Solubility of the Antimicrobial Agent Triclosan in Organic Solvents of Different Hydrogen Bonding Capabilities at Several Temperatures

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The thermodynamic functions of Gibbs energy, enthalpy, and entropy for the solution processes of triclosan (TS) were calculated from solubility values obtained at the temperature interval from (293.15 to 313.15) K. TS solubility was determined in ethanol (EtOH), octanol (ROH), isopropyl myristate (IPM), chloroform (CLF), and heptane (HPT) as pure solvents. The excess Gibbs energy and the activity coefficients of the solutes were also calculated. The TS solubilities were higher in EtOH and CLF with respect to those obtained in ROH, IPM, and HPT. In addition, the thermodynamic quantities relative to the transfer process of this drug from HPT to the other organic solvents were also calculated to estimate the hydrogen bonding contributions.

Introduction

Triclosan (5-chloro-2-(2,4-dichlorophenoxi)-phenol, TS) is a potent synthetic topical bactericide and fungicide with notably high chemical stability and persistent activity.[1] The main limitation in the development of topical pharmaceutical products is the relatively low solubility of the drug in aqueous media.[2] Our research group has recently reported the solubilization of TS by means of inclusion into poloxamine (a four-arm poly(ethylene oxide)−poly(propylene oxide) block copolymer) polymeric micelles in a broad range of pH values.[3] The profuse use of this agent in house-care products has raised important environmental concerns about its accumulation in wastewater streams.[4] Regardless of the impact the dissolution process (e.g., thermodynamic functions) in both organic and aqueous media has on the interaction of the drug with the biological environment and also in the context of the solubilization in polymeric nanocarriers,[3] these fundamental aspects have not yet been thoroughly investigated. As a first stage toward a more thorough understanding of the molecular forces involved, the present work studied the thermodynamics of the solubility of TS in five different organic model solvent systems used for QSAR studies (quantitative structure−activity relationships). This research was done with the basic purpose of presenting more complete and systematic information about the properties of dissolution and transfer for this drug. The solubility at several temperatures was determined in ethanol (EtOH), octanol (ROH), isopropyl myristate (IPM), chloroform (CLF), and heptane (HPT), and the respective dissolution thermodynamic analysis was made by using the van't Hoff and Gibbs equations. Otherwise, by using the values reported for the TS fusion process by Veiga et al.,[5] we also analyzed the contribution due to the mixing process toward the overall dissolution. ROH has been used as a standard organic medium for partition experiments in the development of QSAR studies because the ROH−water partition coefficient (log *P*) is an important parameter for modeling biological membranes and predicting the fate, transport, and distribution of drugs.[6] IPM is best related to skin/transdermal absorption because its polar and nonpolar nature mimics the complex nature (semipolar matrix) of the skin. CLF is an organic solvent that mainly acts as a hydrogen donor in establishing hydrogen bonds. HPT is a purely nonpolar lipophilic hydrocarbon solvent that interacts by London forces, enabling the evaluation of solute−solvent nonspecific interactions.[7]

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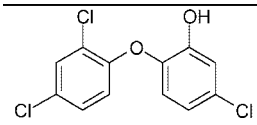
Experimental Section

Materials. Triclosan USP[8] was a kind gift from Ciba C.S. ROH extra-pure quality, IPM for synthesis, HPT for analysis, and absolute EtOH analytical reagent were from Merck. CLF analytical reagent was from Mallinckrodt. Millex 13 mm filters were from Millipore.

