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Thermodynamics of partitioning of some sulfonamides in 1-octanol–buffer and liposome systems†

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ABSTRACT: The thermodynamics of partitioning of some structurally related sulfonamides have been determined in 1-octanol–aqueous buffer and liposome systems. The partition coefficients were approximately tenfold higher in liposomes compared with 1-octanol. The enthalpies of transfer from aqueous media to organic systems were positive in liposomes but negative or positive in 1-octanol, whereas the entropies of transfer were positive in almost all cases.

KEYWORDS: sulfonamides; partition coefficient; liposomes; 1-octanol; thermodynamics of transfer

INTRODUCTION

Sulfonamides are drugs extensively used for the treatment of certain infections caused by Gram-positive and Gram-negative microorganisms, some fungi, and certain protozoa. Although the advent of antibiotics has diminished the usefulness of sulfonamides, they still occupy a relatively small but important place in the therapeutic resources of physicians. Various physical and chemical parameters of these compounds have been correlated with chemotherapeutic activity: pK_a, protein binding, and electronic charge distribution, among others. Unfortunately, no single parameter can explain the action of sulfonamides.[1,2] Nowadays, we do not have enough information to propose suitable mechanisms for the transfer process of sulfonamides between immiscible liquid phases, and between aqueous media and biological membrane models, in order to explain the differences in the pharmacological power as a function of the molecular structure.[3]

The solution thermodynamics of drug molecules can be studied by measuring the partition coefficient as a function of temperature. Such data can be used for the prediction of absorption, membrane permeability, and *in vivo* drug distribution.[4] Semipolar solvents have been found to yield better correlations with partitioning of solutes in model membranes compared with non-polar solvents. In particular, 1-octanol has been found to be a useful reference solvent for extrathermodynamic studies on a variety of systems.[5–7] Nevertheless, the 1-octanol–water system was a poor model system for several drug transport processes and for the correlation among pharmacokinetic parameters. On the other hand, the liposome system has been shown to discriminate against branched solutes more than a bulk oil–water system in the case of some phenols,[8,9] phenothiazines,[10,11] β-blockers,[12] and non-steroidal anti-inflammatory drugs.[4] In addition, the partitioning was higher in liposomes than in 1-octanol for dipyridamole,[13] mefloquine, quinine and other anti-malarial drugs.[14,15]

The objective of this study was to compare the partitioning behavior of some structurally related sulfonamides in the 1-octanol–aqueous buffer, dimyristoyl phosphatidylcholine (DMPC), and dipalmitoyl phosphatidylcholine (DPPC) liposome systems using a thermodynamic approach based on the variation of partitioning with temperature.

MATERIALS AND METHODS

Materials and Equipment

Sulfonamides: sulfanilamide (SA), Merck; sulfapyridine (SP), sulfadiazine (SD), sulfamerazine (SMR), sulfamethazine (SMT), Sigma Chemical Co.; sulfacetamide (SCM), sulfathiazole (STL), sulfamethoxazole (SMX), USP Quality.[16] DMPC ref P-7331, DPPC ref P-5911, Sigma Chemical Co. Solvents: 1-octanol extra pure (ROH), Merck; distilled water (W) conductivity <2 μS, Laboratory of Industrial Pharmacy; chloroform

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A.R., Mallinckrodt. Other materials: potassium chloride A.R., Merck; sodium mono- and di-hydrogen phosphates A.R., Merck; citric acid and sodium hydroxide A.R., Merck; sodium acetate and acetic acid A.R., Merck.

Magni Whirl Blue M. Electric Company water baths; Wrist Action, Burrel, model 75 mechanical shaker; Mistral® Vortex mixer model 1192; Buchler Instruments evaporator; Biofuge 15R Heraeus Instruments centrifuge; Zeiss ICS Kf 2 optical microscope; Mettler AE 160 digital analytical balance, sensitivity of 0.1 mg; Unicam UV–Vis UV2–100 v 4.00 spectrophotometer; Nichiryo® micro pipettes.

