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On the Lipophilicity of the 1,2-Dithiole-3-thione Nucleus

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Lipophilicity of the 1,2-dithiole-3-thione nucleus was studied by stepwise calculation of log *P* values of some dithiolethiones from fragmental lipophilic constants of suitable fragments composing the nucleus, and the results were compared with experimental values. Fragmental constants necessary for these calculations were determined from log *P* values of suitable molecules. The influence of conjugation between the different parts was investigated. Fragmental lipophilic constants of unusual thio-fragments were assessed.

Key words 1,2-dithiole-3-thione; lipophilicity; 1-octanol/water partitioning; log *P*

1,2-Dithiole-3-thiones (**1**, X=S) (Fig. 1) have interesting pharmacological properties[1-3] and exhibit promising chemoprotective effects against hepatic carcinoma.[4,5] This prompted us to determine their water/*n*-octanol partition coefficient: log *P*[6] as a part of our systematic studies of 1,2-dithiole-3-thiones[7,8] and of lipophilicity.[9]

In our previous study,[6] we detected some variation in log *P* values according to the alkyl or aryl nature of the fragment linked at position 4 or 5 of the dithiole nucleus. As a result, we advocated the use of five different fragmental constants for accurate calculation of the log *P* values of new dithiolethiones. The 1,2-dithiole-3-thione nucleus as a whole was included in all these fragments.

At this stage of our research, it seemed interesting to study the intrinsic lipophilicity of the 1,2-dithiole-3-thione nucleus. More precisely, we wanted to study the contribution of the different fragments composing the dithiolethione nucleus to its lipophilicity. Another aim of this work was to obtain values of unknown fragmental constants of unusual thio-fragments.

Principle The strategy we followed was to calculate, step by step, the log *P* values of some dithiolethiones from suitable fragmental constants and to compare the calculated log *P* values with the experimental ones. We focused our attention on the study of tetrahydrobenzodithiolethione **1a** ($R_1=R_2=(CH_2)_4$) because we had previously noted that it exhibits a "normal" log *P* value for a 4,5-dialkyl dithiolethione,[6] and because of the possibility of geometrical isomerism (see below). The sequence we decided to follow to calculate log *P* is shown in Fig. 2.

The reason for this choice was the ease of calculation of the lipophilicity of the A, B and C fragments from the experimental log *P* values of, respectively; cyclohexene, 1-methylthiocyclohexene, and methyl-2-methylthiocyclohexenyl-1-carbodithioate **2a** (Fig. 3).

It is evident that, in **2a**, the ring prevents the formation of *E* and *Z* isomers. Such isomerization might give an inaccurate starting log *P* for the calculation of the C fragmental value. For the sake of comparison, we also performed a similar sequential determination for the dithiolethiones **1b** (R_1R_2 (CH= CH–CH=CH): benzodithiolethione), **1c** (R_1R_2 $(CH_2)_3$) and **1d** ($R_1=H$, $R_2=CH_3O-C_6H_4$, trithioanethole), keeping in mind that these compounds would provide atypical values: **1b** because a conjugative effect is expected; **1c** because the dithiolethione moiety was found to be a somewhat deviant one[6]; **1d** for the reason given above. In one case, lipophilicity of fragment C was also calculated from the log *P* value of the corresponding α-(ethylenedithio)-methylene-thioketone **3c** (R_1R_2: $(CH_2)_3$). Further to study the step B→C, we calculated fragmental values of (S–C=S) after determination of the log *P* values of compounds **4a** and **5a** on the one hand, and of compounds **4b** and **5b** on the other.