Solubility Determinations. An excess of TS was added to 20 cm^3 of each organic solvent evaluated in glass flasks. The solid−liquid mixtures were then stirred in a mechanical shaker (Wrist Action, Burrel, model 75) for 1 h. Samples were then allowed to stand in water baths (Magni Whirl, Blue M. Electric) kept at (313.15 ± 0.05) K for at least 3 days to reach equilibrium. (This equilibrium time was established by quantifying the drug concentration up to obtain a constant value.) Once at equilibrium, supernatant solutions were filtered (under isothermal conditions) to remove insoluble particles before analysis. We determined drug concentrations in ROH and IPM by measuring absorbance after appropriate dilution and interpolation from previously constructed UV spectrophotometry calibration curves for TS in absolute EtOH (UV−vis BioMate 3, Thermo Electron). Otherwise, we determined the drug concentrations in EtOH, CLF, and HPT by mass balance by weighing a specified quantity of the respective saturated solution

10.1021/je800426w CCC: $40.75
Published on Web 10/15/2008

Table 1. Some Physicochemical Properties of Triclosan (TS)

Molecular structure [a]	M g·mol^{-1} [a]	ΔH_{fus} kJ·mol^{-1} [b]	T_{fus} / K [b]
	289.55	17.75	331.1

[a] From Budavari et al.[9] [b] From Veiga et al.[5]

and allowing solvent evaporation up to a constant mass. After the procedures that were already described, the temperature was decreased by 5.0 K; therefore, it was stabilized at 308.15 K for at least two days, allowing the precipitation of the drug dissolved in excess and the quantification of the drug concentration in equilibrium. We repeated this procedure by decreasing the temperature in 5.0 K steps to reach 293.15 K. To allow the conversion between concentration scales, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar, precision ± 0.0001 g·cm^{-3}). All experiments were done at least three times and were averaged.

Results and Discussion

In Table 1, the molecular structure of TS[9] and some of its physicochemical properties are summarized.[5] This drug acts in solution mainly as a Lewis acid (phenolic OH group) to establish hydrogen bonds with proton-acceptor functional groups present in the solvents (oxygen in −OH and >C═O groups).

Ideal and Experimental Solubility of TS. The ideal solubility of a crystalline solute in a liquid solvent can be calculated by eq 1

$$\ln X_2^{id} = -\frac{\Delta H_{fus}(T_{fus}-T)}{RT_{fus}T} + \left(\frac{\Delta C_p}{R}\right)\left[\frac{(T_{fus}-T)}{T} + \ln\left(\frac{T}{T_{fus}}\right)\right] \quad (1)$$

where X_2^{id} is the ideal solubility of the solute in mole fraction, ΔH_{fus} is the molar enthalpy of fusion of the pure solute (at the melting point), T_{fus} is the absolute melting point, T is the absolute solution temperature, R is the gas constant (8.314 J·mol^{-1}·K^{-1}), and ΔC_p is the difference between the molar heat capacity of the crystalline form and the molar heat capacity of the hypothetical supercooled liquid form, both at the solution temperature.[10] Because the experimental determination of ΔC_p is difficult, its value is usually approximated to the entropy of fusion, ΔS_{fus}.

Table 2 summarizes the experimental solubilities of TS, expressed in mole fraction, in addition to the ideal solubilities calculated by means of eq 1 from ΔH_{fus} and T_{fus} presented in Table 1. In almost all cases, the coefficients of variation for experimental solubility were smaller than 2.0 %.

It may be observed that the highest solubility value in mole fraction for TS was obtained in pure EtOH at 313.15 K whereas the lowest value was found in ROH at 293.15 K. At 303.15 K, the order obtained was EtOH > CLF > ROH > IPM > HPT. However, no reports on solubility values for this drug are available; therefore, no direct comparison is possible. It is interesting that the solubility of this drug in ROH increases 32-fold because of a temperature increase of 20 K. This event will be further explained because it implies important thermodynamic quantities for the solution process.

Table 3. Solute Activity Coefficient of TS in Five Different Organic Solvents at Several Temperatures

	temperature				
solvent	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
EtOH	1.73	1.13	0.99	0.96	0.93
CLF	1.38	1.23	1.13	1.12	1.10
IPM	10.81	10.73	10.75	11.19	11.77
ROH	51.47	20.36	7.22	4.01	2.45
HPT	29.27	17.78	13.47	10.41	8.67

TS Activity Coefficients. The solute activity coefficient in the solution (γ_2) is calculated as X_2^{id}/X_2 and is an indication of the deviation presented by TS from its ideal behavior.[10] Table 3 shows activity coefficients as a function of temperature.