1-Octanol–aqueous buffer partitioning

Both solvents were mutually saturated before performing the experiments. Solutions of sulfonamides of known concentration, about 5×10^{-5} mol l^{-1}, were prepared in aqueous buffer solutions, adjusted to the isoelectric points at ionic strength of 0.15 mol l^{-1}. Then 10.0 ml of 1-octanol were added to 10.0 ml of the aqueous sulfonamide solution in glass flasks. The mixtures were then stirred in a mechanical shaker for 1 h. Samples were allowed to stand in water baths kept at the appropriate temperature ±0.1 °C for at least 72 h. After this time the aqueous phases were isolated and the sulfonamide concentrations were determined by measuring the UV absorbances and interpolating from previously constructed calibration curves.[17] The partition coefficient was calculated from the mass balance. All the partitioning experiments were repeated at least three times and averaged.

Liposome–aqueous buffer partitioning

Liposomes were prepared by a modified Bangham method. Thin films of 50 mg of DMPC or DPPC were formed on the walls of 50 ml round-bottom flasks following rotary evaporation of 5 ml aliquots of a chloroform solution. Then, the flasks were placed in an oven at 40 °C for 24 h. The films were dispersed in 5 ml of aqueous drug solution (the same used in the 1-octanol–aqueous buffer partitioning), heated at 30 or 45 °C, and vortex-mixed until all the film was removed from the walls of the flasks.[18] This resulted in the formation of multilamellar vesicles (MLVs), which was verified by microscopy according to reported methods.[19] Drug distribution was determined in 48 h temperature-equilibrated MLVs in 1.2 ml samples, followed by centrifugation (25 000*g* for 60 min) at the specified temperature, from spectrophotometric analysis and mass balance calculations over the range 25 to 40 °C.[17] All partitioning experiments were repeated at least three times and averaged.

Determination of partition coefficients and the thermodynamic functions of transfer

The 1-octanol–aqueous buffer partition coefficients P were calculated as the equilibrium concentration ratio expressed in molarity between the organic and aqueous phases. The molal liposome/buffer partition coefficients $K_{l/w}$ were calculated using

$$K_{l/w} = W_{aq}(c_o - c_f)/(c_f W_{pl}) \quad (1)$$

where c_o and c_f (μg ml^{-1}) are respectively the initial and final concentrations of sulfonamide in the aqueous buffer phase before and after equilibration, W_{aq} (g) is the mass of aqueous phase, and W_{pl} (g) is the mass of phospholipid in the sample.

The standard free-energy of transfer $\Delta G_{w\to o}$ from aqueous media to organic systems was calculated thus:

$$\Delta G_{w\to o} = -RT \ln K \quad (2)$$

where K is equivalent to P expressed in molarity or $K_{l/w}$ expressed in molality.

The temperature dependence of partitioning (van't Hoff method) was employed to obtain data on the enthalpy of transfer $\Delta H_{w\to o}$, based on Eqn. (3), assuming that $\Delta H_{w\to o}$ is approximately independent of temperature over the range of interest.

$$\Delta H_{w\to o} = -bR \quad (3)$$

In Eqn. (3) the term b is the slope of the respective ln K versus T^{-1} weighted curve, obtained by using linear regression by the least-squares method.

The entropy of transfer $\Delta S_{w\to o}$ was obtained using

$$\Delta S_{w\to o} = (\Delta H_{w\to o} - \Delta G_{w\to o})/T \quad (4)$$

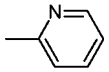
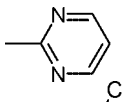
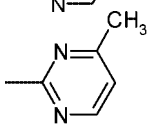
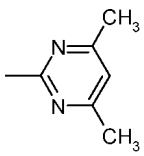
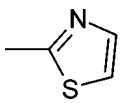
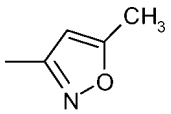
$\Delta H_{w\to o}$ and $\Delta S_{w\to o}$ represent the changes in enthalpy and entropy respectively when one mole of sulfonamide is transferred from the aqueous medium to the organic system at infinite dilution, in molarity for 1-octanol and in molality for liposomes.

