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Preferential solvation of some sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K according to the inverse Kirkwood-Buff integrals method

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Abstract

The preferential solvation parameters, that is, the difference between the local and bulk mole fractions of the solvents in solutions of some structurally related sulfonamides in 1,4-dioxane + water binary mixtures are derived from their thermodynamic properties by means of the inverse Kirkwood-Buff integrals method. From solvent effect studies, it was found that all the sulfonamides considered were very sensitive to solvation effects, so the preferential solvation parameter, $\delta x_{D,S}$, was negative in water-rich and 1,4-dioxane-rich mixtures but positive in intermediate co-solvent compositions. It may be possible that in water-rich mixtures the hydrophobic hydration around the non-polar groups plays a relevant role in the solvation. The greater solvation by 1,4-dioxane in mixtures of similar co-solvent compositions could be due mainly to polarity effects. Finally, the preference of these drugs for water in 1,4-dioxane-rich mixtures could be explained in terms of the acidic behavior of water interacting with the hydrogen-acceptor groups in the sulfonamides.

Key words: Sulfonamides, solubility, inverse Kirkwood-Buff integrals, preferential solvation.

Solvatación preferencial de algunas sulfonamidas en mezclas cosolventes 1,4-dioxano + agua a 298,15 K según el método de las integrales inversas de Kirkwood-Buff

Resumen

A partir de algunas propiedades termodinámicas clásicas, en este trabajo se calcularon en mezclas binarias 1,4-dioxano + agua, y mediante el método de las integrales inversas de Kirkwood-Buff, los parámetros de solvatación preferencial, esto es, las diferencias entre las fracciones molares locales alrededor de los solutos y en el grueso de la solución, de algunas sulfonamidas estructuralmente relacionadas. Con base en los valores obtenidos, se infirió que las sulfonamidas estudiadas fueron altamente sensibles a los efectos de la solvatación según la composición de las mezclas. Así, el parámetro de solvatación preferencial por 1,4-dioxano, $\delta x_{D,S}$, fue negativo en mezclas ricas en agua y en mezclas ricas en 1,4-dioxano, pero positivo en mezclas de composición intermedia. Se podría plantear que en mezclas ricas en agua la hidratación hidrofóbica alrededor de los grupos no polares de las sulfonamidas juega un papel relevante en la solvatación. La mayor solvatación de las sulfonamidas por el 1,4-dioxano en mezclas de composición cosolvente intermedia podría deberse principalmente a efectos de polaridad. Finalmente, la preferencia de estos fármacos por el agua en mezclas ricas en 1,4-dioxano podría explicarse en términos del comportamiento ácido del agua que estaría interactuando con grupos aceptores de protones en las sulfonamidas.

Palabras clave: sulfonamidas, solubilidad, integrales inversas de Kirkwood-Buff, solvatación preferencial.

Introduction

Solubility of drugs in co-solvent mixtures is a very important topic for pharmaceutical scientists involved in several development stages such as drug purification and design of liquid medicines (**Jouyban, A.** 2010). Although co-solvency has been employed in pharmacy for several decades, it is recently that the mechanisms involved to increase or decrease drugs solubility have been approached from a physicochemical point of view (**Rubino, J.T.** 1988).

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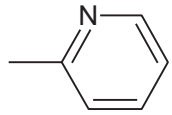
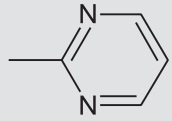
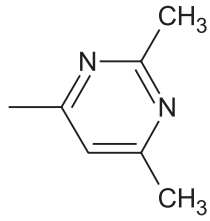
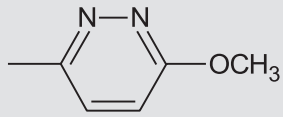
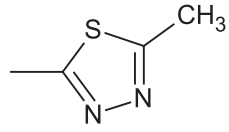
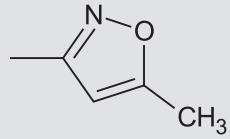
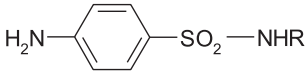
Sulfonamides are drugs extensively used for the treatment of certain infections caused by gram-positive and gram-negative microorganisms, some fungi, and certain protozoa. Although the advent of the antibiotics has diminished the usefulness of sulfonamides, these drugs still occupy an important place in the therapeutic resources of physicians and veterinarians (**Korolkovas, A.** 1988; **Gelone, S. & O'Donnell, J.A.** 2005).