From the γ_2 values presented in Table 3, an approximate estimation of solute−solvent intermolecular interactions can be made by considering the following expression

$$\ln \gamma_2 = (w_{11} + w_{22} - 2w_{12})\frac{V_2\phi_1^{\,2}}{RT} \quad (2)$$

where w_{11}, w_{22}, and w_{12} represent the solvent−solvent, solute−solute, and solvent−solute interaction energies, respectively, V_2 is the molar volume of the supercooled liquid solute, and ϕ_1 is the volume fraction of the solvent. In a first approach, the term $(V_2\phi_1^{\,2}/RT)_{T,P}$ may be considered to be approximately constant at the same temperature; then, γ_2 depends almost exclusively on w_{11}, w_{22}, and w_{12}.[10] Whereas the term w_{12} term favors the solution process, both w_{11} and w_{22} terms are unfavorable for solubility. The contribution of w_{22} represents the work that is necessary to transfer drug molecules from the solid to the vapor state; therefore, it is constant in all organic solvents.

The solution in pure IPM that has γ_2 values around 10 implies low w_{12} values. In EtOH and CLF solutions that have γ_2 values near 1, the w_{11} values are relatively low. In contrast, the w_{12} values are higher. In ROH and HPT solutions, which have γ_2 values that are strongly dependent on temperature, the analysis in relation to w_{11} and w_{12} terms is less clear.

Thermodynamic Functions of Solution. According to van't Hoff analysis, the apparent standard enthalpy change of solution is obtained from the slope of the ln X_2 versus 1/T plot. Nevertheless, in recent thermodynamic treatments, some modifications have been introduced in the van't Hoff equation to diminish the propagation of errors and consequently to separate the chemical effects from those due to statistical treatments used when enthalpy−entropy compensation plots are developed. For

Table 2. Experimental Solubility of TS in Five Different Organic Solvents Expressed in Mole Fraction Including Ideal Solubility at Several Temperatures

	temperature				
solvent	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
EtOH	0.332 (0.003)	0.449 (0.002)	0.570 (0.005)	0.654 (0.003)	0.751 (0.003)
CLF	0.330 (0.001)	0.412 (0.004)	0.501 (0.004)	0.561 (0.005)	0.633 (0.002)
IPM	0.0422 (0.0001)	0.0475 (0.0002)	0.0527 (0.0002)	0.0563 (0.0005)	0.0594 (0.0004)
ROH	0.0089 (0.0001)	0.0250 (0.0003)	0.0785 (0.0008)	0.157 (0.001)	0.285 (0.002)
HPT	0.0156 (0.0001)	0.0286 (0.0003)	0.0421 (0.0001)	0.0605 (0.0005)	0.0806 (0.0006)
ideal	0.4565	0.5091	0.5668	0.6299	0.6987

this reason, the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis. T_{hm} is calculated as $n/\sum_{i=1}^{n}(1/T)$, where n is the number of temperatures studied.[11,12] In the present case, the T_{hm} value obtained is only 303 K. The modified expression that is more widely used is[11,12]

$$\left(\frac{\partial \ln X_2}{\partial(1/T-1/T_{hm})}\right)_P = -\frac{\Delta H^{0app}_{soln}}{R} \quad (3)$$

The modified van't Hoff plot for TS in EtOH and CLF and in ROH, HPT, and IPM are presented in Figures 1 and 2, respectively. In general, parabolic regression models with good determination coefficients were obtained in all cases studied.