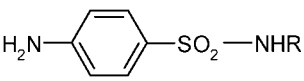
RESULTS AND DISCUSSION

Physicochemical properties of sulfonamides

The molecular structures of each sulfonamide, their abbreviations, and some of their physicochemical properties are summarized in Table 1. The pK_{a1} and pK_{a2} values were corrected to ionic strength values $\mu = 0.15$ mol l^{-1}, similar to the gastrointestinal tract value,[20] by means of the Debye–Hückel equation.[21] The pK_a values were taken from the literature.[22,23] For sulfamethoxazole, only pK_{a2} has been published;[23] then, a pK_{a1} average value with

Table 1. Some physicochemical properties of the sulfonamides

Sulfonamide	Abbreviation	R[a]	MW/g mol^{-1}	pK_{a1}[b]	pK_{a2}[b]	pI[c]	λ_{max}/nm[d]
Sulfanilamide	SA	—H	172.2	2.54	10.28	6.41	258 262 538
Sulfacetamide	SCM	—CO—CH_3	214.2	1.94	5.26	3.60	269 271 543
Sulfapyridine	SP		249.3	2.74	8.29	5.52	261 270 538
Sulfadiazine	SD		250.3	2.14	6.34	4.24	264 270 540
Sulfamerazine	SMR		264.3	2.24	6.92	4.58	263 270 541
Sulfamethazine	SMT		278.3	2.54	7.22	4.88	262 270 543
Sulfathiazole	STL		255.3	2.54	6.98	4.76	283 289 542
Sulfamethoxazole	SMX		253.3	2.5	5.45	4.0	267 269 537

[a] Substituent on the basic structure of sulfanilamide: 

[b] Corrected to $\mu = 0.15$ mol l^{-1} by means of the Debye–Hückel equation.
[c] $pI = (pK_{a1} + pK_{a2})/2$.
[d] First value in water at the isoelectric point, second in absolute ethanol, and third as azo-colorant derivative in water.

respect to other sulfonamides was used. Since the partitioning of sulfonamides in water is pH dependent (the compounds studied are amphoteric), this property was determined at the isoelectric point (pI), where $pI = (pK_{a1} + pK_{a2})/2$. At this pH the sulfonamides have their largest partitioning because the molecular compound without ionization dominates.[24] Each pH value was buffered by acetate (SP, SD, SMR, SMT, STL, SMX), citrate (SCM), or phosphate (SA) buffers, having a buffer capacity β between 0.01 and 0.02 using pK_a values corrected to $\mu = 0.15$ mol l^{-1}.

Partition coefficients

Table 2 summarizes the temperature dependence of the partition coefficients of the sulfonamides in 1-octanol (molarity), and DMPC or DPPC liposomes (molality). The P values increase with temperature for SP, SD, SMR, and SMT, but decrease for SA, SCM, STL, and SMX. The partitioning is greatest for sulfamethoxazole and is least for sulfanilamide. However, DMPC and DPPC $K_{l/w}$ values increase with temperature in all cases. At 25.0 °C the partitioning is a maximum with sulfamethoxazole, and it is a minimum for sulfanilamide in DMPC liposomes and for sulfamethazine in DPPC liposomes.

The temperature dependence of partitioning, as ln K versus T^{-1} (van't Hoff plots), of SCM, SD, and SMX is presented in Figs 1 to 3 respectively. These sulfonamides are the most used in medical practice. In all cases, straight lines with correlation coefficients r near to 0.95 were obtained for the three partitioning systems evaluated. The r values of regression analyses of the other sulfonamides were also near to 0.95; therefore, the van't Hoff method is useful for their thermodynamic analysis.

Table 2. 1-Octanol–buffer and liposomes–buffer partition coefficients of sulfonamides (in molarity and molality respectively) at several temperatures (plus/minus standard deviation)