Several thermodynamic works have been published based on the enthalpic and entropic contributions to the Gibbs energy of solution of sulfonamides (**Delgado, D.R., *et al.*,** 2011a, 2012, 2013; **Delgado, D.R. & Martínez, F.** 2013). Nevertheless, the drug preferential solvation, *i.e.* the co-solvent specific composition around the drug molecules, has not been studied for sulfonamides. Therefore, the main goal of this paper was to evaluate the preferential solvation of some structurally related sulfonamides in 1,4-dioxane + water co-solvent mixtures, based on thermodynamic definitions. Sulfonamides under study were sulfanilamide, sulfapyridine, sulfadiazine, sulfisomidine, sulfamethoxypyridazine, sulfamethizole, and sulfamethoxazole (Table 1). Thus, this work is similar to the ones presented previously in the literature for some analgesic drugs in co-solvent mixtures (**Ruidíaz, M.A., *et al.*,** 2010; **Delgado, D.R., *et al.*,** 2011b; **Holguín, A.R., *et al.*,** 2011).The availability of these data is very important for understanding the intermolecular interactions involved in the solubility of therapeutically useful solutes in co-solvent mixtures. As has been indicated earlier, this knowledge is relevant in almost all the areas of the pharmaceutical sciences.

Table 1. Molecular structure and CAS number of the sulfonamides

Sulfonamide	Abbreviation	CAS RN[a]	R substituent[b]
Sulfanilamide	SA	63-74-1	–H
Sulfapyridine	SP	144-83-2	
Sulfadiazine	SD	68-35-9	
Sulfisomidine	SSM	515-64-0	
Sulfamethoxypyridazine	SMP	80-35-3	
Sulfamethizole	SMZ	144-82-1	
Sulfamethoxazole	SMX	723-46-6	

[a] Chemical Abstracts Service Registry Number
[b] Substituent group on the basic structure of sulfanilamide:



The inverse Kirkwood-Buff integral (IKBI) is a powerful tool for evaluating the preferential solvation of nonelectrolytes in solvent mixtures, describing the local compositions around a solute with respect to the different components present in the solvent mixture (**Ben-Naim, A.** 1988, 1990; **Marcus, Y.** 1990).

In the present case, this treatment depends on the values of the standard molar Gibbs energies of transfer of the sulfonamides from neat water to the 1,4-dioxane + water solvent mixtures and the excess molar Gibbs energy of mixing for the co-solvent binary mixtures. As mentioned before, this treatment is very important in pharmaceutical sciences to understand the molecular interactions solute-solvent because most of the solubility studies developed have been directed towards correlating or modeling the solubilities and possibly predicting them from the solubilities in the neat solvents, but not to analyzing the local environment around the drug molecules describing the local fraction of the solvent components (D or W) in the surrounding of the solute (S) (Marcus, Y. 2002, 2008).

In this paper the IKBI approach was applied to evaluate the preferential solvation of some structurally related sulfonamides in the binary mixtures conformed by 1,4-dioxane (D) and water (W). The results are expressed in terms of the preferential solvation parameter $\delta x_{D,S}$ of the solute by the co-solvent 1,4-dioxane.

Theoretical background

The Kirkwood-Buff integrals, G_i,S (KBI) are given by the expression,

$$G_{i,\mathrm{S}} = \int_{r_{\mathrm{cor}}}^{0} (g_{i,\mathrm{S}} - 1) 4\pi r^2 \, dr, \qquad (1)$$

where $g_{i,s}$ is the pair correlation function for the molecules of the solvent i in the 1,4-dioxane + water mixtures around the sulfonamides, r, the distance between the centers of the molecules of sulfonamide and 1,4-dioxane or water, and r_{cor} is a correlation distance for which $g_{i,s}(r > r_{\mathrm{cor}}) \approx 1$. Thus, for all distances $r > r_{\mathrm{cor}}$ up to infinite, the value of the integral is essentially zero. Therefore, the results are expressed in terms of the preferential solvation parameter $\delta x_{i,s}$ for the solute in solution by the component solvents 1,4-dioxane and water (**Newman, K.E.** 1994). For 1,4-dioxane (D) this parameter is defined as