The apparent standard free energy change for the solution process (ΔG^{0app}_{soln}), considering the approach proposed by Krug et al.[11] is calculated by means of

$$\Delta G^{0app}_{soln} = -RT_{hm} \cdot \text{intercept} \quad (4)$$

in which the intercept used is the one obtained in the analysis by treatment of ln X_2 as a function of $1/T - 1/T_{hm}$ (eq 3).[12]

The standard entropic change for the solution process (ΔS^0_{soln}) is obtained from the respective ΔH^0_{soln} and ΔG^0_{soln} values by using

$$\Delta S^0_{soln} = \frac{(\Delta H^0_{soln} - \Delta G^0_{soln})}{T_{hm}} \quad (5)$$

Table 4 summarizes the apparent standard thermodynamic functions for the experimental solution process of TS in all of the organic solvents investigated, including those functions for the ideal process. To calculate the thermodynamic magnitudes of the experimental solution, some methods to calculate the propagation of errors were used.[13] It is found that the standard free energy of solution is positive in all

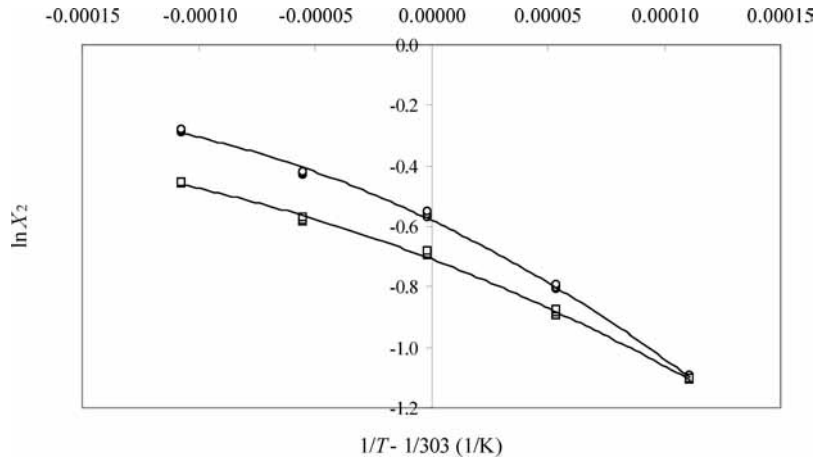


Figure 1. van't Hoff plot for TS solubility in: ○, EtOH; □, CLF.

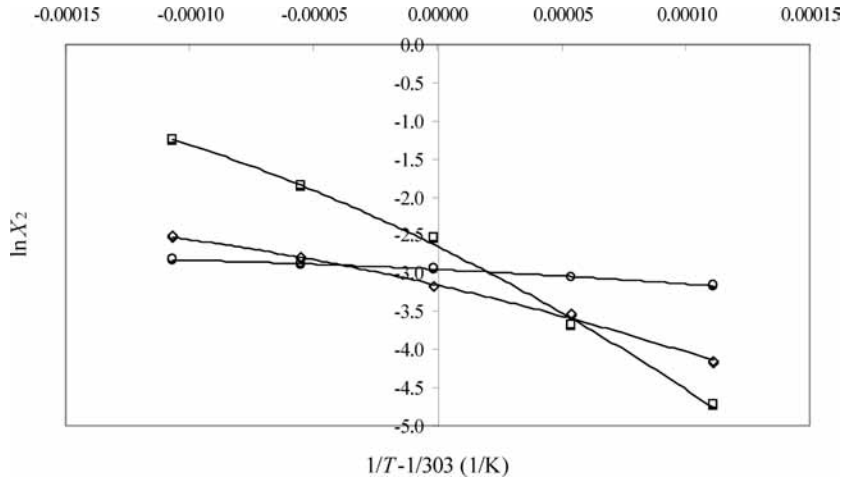


Figure 2. van't Hoff plot for TS solubility in: □, ROH; ◇, HPT; ○, IPM.