		Partition coefficient		
Compound	t/°C	P	DMPC $K_{l/w}$	DPPC $K_{l/w}$
SA	20.0	0.197 (0.005)	–	–
	25.0	0.192 (0.001)	3.407 (0.043)	2.110 (0.009)
	30.0	0.187 (0.002)	5.203 (0.045)	2.688 (0.008)
	35.0	0.177 (0.001)	7.060 (0.062)	3.420 (0.010)
	40.0	0.173 (0.002)	10.47 (0.19)	4.162 (0.012)
	50.0	0.169 (0.001)	–	–
SCM	20.0	0.660 (0.004)	–	–
	25.0	0.643 (0.008)	6.672 (0.028)	2.666 (0.022)
	30.0	0.623 (0.623)	8.234 (0.035)	3.515 (0.007)
	35.0	0.573 (0.009)	10.83 (0.09)	4.596 (0.095)
	40.0	0.540 (0.007)	12.53 (0.06)	–
	50.0	0.501 (0.010)	–	–
SP	20.0	0.976 (0.010)	–	–
	25.0	0.995 (0.002)	6.70 (0.19)	2.572 (0.015)
	30.0	1.013 (0.007)	8.02 (0.15)	3.390 (0.040)
	35.0	1.035 (0.003)	9.82 (0.14)	4.221 (0.068)
	40.0	1.045 (0.008)	11.21 (0.14)	5.066 (0.010)
	50.0	1.077 (0.008)	–	–
SD	20.0	0.805 (0.010)	–	–
	25.0	0.826 (0.016)	5.27 (0.19)	1.563 (0.021)
	30.0	0.856 (0.005)	5.69 (0.15)	2.248 (0.040)
	35.0	0.899 (0.006)	6.31 (0.13)	3.176 (0.022)
	40.0	0.931 (0.014)	6.75 (0.11)	4.121 (0.028)
	50.0	0.974 (0.020)	–	–
SMR	20.0	1.346 (0.037)	–	–
	25.0	1.406 (0.010)	5.622 (0.023)	1.358 (0.010)
	30.0	1.455 (0.009)	7.179 (0.044)	2.151 (0.008)
	35.0	1.487 (0.005)	8.513 (0.035)	3.363 (0.013)
	40.0	1.520 (0.010)	10.35 (0.09)	4.396 (0.017)
	50.0	1.577 (0.006)	–	–
SMT	20.0	1.711 (0.055)	–	–
	25.0	1.811 (0.015)	5.962 (0.038)	0.804 (0.003)
	30.0	1.965 (0.012)	8.031 (0.035)	1.621 (0.013)
	35.0	2.09 (0.11)	10.67 (0.05)	2.871 (0.041)
	40.0	2.261 (0.007)	12.93 (0.12)	4.587 (0.057)
	50.0	2.404 (0.044)	–	–
STL	20.0	1.154 (0.027)	–	–
	25.0	1.101 (0.010)	10.24 (0.05)	1.523 (0.026)
	30.0	1.042 (0.026)	11.27 (0.05)	1.966 (0.034)
	35.0	0.999 (0.027)	12.33 (0.03)	2.622 (0.069)
	40.0	0.940 (0.021)	13.67 (0.07)	3.32 (0.13)
	50.0	0.890 (0.042)	–	–
SMX	20.0	8.610 (0.047)	–	–
	25.0	8.222 (0.026)	76.83 (0.89)	21.26 (0.33)
	30.0	7.81 (0.15)	83.2 (3.0)	26.22 (0.43)
	35.0	7.27 (0.14)	90.1 (2.8)	30.12 (0.42)
	40.0	6.749 (0.074)	98.3 (2.6)	35.5 (1.2)
	50.0	6.10 (0.33)	–	–

Thermodynamic aspects of transfer

Table 3 summarizes the thermodynamic functions related to the transfer of sulfonamides from the aqueous media to organic systems (1-octanol, DMPC or DPPC liposomes). In 1-octanol, $\Delta G_{w\rightarrow o}$ at 25.0 °C is positive for SA, SCM, SP, and SD, but negative for SMR, SMT, STL, and SMX. Thus, the transfer of the former group of sulfonamides is not spontaneous, whereas it is for the latter group. The magnitudes of these properties are also proportional to the degree of lipophilicity. The enthalpies of transfer $\Delta H_{w\rightarrow o}$ are negative for SA, SCM, STL, and SMX, and