Experimental

Chemicals Dithiolethiones **1a**, **1b**, and **1c** were prepared according to the literature.[6] Trithioanethole **1d** was kindly supplied by Solvay-pharma. Methyl 3-methylthiopropenedithioates **2b**, **2c**, and **2d** were prepared according to the literature.[10] This method failed to afford **2a**. Therefore **2a** was prepared by phosphoruspentasulfide reaction of α-bis(methylthio) methylenecyclohexanone in toluene for 1/2 h, at room

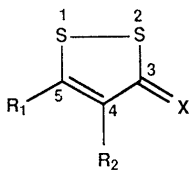

Fig. 1

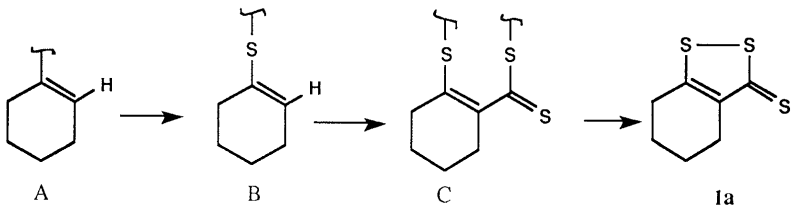

Fig. 2

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temperature, followed by chromatography on silica-gel (Fig. 4).

Methyl 2-Methylthiocyclohexenyl-1-carbodithioate **2a**: Red liquid: NMR ($CDCl_3$); δ (ppm/TMS): 3H; s; 2.2–3H; s; 2.6–4H; 1.7—4H; m; 2.4. Compound **3c** has been described in literature.[11] Products **4a** and **4b** were commercial products (Janssen). The dithioesters **5a** and **5b** have been described.[12,13] 1-Methylthio-1-cyclohexane was prepared according to the literature.[14] Purity of all compounds was checked by TLC with two solvent systems before log *P* determination.

Determination of log *P* The chief difficulty of this determination was the extreme insolubility of the compounds in water and, as a result, transfer of the solute from *n*-octanol into water could not be assessed from the change of concentration in the organic phase, since this was not appreciable. Therefore, we had to determine the concentration of solutes in water after partitioning equilibrium was reached. We employed RP-HPLC with spectrophotometric detection for this purpose, and log *P* was calculated as the ratio of concentrations in octanol and in water. Use of the concentrations in place of the activities was legitimate because the concentrations of solute in water are very low and because the solutes are not ionic ones.[15] Our methodology was similar to that followed by Camilleri *et al.*[16] and by Hansch *et al.*[17]

An octanolic solution of a solute (10 ml) was introduced with 50 ml of water into a 250 ml separatory funnel and the mixture was mechanically shaken for 30 min at ambient temperature (20±1 °C). (We confirmed that shaking for more than 30 min did not significantly change the log *P* values.) The solutions were then left to stand for 2 h until the two layers were separated. The aqueous phase was centrifuged in stoppered tubes at 20±1 °C at 6000 rpm for 30 min and the residual octanol on the water layer was removed by aspiration. The water layer was directly analyzed by RP-HPLC through a 100 μl sample loop. The sample concentration was determined from a calibration curve constructed with five concentrations chosen in the same range as the measured one. For each compound, the resultant aqueous phase was divided into 4 portions. Each one was analyzed 3 times. The aqueous concentration introduced in calculations was the mean value of the 12 data. Each point of the calibration curve was similarly established. For example, if we consider the methyl 3-methylthiopropenedithioate **2c**, its water solubility was determined as 4×10^{-5} mol l^{-1}; in the shaken-flask experiment, the **2c** concentration in the octanolic phase was 5×10^{-3} mol l^{-1} and after partition, the **2c** concentration found in the aqueous phase was 1.26×10^{-6} mol l^{-1}.

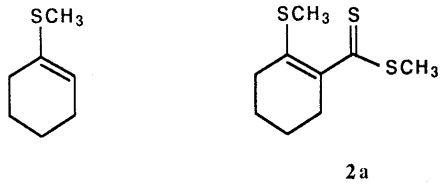
Materials The HPLC chromatograph was an LDC-Milton Roy system (Constametric III isocratic pump with a Spectromonitor II UV-visible detector. The RP-HPLC column was stainless steel tubing (i.d. 4.5 μm in diameter and 15 cm long) filled with 5 μm ODS2 stationary phase. The mobile phase was water–methanol mixtures (20–30/80–70, v/v). Water was doubly deionized on an ion-exchange resin. Water and *n*-octanol were mutually saturated before use. The UV-visible spectrophotometer was a double-beam Uvikon 930 (Kontron) with baseline correction.