Table 4. Apparent Thermodynamic Functions Relative to Solution Process of TS in Five Organic Solvents Including Ideal Process at 303 K

solvent	ΔG^0_{soln} / kJ·mol^{-1}	ΔH^0_{soln} / kJ·mol^{-1}	ΔS^0_{soln} / J·mol^{-1}·K^{-1}	$T\Delta S^0_{soln}$ / kJ·mol^{-1}	% ζ_H[a]	% ζ_{TS}[a]
EtOH	1.46 (0.01)	30.4 (0.4)	95.6 (1.5)	29.0 (0.5)	51.23	48.77
CLF	1.78 (0.01)	24.4 (0.3)	74.6 (1.1)	22.6 (0.3)	51.90	48.10
IPM	7.43 (0.01)	12.9 (0.2)	18.1 (0.2)	5.49 (0.08)	70.18	29.82
ROH	6.68 (0.07)	133.4 (1.9)	418 (7)	126.7 (2.2)	51.28	48.72
HPT	7.96 (0.03)	61.2 (0.7)	175.9 (2.2)	53.3 (0.7)	53.47	46.53
ideal	1.434 (0.002)	16.24 (0.09)	48.9 (0.3)	14.81 (0.09)	52.31	47.69

[a] % ζ_H and % ζ_{TS} are the relative contributions by enthalpy and entropy to free energy of solution. These values were calculated by means of eqs 6 and 7, respectively.

Table 5. Thermodynamic Functions Relative to Mixing Process of TS in Five Organic Solvents at 303 K

solvent	ΔG^0_{mix} kJ·mol^{-1}	ΔH^0_{mix} kJ·mol^{-1}	ΔS^0_{mix} J·mol^{-1}·K^{-1}	$T\Delta S^0_{mix}$ kJ·mol^{-1}	% ζ_H[a]	% ζ_{TS}[a]
EtOH	0.03	14.2	46.8	14.2	50.05	49.95
CLF	0.35	8.1	25.7	7.8	51.10	48.90
IPM	6.00	−3.3	−30.8	−9.32	26.27	73.73
ROH	5.24	117.1	369	111.9	51.15	48.85
HPT	6.52	45.0	127.0	38.49	53.91	46.09

[a] % ζ_H and % ζ_{TS} are the relative contributions by enthalpy and entropy toward free energy of mixing. These values were calculated by means of equations analogous to eqs 6 and 7, respectively.

cases; that is, the solution process apparently is not spontaneous, which may be explained in terms of the concentration scale used (mole fraction) where the reference state is the ideal solution that has the unit as the concentration of TS (the solid pure solute).

With the aim to compare the relative contributions by enthalpy (% ζ_H) and by entropy (% ζ_{TS}) to the solution process, eqs 6 and 7 were employed, respectively[14]

$$\% \zeta_H = 100 \frac{|\Delta H^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \quad (6)$$

$$\% \zeta_{TS} = 100 \frac{|T\Delta S^0_{soln}|}{|\Delta H^0_{soln}| + |T\Delta S^0_{soln}|} \quad (7)$$

From Table 4, it follows that in almost all cases, the enthalpy and entropy contribute in a similar way to the standard Gibbs energy of the TS solution process, except for IPM, where the main contributor was the enthalpy. It is interesting that except for IPM, enthalpy and entropy contributions for all of the organic solvents are almost equal to those obtained for the ideal solution process.

Thermodynamic Functions of Mixing. The solution process may be represented by the following hypothetical stages[10]

$$\text{Solute}_{(\text{Solid})} \rightarrow \text{Solute}_{(\text{Liquid})} \rightarrow \text{Solute}_{(\text{Solution})}$$

where the respective partial processes toward the drug dissolution are solute fusion and mixing at the same temperature (303 K), which permits the calculation of the partial thermodynamic contributions to the overall solution process by means of eqs 8 and 9, respectively