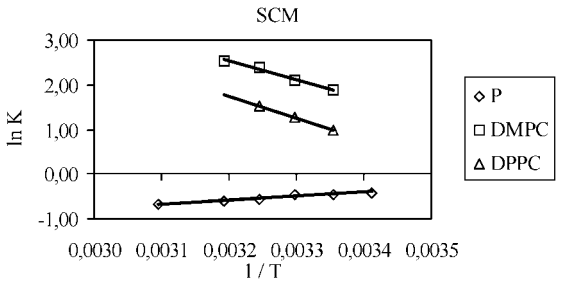


Figure 1. Partitioning temperature dependence for SCM

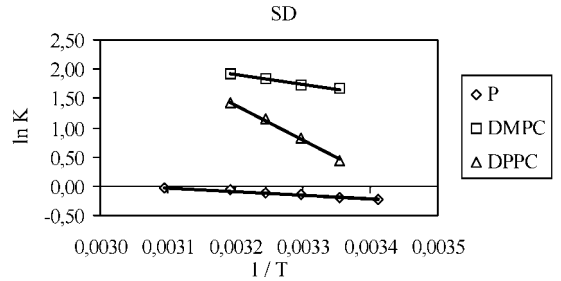


Figure 2. Partitioning temperature dependence for SD

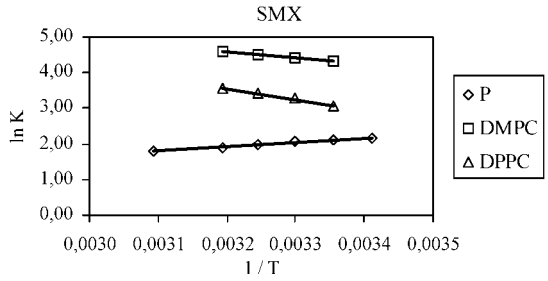


Figure 3. Partitioning temperature dependence for SMX

positive for SP, SD, SMR, and SMT. Negative enthalpies indicate the presence of significant hydrogen bonding between molecules of these sulfonamides and 1-octanol, mainly as hydrogen acceptor, except for SA (donor). The entropies of transfer $\Delta S_{w\to o}$ are negative for SA, SCM, STL, and SMX, and positive for SP, SD, SMR, and SMT, indicating that the transfer of the former group of compounds is enthalpy driven, whereas it is entropy driven for the latter group. The increase in entropy may be attributed to disorder due to the greater molal volume of the latter group of sulfonamides.[17]

In DMPC and DPPC liposomes, $\Delta G_{w\to o}$ at 25.0 °C is

Table 3. Thermodynamic functions of transfer of sulfonamides from aqueous media to 1-octanol or liposomes (plus/minus standard deviation)

		Partitioning system		
Compound	Function[a]	*P*	DMPC $K_{l/w}$	DPPC $K_{l/w}$
SA	$\Delta G_{w\to o}$	4.09 (0.01)	−3.04 (0.03)	−1.85 (0.01)
	$\Delta H_{w\to o}$	−4.36 (0.31)	57.0 (1.1)	35.40 (0.42)
	$\Delta S_{w\to o}$	−28.4 (1.1)	201.5 (3.7)	124.9 (1.4)
SCM	$\Delta G_{w\to o}$	1.10 (0.03)	−4.70 (0.01)	−2.43 (0.02)
	$\Delta H_{w\to o}$	−7.77 (0.38)	33.6 (1.1)	41.60 (0.74)
	$\Delta S_{w\to o}$	−29.8 (1.3)	128.6 (3.7)	147.7 (2.5)
SP	$\Delta G_{w\to o}$	0.01 (0.01)	−4.72 (0.07)	−2.34 (0.02)
	$\Delta H_{w\to o}$	2.59 (0.12)	27.16 (0.92)	35.02 (0.95)
	$\Delta S_{w\to o}$	8.63 (0.41)	106.9 (3.1)	125.3 (3.2)
SD	$\Delta G_{w\to o}$	0.47 (0.05)	−4.72 (0.09)	−1.11 (0.03)
	$\Delta H_{w\to o}$	5.30 (0.28)	13.13 (0.98)	50.6 (1.1)
	$\Delta S_{w\to o}$	16.17 (0.95)	57.9 (3.3)	173.3 (3.5)
SMR	$\Delta G_{w\to o}$	−0.85 (0.02)	−4.30 (0.01)	−0.76 (0.02)
	$\Delta H_{w\to o}$	4.07 (0.26)	30.74 (0.59)	61.7 (2.0)
	$\Delta S_{w\to o}$	16.47 (0.87)	117.5 (2.0)	209.6 (6.7)
SMT	$\Delta G_{w\to o}$	−1.47 (0.02)	−4.43 (0.01)	0.54 (0.01)
	$\Delta H_{w\to o}$	9.39 (0.44)	40.5 (1.1)	90.1 (2.2)
	$\Delta S_{w\to o}$	36.5 (1.5)	150.8 (3.6)	304.0 (7.3)
STL	$\Delta G_{w\to o}$	−0.24 (0.02)	−5.77 (0.01)	−1.04 (0.04)
	$\Delta H_{w\to o}$	−7.05 (0.49)	14.86 (0.24)	40.77 (0.15)
	$\Delta S_{w\to o}$	−22.9 (1.7)	69.19 (0.80)	140.2 (3.5)
SMX	$\Delta G_{w\to o}$	−5.22 (0.01)	−10.76 (0.03)	−7.58 (0.04)
	$\Delta H_{w\to o}$	−9.36 (0.34)	12.7 (1.0)	26.0 (1.0)
	$\Delta S_{w\to o}$	−13.9 (1.1)	78.7 (3.4)	112.6 (3.3)