Results and Discussion

Determined log *P* values necessary to perform this study are summarized in Table 1.

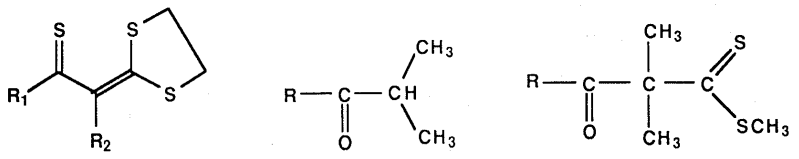
Step (A)→(B) The fragmental constant of A (2.68) was obtained in a straight-forward manner from the experimental cyclohexene log *P* (2.86)[18] lowered by f_H (0.18).[19] The fragmental constant of B (2.61) was likewise obtained from the 1-methylthiocyclohexene log *P* (Table 1) lowered by f_{CH_3} (0.69).[19] According to these two results, the step A→B, which simply corresponds to the addition of fragment f_S, reduces the lipophilicity by (−0.07). This results is not in agreement with the values f_S(al) = −0.51 and f_S(ar) = +0.11 given by Rekker and de Kort.[20] This may imply that there is some sort of conjugation of one of the doublets of the thio atom with the double bond in 1-methylthiocyclohexene (Fig. 5).

Step B→C Starting from log *P* values of 1-methylthiocyclohexene and methyl-3-thiopropenedithioate **2a** (Table 1) and taking into account f_H, we obtained f(S–C=S)≈0. Since no f(S–C=S) value has been reported in the literature, we tried to gain some independetn insight into the plausibility of this value. For this, we addressed ourselves to the β-ketonic dithioesters **5a** and **5b**, in the structures of which the α-methyl substituents prevent enethiolization. From the log *P* values of the ketones **4a** and **4b** and those of the β-ketonic dithioesters **5a** and **5b** we found f(S–C=S)≈0.82. This value is much higher than that found for the transformation B→C (f(S–C=S)≈0). The discrepancy is probably the result of steric hindrance by the two methyl groups which prevent solvatation in water of the thiocarbonyl moiety in the dithioesters **5a**, **b**. Likewise, we found that 4-alkyldithiolethiones were more lipophilic than expected.[6] In view of these findings, it is impossible to ascribe an increase in lipophilicity to step B→C because of the conjugation between S–C=S and B fragments.



2a

Fig. 3



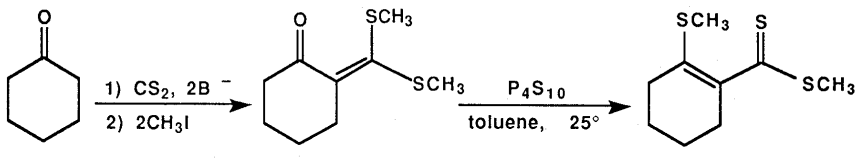
3c

4a R = CH_3

4b R = C_6H_5

5a R = CH_3

5b R = C_6H_5



2a

Fig. 4

Table 1. Experimental log *P* Values

Methyl 3-methylthio-propene dithioate **2**	**2a** 3.81	**2b** 3.74	**2c** 3.59	**2d** (*E*+*Z*) 4.10
Ketones **4**	R=CH_3 1.44		R=C_6H_5 2.59	
β-Ketonic-dithioesters **5**	R=CH_3 2.80		R=C_6H_5 3.90	
Miscellaneous	1-Methylthiocyclohexene 3.30			**3c** 3.12