$$\delta x_{\mathrm{D,S}} = x_{\mathrm{D,S}}^{L} - x_{\mathrm{D}} = -\delta x_{\mathrm{W,S}}, \qquad (2)$$

where x_{D} is the mole fraction of 1,4-dioxane in the bulk co-solvent mixture and $x_{D,S}^{L}$ is the local mole fraction of 1,4-dioxane in the environment near to the drug. If $\delta x_{D,S} > 0$, then the sulfonamide is preferentially solvated by 1,4-dioxane; on the contrary, if it is < 0, the drug is preferentially solvated by water within the correlation volume, $V_{\mathrm{cor}} = (4\pi / 3)\, r^3_{\mathrm{cor}}$, and the bulk mole fraction of 1,4-dioxane, x_{D}. Values of $\delta x_{\mathrm{D,S}}$ are obtainable from those of $G_{\mathrm{D,S}}$, and these, in turn, from thermodynamic data of the co-solvent mixtures with the solute dissolved on them, as shown below (**Marcus, Y.** 2002).

Algebraic manipulation of the basic expressions presented by **Newman, K.E.** (1994) leads to expressions for the Kirkwood-Buff integrals (in $cm^3\ mol^{-1}$) for the individual solvent components in terms of some thermodynamic quantities as shown in equations (3) and (4) (**Ben-Naim, A.** 1988; **Marcus, Y.** 2002, 2008):

$$G_{\mathrm{D,S}} = RT\kappa_T - V_{\mathrm{S}} + x_{\mathrm{W}} V_{\mathrm{W}} D / Q, \qquad (3)$$

$$G_{\mathrm{W,S}} = RT\kappa_T - V_{\mathrm{S}} + x_{\mathrm{D}} V_{\mathrm{D}} D / Q, \qquad (4)$$

where κ_T is the isothermal compressibility of the 1,4-dioxane + water co-solvent mixtures free of drug (in GPa^{-1}), V_{D} and V_{W} are the partial molar volumes of the solvents in the mixtures (in $cm^3\ mol^{-1}$); similarly, V_{S} is the partial molar volume of solute in these mixtures (in $cm^3\ mol^{-1}$). Function D is the derivative of the standard molar Gibbs energies of transfer of the drug (from neat water to 1,4-dioxane + water mixtures) with respect to the solvent composition (in kJ mol^{-1}, as RT also is), and function Q involves the second derivative of the excess molar Gibbs energy of mixing of the two solvents ($G_{\mathrm{D+W}}^{Exc}$) with respect to the water proportion in the mixtures (also in kJ mol^{-1}) (**Marcus, Y.** 2002, 2008; **Cortez-Nunez, N.G.** 2010):

$$D = \left(\frac{\partial \Delta_{\mathrm{tr}} G^{0}_{(\mathrm{S,W \rightarrow D+W})}}{\partial x_{\mathrm{D}}} \right)_{T,p}, \qquad (5)$$

$$Q = RT + x_{\mathrm{D}} x_{\mathrm{W}} \left(\frac{\partial^2 G_{\mathrm{D,W}}^{Exc}}{\partial x_{\mathrm{W}}^2} \right)_{T,p}. \qquad (6)$$

Because the dependence of κ_T on composition is not known for a lot of the systems investigated and given the small contribution of $RT\kappa_T$ to the IKBI calculations, the dependence of κ_T on composition could be approximated by additive contributions as described by equation (7) (**Marcus, Y.** 1998):

$$\kappa_{\mathrm{mix}} = \sum_{i=1}^{\mathrm{n}} x_i \kappa_i^{0}, \qquad (7)$$

where x_i is the mole fraction of component i in the mixture and κ_i° is the isothermal compressibility of the pure component i.