[a] Units: $\Delta G_{w\to o}$ = kJ mol^{-1}; $\Delta H_{w\to o}$ = kJ mol^{-1}; $\Delta S_{w\to o}$ = J mol^{-1} K^{-1}. $\Delta G_{w\to o}$ and $\Delta S_{w\to o}$ at 25.0 °C.

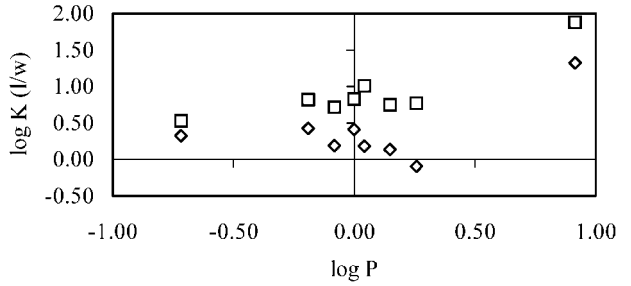


Figure 4. Correlation of the partition coefficients of sulfonamides in the 1-octanol–buffer and DMPC (squares), and DPPC (rhombic) liposome–buffer system at the isoelectric point and 25 °C

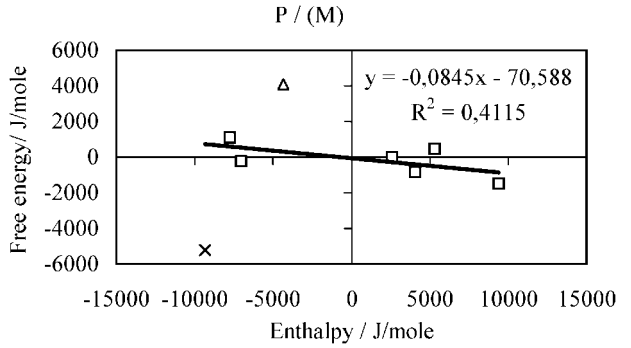


Figure 5. Enthalpy–entropy compensation of sulfonamides in 1-octanol–buffer system at 25 °C: (△) is SA and (×) is SMX

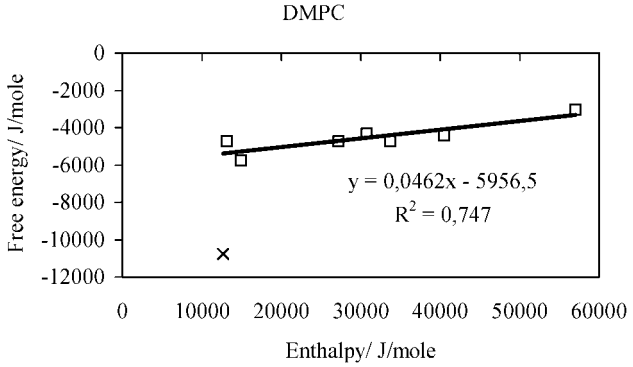


Figure 6. Enthalpy–entropy compensation of sulfonamides in DMPC liposomes–buffer system at 25 °C: (×) is SMX