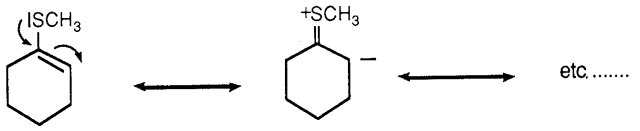


Fig. 5

Table 2. Ring Closure Effect on Lipophilicity of Dithiolethiones

Dithiolethiones	C fragment	log *P*(exp)	*Δ*
2a	2.43	3.10	+0.67
2b	2.36	3.57	+1.21
2c	2.21	2.53	+0.32
	2.08[a]		+0.45
2d	2.72	2.82	+1.10

a) Calculated after **3c** (see Table 1) with $f_{CH_2}=0.52$.[20]

Step C→1a This step quantifies the effect on lipophilicity of ring closure with the acquisition of aromaticity, since 1,2-dithiole-3-thiones are considered as aromatic compounds.[21-23] From the value $f(C)=2.43$ and **1a**'s log $P=3.10$ we found a large increase in lipophilicity. Table 2 gives the calculated increases in lipophilicity upon ring closure for the dithiolethiones: **1a**, **1b**, **1c**, and **1d**. (In the above calculations from the **3c** log *P* (see Table 1), we used $f_{CH_2}=0.52$[20]).

Fragmental Lipophilic Constants of Unusual Thiofragments Table 2 indicates that ring closure undoubtedly generates an increase of lipophilicity, because it allows a more extended conjugation which indeed confers an aromatic character upon 1,2-dithiole-3-thiones. For the reason given above, $\Delta=+0.67$ found with tetrahydrobenzodithiolethione can be considered as typical. The $\Delta=+0.32$ and $+0.45$ values found with **2c** are probably slightly low owing to the fact that this dithiolethione is somewhat deviant, because it was less lipophilic than excepted.[6] High Δ values of 1.21 and 1.10 found with benzo and 5-*para*-methoxyphenyl-dithiolethiones **2b**, **2d** are the results of strong conjugation between the nucleus and substituent. Moreover, $\Delta=+1.10$ found with **2d** is somewhat questionable for the reason given above.

Finally, we were interested in finding the values of $f_{C=S}$ and $f_{S-C=S}$ in 1,2-dithiole-3-thiones: *i.e.* the values of conjugated $f_{C=S}$ and $f_{S-C=S}$ fragmental constants. Owing to the fact that dithiolethiones are aromatic compounds, we decided to check, as a first step, the feasiliblity of attributing f_S (0.37)[19] to the thio atoms as found for the sulfur atom of thiophene. In order to do that, we calculated the log *P* value for the parent 1,2-dithiole-3-one ($R_1=R_2=H$; X=O) according to the equation:

$$\log P = 2f_S + f_{C=O} + 2f_C + f_H + f_{H^*}$$

(H*: H linked to a strongly attractive group[19])

where $f_S=0.37$[19]; $f_{C=O(ar)}=-0.89$[19]; $f_H=0.18$[19]; $f_C=0.15$[19]; $f_{H^*}=0.46$[18] (f_{H^*} was chosen for the H substituent at position 5 because the 5-(1,2-dithiole-3-thione)yl group is a very attractive one[24-26]).

We found log *P*(cal)=0.79, in good agreement with the sequential value log *P*(exp)=0.82.[6] This first step demonstrated that it is reasonable to ascribe to the 1,2-thio atoms of the dithiole nulceus the fragmental constant $f_S=0.37$. In the second step, we determined $f_{C=S}$ by working with log *P* of the parent dithiolethione ($R_1=R_2=H$, X=S) (log $P=1.58$[6]). We applied the relation

$$f_{C=S}=1.58-(2f_S+2f_C+f_H+f_{H^*})$$

and found $f_{C-S}=-0.10$ and, hence, $f_{S-C=S}=+0.27$. These values must be considered valid only for C=S and S–C=S in an aromatic group. It should be noted that calculations from scratch of the log *P* values of dithiolethiones, with $f_{S-C=S}=0.27$ and $f_S=0.37$, did not work very well. The values obtained were understimated.

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