Ben-Naim, A. (1988) showed that the preferential solvation parameter can be calculated from the Kirkwood-Buff integrals as follows:

$$\delta x_{D,S} = \frac{x_D x_W \left(G_{D,S} - G_{W,S}\right)}{x_D G_{D,S} + x_W G_{W,S} + V_{cor}}. \quad (8)$$

The correlation volume, V_{cor}, is obtained by means of the following expression proposed by **Marcus, Y.** (2008, 2009):

$$V_{cor} = 2522.5\left(r_D + 0.1363\left(x_{D,S}^L V_D + x_{W,S}^L V_W\right)^{1/3} - 0.085\right)^3, \quad (9)$$

where r_S is the radius of the solute (in nm), calculated as:

$$r_S = \left(\frac{3 \cdot 10^{21} V_S}{4\pi N_{Av}}\right)^{1/3}, \quad (10)$$

where N_{Av} is the Avogadro number. However, the definitive correlation volume requires iteration, because it depends on the local mole fractions. This iteration is achieved by replacing $\delta x_{D,S}$ in the equation (2) to calculate $x_{D,S}^L$ until a non-variant value of V_{cor} is obtained.

Results and discussion

Sulfonamides under study are shown in Table 1. The solubility of these compounds in 1,4-dioxane + water mixtures (Table 2) was taken from the literature (**Martin, A., *et al.,*** 1985; **Bustamante, P., *et al.,*** 1993; **Reillo, A., *et al.,*** 1993, 1995a, 1995b). Standard molar Gibbs energy of transfer of these sulfonamides from neat water to 1,4-dioxane + water mixtures is calculated and correlated to specific polynomials from the drug solubility data by using equation (11). Figure 1 and Table 3 show the Gibbs energy of transfer for all the sulfonamides studied. Polynomial coefficients are shown in Table 4.

$$\Delta_{tr} G^0_{S,W\to D+W} = RT \ln\left(\frac{x_{S,W}}{x_{S,D+W}}\right) = a + bx_D + cx_D^{1.5} + dx_D^2 + ex_D^3. \quad (11)$$

Table 2. Mole fraction solubility (x_S) of the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

f_D	x_D	SA[a]	SP[b]	SD[c]	SSM[d]	SMP[c]	SMZ[e]	SMX[c]
0.00	0.000	6.45E–4	1.77E–5	4.40E–6	8.95E–5	3.73E–5	3.55E–5	2.32E–5
0.10	0.023	1.83E–3	–	1.45E–5	2.74E–4	1.66E–4	1.46E–4	1.01E–4
0.20	0.050	5.80E–3	5.21E–5	6.08E–5	7.13E–4	–	2.35E–4	4.42E–4
0.30	0.083	1.36E–2	–	1.37E–4	1.58E–3	1.47E–3	4.92E–4	1.75E–3
0.35	0.102	–	–	–	2.35E–3	–	–	–
0.40	0.123	3.11E–2	1.60E–4	2.10E–4	3.03E–3	3.80E–3	9.59E–4	3.04E–3
0.45	0.147	–	–	–	3.79E–3	–	–	–
0.50	0.174	6.05E–2	2.75E–4	5.52E–4	–	1.13E–2	2.12E–3	8.01E–3
0.55	0.205	–	–	–	5.98E–3	1.57E–2	–	–
0.57	0.218	–	–	–	–	1.85E–2	–	–
0.60	0.240	9.18E–2	4.53E–4	8.41E–4	7.48E–3	2.55E–2	4.11E–3	1.66E–2
0.65	0.281	–	6.10E–4	–	8.39E–3	–	–	–
0.70	0.330	0.127	7.46E–4	1.26E–3	1.03E–2	3.86E–2	5.87E–3	2.80E–2
0.75	0.387	0.154	8.28E–4	1.62E–3	1.12E–2	5.39E–2	7.17E–3	4.18E–2
0.77	0.414	–	–	–	1.18E–2	–	6.87E–3	–
0.80	0.457	0.188	9.30E–4	1.76E–3	1.19E–2	6.11E–2	8.19E–3	5.30E–2
0.85	0.544	0.195	1.03E–3	1.81E–3	1.16E–2	7.09E–2	7.70E–3	6.13E–2
0.86	0.564	–	–	–	–	7.00E–2	–	–
0.87	0.585	–	1.07E–3	1.77E–3	–	–	7.73E–3	–
0.90	0.655	0.181	9.98E–4	1.62E–3	1.01E–2	6.42E–2	7.06E–3	6.08E–2
0.92	0.708	–	9.62E–4	–	9.56E–3	–	6.23E–3	–
0.94	0.767	0.175	8.63E–4	1.36E–3	7.93E–3	5.50E–2	4.95E–3	5.56E–2
0.96	0.835	0.155	7.22E–4	1.09E–3	6.43E–3	5.07E–2	3.90E–3	5.21E–2
0.98	0.912	0.130	5.79E–4	7.73E–4	4.71E–3	4.19E–2	2.26E–3	–
1.00	1.000	8.03E–2	3.39E–4	4.97E–4	2.51E–3	2.37E–2	9.64E–4	3.00E–2