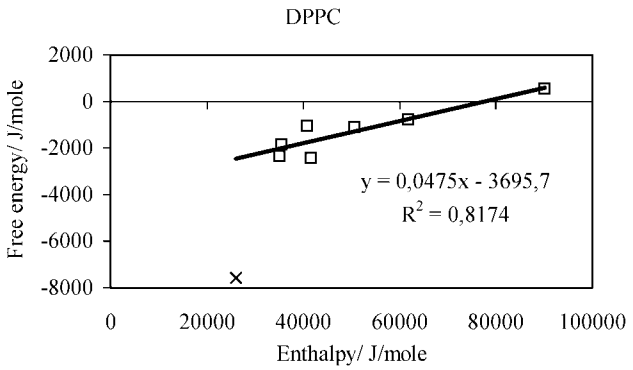


Figure 7. Enthalpy–entropy compensation of sulfonamides in DPPC liposomes–buffer system at 25 °C: (×) is SMX

negative for all sulfonamides (except for SMT in DPPC), indicating the spontaneity of the partition process in these systems. The enthalpy of transfer in all cases is positive, which indicates an endothermic process; the entropy of transfer is also positive in all cases and, therefore, the transfer of these sulfonamides from aqueous media to phospholipid vesicles is driven by entropy. The increase in entropy is probably due to disorder produced in the hydrophobic core of the bilayers.[11,13,14]

In the temperature range studied for liposomes (25 to 40 °C), DMPC liposomes are in the state of a liquid crystal (fluid), whereas DPPC liposomes are in the gel state (rigid), because their transition temperatures t_c are 23.6 ± 1.5 °C and 41.3 ± 1.8 °C respectively.[25,26]

In all cases, except for SA, the enthalpies of transfer from aqueous buffer to DPPC liposomes are greater than those for DMPC liposomes, i.e. more energy is required for accommodation of sulfonamides into DPPC bilayers than into DMPC bilayers. This may be attributed to the larger van der Waals interactions between hydrophobic tails in DPPC due to their length (two methylene groups more). In the same way, in all cases, except for SA, the entropies of transfer are greater in DPPC liposomes than DMPC liposomes, due to the larger disorder produced in separating the DPPC hydrophobic tails to accommodate the solute molecules, compared with DMPC.

Correlations

A plot of log P vs log $K_{l/w}$ (for DMPC and DPPC) is given in Fig. 4. This shows that the partitioning (lipophilicity) of sulfonamides does not correlate in the 1-octanol–aqueous buffer and liposomes systems. However a poor correlation is obtained with DMPC liposomes, which are in a fluid state, whereas with DPPC liposomes (in a rigid state) there is no correlation found.

Linear relationships obtained from enthalpy–entropy compensation plots suggest a single mechanism for transfer for a series of solutes.[27,28] For the 1-octanol–aqueous buffer system a poor correlation is obtained between $\Delta H_{o\rightarrow w}$ and $\Delta G_{o\rightarrow w}$ (Fig. 5). To a first approximation, this may be an indication that all sulfonamides, except SA and SMX, produce similar structural alterations in the microstructure of the organic medium, which consists of water-centered aggregates.[7,12] The apparent anomalous behavior of SA and SMX is probably related to their solubilities[29] and their partial molar volumes[30] in aqueous media and organic solvents, i.e. SA is the most hydrophilic compound and SMX is the most lipophilic compound among the sulfonamides evaluated.

In DMPC and DPPC liposomes, good correlations

were obtained between $\Delta H_{o\rightarrow w}$ and $\Delta G_{o\rightarrow w}$ for all sulfonamides, except for SMX (Figs 6 and 7). This may be an indication that all sulfonamides, with the exception of SMX, interact with phospholipid bilayers in the same manner. However, for some phenols and β-blockers no good correlations are obtained.[9,12]

From the values of $\Delta H_{o\rightarrow w}$ and $\Delta S_{w\rightarrow o}$ it can be concluded that the transfer in half of the sulfonamides studied from aqueous media to 1-octanol is mainly driven by hydrogen-bond interactions, whereas the partitioning into liposomes is almost exclusively driven by the hydrophobic immobilization of the solutes in the phospholipidic bilayers.

The partitioning values presented here have been used by us[17] in establishing empirical relationships from some quantitative values of biological activity for sulfonamides presented by Yamazaki *et al.*[31] The classical logarithmic equation developed by Hansch and Leo[32] was used. A good correlation in activities was found, such as in bacteriostatic activity against *Escherichia coli*, and in the binding to human plasmatic proteins, especially when the 1-octanol–aqueous buffer and DMPC liposomes partition coefficients were used in the calculations.[17]

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