$$\Delta H^0_{soln} = \Delta H^{303}_{fus} + \Delta H^0_{mix} \quad (8)$$

$$\Delta S^0_{soln} = \Delta S^{303}_{fus} + \Delta S^0_{mix} \quad (9)$$

where ΔH^{303}_{fus} and ΔS^{303}_{fus} represent the thermodynamic functions of the fusion process at the harmonic temperature (303 K). ΔH^{303}_{fus} was calculated as $\Delta H^{MP}_{fus} - \Delta C_p(T_{fus} - T)$ by using ΔS^{MP}_{fus} instead of ΔC_p, and a value of 16.24 kJ·mol^{-1} was obtained, which is in agreement with the enthalpic change for an ideal solution (Table 4). In contrast, the entropy of fusion at 303 K (53.6 J·mol^{-1}·K^{-1}) is not coincident with the entropy of the ideal solution at this temperature (48.9 J·mol^{-1}·K^{-1}). For this reason, for practical purposes in this analysis, the ΔS^{0id}_{soln} value was used instead of ΔS^{303}_{fus} because it was made previously with several other drugs.[10,15] In Table 5, the thermodynamic functions of the mixing of TS are summarized.

The partial contributions by the ideal solution (related to solute fusion process) and mixing processes to the enthalpy and entropy of drug solution show that ΔH^{0id}_{soln} and ΔS^{0id}_{soln} are positive (Table 4), whereas the contribution of the thermodynamic functions relative to the mixing process to the solution process is almost the same; that is, ΔH^0_{mix} and ΔS^0_{mix} are positive in the majority of solvents, except for IPM. It can be concluded that the solution process of this drug in EtOH, CLF, ROH, and HPT is mainly driven by the entropy of mixing, whereas for IPM, the process is driven by the enthalpy of mixing (negative value: Table 5).

The net variation in ΔH^0_{mix} values results from the contribution of several kinds of interactions. The enthalpy of cavity formation (required for solute accommodation) is endothermic because energy must be supplied against the cohesive forces of the solvent. This process decreases solubility. The enthalpy of solute−solvent interaction is exothermic and mainly results from van der Waals and Lewis acid−base interactions.

The values obtained for the thermodynamic functions of mixing for ROH are very interesting because they are so much greater than those obtained for HPT. This result implies that a high quantity of energy is required to overcome the fatty alcohol solvent structure (on the basis of solvent−solvent hydrogen bonds and packed tails by van der Waals forces)[6] to accommodate the TS molecules. This required energy is therefore greater than the energy released when the hydrogen bonds between solute and solvent molecules are established. Otherwise, the negative values obtained in enthalpy and entropy of mixing for IPM could indicate that the hydrogen bonds established between TS and IPM are so much greater than the IPM−IPM intermolecular interactions, which leads to energy release upon the mixing process.

Apparent Thermodynamic Functions of Transfer of TS from HPT to Other Organic Solvents. To contribute to the generation and systematization of thermodynamic quantities of transfer useful in QSAR studies, we calculated these values for the transfer of TS from HPT to the organic solvents.

In Table 6, the Gibbs energy, enthalpy, and entropy of transfer are shown including the respective % ζ_H and % ζ_{TS} values. The thermodynamic quantities were calculated as the difference between the solution functions in the organic solvents (Table 4) and those for HPT presented in the same table. According to Table 6, the transfer process of this drug from HPT to all other organic solvents is spontaneous ($\Delta G^0_{w\rightarrow o} < 0$) and driven by enthalpy for EtOH, CLF, and IPM ($\Delta H^0_{w\rightarrow o} < 0$ and $\Delta S^0_{w\rightarrow o} < 0$), whereas the transfer is entropy driven for ROH ($\Delta H^0_{w\rightarrow o}$

Table 6. Thermodynamic Functions of Transfer of TS from Heptane up to the Other Organic Solvents at 303 K[a]

solvent	$\Delta G^0_{hept\rightarrow org}$ kJ·mol^{-1}	$\Delta H^0_{hept\rightarrow org}$ kJ·mol^{-1}	$\Delta S^0_{hept\rightarrow org}$ J·mol^{-1}·K^{-1}	$T\Delta S^0_{hept\rightarrow org}$ kJ·mol^{-1}	% ζ_H[b]	% ζ_{TS}[b]
EtOH	−6.49 (0.03)	−30.8 (0.8)	−80.3 (2.7)	−24.3 (0.8)	55.89	44.11
CLF	−6.17 (0.03)	−36.9 (0.8)	−101.3 (2.5)	−30.7 (0.7)	54.57	45.43
IPM	−0.52 (0.03)	−48.3 (0.8)	−157.8 (2.2)	−47.8 (0.7)	50.27	49.73
ROH	−1.28 (0.07)	72.1 (2.0)	242 (8)	73.4 (2.3)	49.56	50.44