[a] Data from **Reillo, A., *et al.,*** (1993); [b] Data from **Reillo, A., *et al.,*** (1995a); [c] Data from **Bustamante, P., *et al.,*** (1993); [d] Data from **Martín, A., *et al.,*** (1985); [e] Data from **Reillo, A., *et al.,*** (1995b).

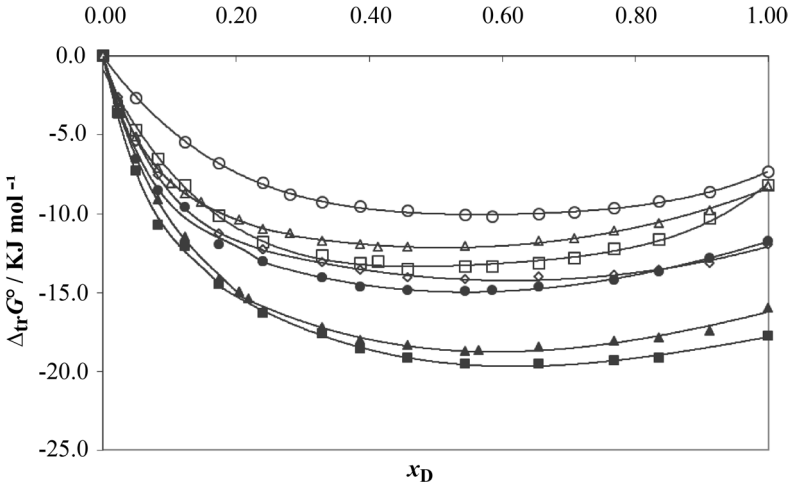


Figure 1. Gibbs energy of transfer of the sulfonamides under study from neat water to 1,4-dioxane + water binary co-solvent mixtures at 298.15 K. (◊): SA; (○): SP; (●): SD; (Δ): SSM; (▲): SMP; (□): SMZ; (■): SMX.

Table 3. Gibbs energy of transfer (kJ mol^{-1}) of the sulfonamides from neat water to 1,4-dioxane + water co-solvent mixtures at 298.15 K

f_D	x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	0.000	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.10	0.023	–2.59	–	–2.95	–2.77	–3.70	–3.51	–3.64
0.20	0.050	–5.45	–2.68	–6.51	–5.14	–	–4.68	–7.31
0.30	0.083	–7.56	–	–8.52	–7.11	–9.11	–6.52	–10.72
0.35	0.102	–	–	–	–8.10	–	–	–
0.40	0.123	–9.61	–5.46	–9.58	–8.73	–11.47	–8.18	–12.08
0.45	0.147	–	–	–	–9.28	–	–	–
0.50	0.174	–11.26	–6.80	–11.98	–	–14.17	–10.14	–14.49
0.55	0.205	–	–	–	–10.42	–14.98	–	–
0.57	0.218	–	–	–	–	–15.39	–	–
0.60	0.240	–12.29	–8.04	–13.02	–10.97	–16.18	–11.78	–16.29
0.65	0.281	–	–8.78	–	–11.26	–	–	–
0.70	0.330	–13.10	–9.28	–14.03	–11.75	–17.21	–12.67	–17.59
0.75	0.387	–13.57	–9.53	–14.64	–11.97	–18.04	–13.16	–18.58
0.77	0.414	–	–	–	–12.10	–	–13.06	–
0.80	0.457	–14.06	–9.82	–14.85	–12.12	–18.35	–13.49	–19.17
0.85	0.544	–14.16	–10.08	–14.92	–12.06	–18.72	–13.34	–19.53
0.86	0.564	–	–	–	–	–18.69	–	–
0.87	0.585	–	–10.18	–14.86	–	–	–13.35	–
0.90	0.655	–13.98	–10.00	–14.65	–11.72	–18.47	–13.12	–19.52
0.92	0.708	–	–9.91	–	–11.58	–	–12.81	–
0.94	0.767	–13.89	–9.64	–14.22	–11.12	–18.09	–12.24	–19.29
0.96	0.835	–13.59	–9.20	–13.65	–10.60	–17.88	–11.65	–19.13
0.98	0.912	–13.15	–8.65	–12.81	–9.83	–17.41	–10.29	–
1.00	1.000	–11.96	–7.32	–11.72	–8.26	–16.00	–8.19	–17.76

