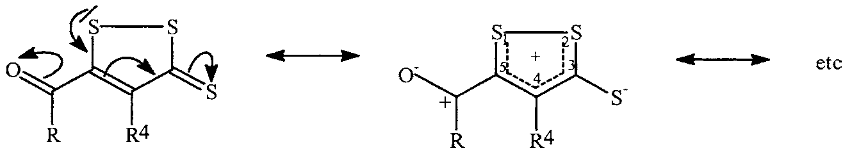
- *p*-methylbenzoic acid partitioning is both enthalpic- and entropic-driven whereas that of *p*-formylbenzoic acid is roughly solely an enthalpic process with a very weak entropic effect. Hence, in this series, replacing a methyl group by a formyl one leads to a marked decrease in the transfer enthalpy. It may be explained by the fact that the formyl group is more solvated in octanol than in water;
- it is exactly the opposite case for dithiolethiones **3** and **4**. Transfer entropy is greatly enhanced when the methyl group is replaced by the formyl one. It is interesting to notice that in dithiolethiones **3** there exists a conjugation between the formyl and the dithiole nucleus, which groups are both strong electron-withdrawing ones (Scheme 1).

Table 2
Thermodynamic parameters of water/*n*-octanol transfer of derivatives **1**, **2**, **5**, **6** at $T = 298\,K$

	ΔH°_T ($kJ\,mol^{-1}$)	ΔG°_T ($kJ\,mol$)	$\log P$	ΔS°_T ($J\,K^{-1}\,mol^{-1}$)
5-Methyldithiolethione (**1**)	−9.59	−11.63	2.04	6.85
5-Formyldithiolethione (**2**)	−11.05	−15.57	2.73	15.16
p-Toluic acid (**5**)	−9.99[a]	−13.40	2.35	11.47[a]
p-Formylbenzoic acid (**6**)	−7.85[b]	−8.67	1.52	2.74[b]

[a] $\Delta H^\circ_T = -10.78\,kJ\,mol^{-1}$ and $\Delta S^\circ_T = -6.86\,J\,K^{-1}\,mol^{-1}$ [29].

[b] $\Delta H^\circ_T = -17.04\,kJ\,mol^{-1}$ and $\Delta S^\circ_T = -22.84\,J\,K\,mol^{-1}$ [29].



Scheme 1.

This is exactly the case in *p*-formylbenzoic acid **6**. But, no abnormal $\log P$ values are mentioned for benzaldehydes substituted by electron-withdrawing groups. Hence, the behaviour of **3** with respect with that of **6** is quite different, notwithstanding the existence in both derivatives of two conjugated electron-withdrawing groups in opposition.

A possible explanation is that there exists a strong solvation in water of 5-acyldithiolethiones **1** 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 1 (or even the whole dithiole nucleus) and the negative one of the oxygen atom (Scheme 1). 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. In the particular case of 5-acyldithiolethiones the polarization of the dithiole nucleus and of the carbonyl group is confirmed by theoretical calculations (Scheme 1) which show the occurrence of both the withdrawing groups [27].

To our knowledge there exists in the literature another case of particular behaviour of heteroaromatic ketones with a thioatom in the heterocycle. Proton equilibria and the corresponding proton affinities concerning 2-thienylketones differ, indeed, markedly from a mechanistic standpoint from those concerning other aryl or keteroarylmethylketones [28]. In this case, the hypothesis of a particular solvation in relation with the proximity of the sulfur atom of the thiophen nucleus and of the carbonyl group may also be retained. Thus, it seems that, the part played by the sulfur atom 1 of derivatives **1** and that played by the sulfur atom of the thiophene ring is crucial.

Finally, it must be noted that the results we obtained with *p*-formylbenzoic acid **6** are quite different from those already reported in the literature. In particular, the partitioning enthalpies differ considerably. This is not the case with *p*-toluic-acid **5** for which discrepancies appear only with $\log P$ ($\Delta G^\circ_\mathrm{T}$). The results reported in the literature were obtained by using the Van't Hoff isochore principle.

Acknowledgements

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