[a] These magnitudes were calculated as $\Delta\Psi^0_{1\rightarrow 2} = \Delta\Psi^0_{mix-(organic)} - \Delta\Psi^0_{mix-(hept)}$ where Ψ is G, H, or S. [b] % ζ_H and % ζ_{TS} are the relative contributions by enthalpy and entropy toward free energy of transfer. These values were calculated by means of equations analogous to eqs 6 and 7, respectively.

> 0 and $\Delta S^0_{w\rightarrow o}$ > 0). The enthalpy is the main contributor to the transfer process in EtOH and CLF (% $\zeta_H \approx 55$ %), whereas for IPM and ROH, the contributions are similar.

In the net drug transfer process between hydrocarbons and organic solvents with hydrogen-bonding capability as donors or acceptors, the enthalpic and entropic changes imply, respectively, the energetic requirements and the molecular randomness (increase or decrease in the molecular disorder). In general terms, the behavior presented in each phase should be independently considered before and after the partitioning process.

Because hypothetically, the solute is initially present only in the hydrocarbon phase, the generation of a cavity in the hydrogen-bonding organic medium is required to accommodate the solute after the transfer process. This is an endothermic phenomenon because an energy supply is necessary to overcome the solvent−solvent interaction of hydrogen-bonded organic solvent molecules. When the solute molecules are accommodated in the organic phase, an amount of energy is released that is mainly due to the formation of hydrogen bonds between the molecules of the drug and the solvent.

After a certain number of solute molecules have migrated from the hydrocarbon to the organic phase to reach the hypothetical equilibrium, the original cavities occupied by the drug in the hydrocarbon phase become occupied by HPT molecules. This event produces an energy release due to HPT−HPT interactions. Therefore, the negative enthalpy values of transfer obtained could be explained as the strong interactions due to hydrogen-bonding among TS and the solvents, which diminishes the entropy by drug immobilization inside the solvents. The opposite behavior of ROH could be explained in terms of the high energy required to overcome the solvent−solvent hydrogen bonds, which is required for the accommodation of the TS molecules. This required energy is therefore greater than the energy released when the solute−solvent bonds are established.

As in the case of the preformulation and formulation processes of pharmaceutical preparations, the toxicity to aquatic life and the appearance of this drug in drinking water is directly related to solubility in water. To present more complete thermodynamic information about the transfer properties of this drug, the values in aqueous media are required. Nevertheless, in the literature, only the aqueous solubility and ROH−water partition coefficient for TS at 25.0 °C have been previously reported.[16] The study of the solubility of TS in aqueous media was out of the scope of the present work, though these aspects are currently under investigation in our groups, and the results will be reported separately. In this framework, the partitioning of this drug in different organic solvent/buffer systems at several temperatures is also being studied. These values will contribute to the understanding of the mechanisms involved in the drug transfer from aqueous media to organic systems. Besides, this physicochemical information could be compared with the biological activity previously reported for this drug.[17]

Conclusions

From all topics previously discussed, it can be concluded that the solution process of TS in the organic solvents studied is complex depending on the solvent nature. The solubility of this drug was greater in EtOH and CLF than it was in the other organic solvents. Finally, it can be said that the data presented in this report extend the physicochemical information available on this extensively used topical antibacterial agent.

Acknowledgment

We thank the Department of Pharmacy of NUC for facilitating the equipment and laboratories used.

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Received for review June 13, 2008. Accepted September 11, 2008. We thank the DIB-DINAIN of the National University of Colombia (NUC) for the financial support.

JE800426W