Table 4. Coefficients of equation (11) (kJ mol^{-1}) applied to the Gibbs energy of transfer of the sulfonamides from neat water to 1,4-dioxane + water co-solvent mixtures at 298.15 K

Coefficient	SA	SP	SD	SSM	SMP	SMZ	SMX
a	0.17	0.10	–0.10	–0.05	–0.03	–0.32	–0.06
b	–193.79	–88.95	–199.58	–178.04	–213.86	–149.20	–240.63
c	439.49	154.39	447.26	414.10	439.25	309.87	529.58
d	–323.23	–89.44	–325.07	–310.59	–293.66	–216.09	–381.26
e	65.36	16.45	65.92	66.34	52.16	47.48	74.71

Table 5. *D* values (kJ mol^{-1}) for the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	–193.79	–88.95	–199.58	–178.04	–213.86	–149.20	–240.63
0.10	–48.01	–33.11	–50.47	–41.74	–62.67	–44.01	–63.44
0.20	–20.42	–19.18	–21.67	–16.52	–30.40	–22.07	–28.92
0.30	–9.01	–11.33	–9.37	–6.26	–15.09	–11.45	–14.12
0.40	–4.07	–6.14	–3.69	–1.81	–7.04	–5.32	–7.38
0.50	–1.85	–2.30	–0.83	0.35	–2.50	–1.02	–4.16
0.60	–0.44	0.87	1.19	2.04	0.45	2.80	–2.15
0.70	1.32	3.77	3.52	4.35	2.95	6.95	0.04
0.80	4.17	6.66	6.93	7.96	5.75	11.95	3.29
0.90	8.63	9.73	11.94	13.38	9.37	18.16	8.24
1.00	15.07	13.10	18.92	20.95	14.18	25.86	15.33

Thus, *D* values were calculated from the first derivative of polynomial models (equation 12) solved according to the co-solvent mixtures composition. This procedure was done varying by 0.05 in mole fraction of 1,4-dioxane, but in the following tables the respective values are reported varying only by 0.10. *D* values are reported in Table 5.

$$D = b + 1.5cx_D^{0.5} + 2dx_D + 3ex_D^2 \qquad (12)$$

In order to calculate the Q values, the excess molar Gibbs energies of mixing $G_{D,W}^{Exc}$ at 298.15 K are required. In this way, $G_{D,W}^{Exc}$ values were calculated at 298.15 K by using equation (13) as reported by **Marcus, Y.** (2002):

$$G_{D,W}^{Exc} = x_D x_W \left(3835 - 973(1-2x_D) - 421(1-2x_D)^2\right). \qquad (13)$$

It is important to note that a quartic regular polynomial of $G_{D,W}^{Exc}$ as a function of the mole fraction of water was obtained. *Q* values are shown in Table 6. On the other hand, Table 6 also shows the $RT\kappa_T$ values calculated by assuming additive behavior of κ_T (equation 7) with the values 0.738 and 0.457 GPa^{-1} for 1,4-dioxane and water, respectively (**Marcus, Y.** 1998).

The partial molar volumes of 1,4-dioxane and water (Table 6) were calculated by means of equations (14) and (15) from the density (ρ) values of 1,4-dioxane + water mixtures reported by **Ruidíaz, M.A.** & **Martínez, F.** (2009) at 298.15 K. *V* is the molar volume of the mixtures and it is calculated as $V = (x_D M_D + x_W M_W)/\rho$. Here M_D and M_W are 88.11 and 18.02 g mol^{-1}, respectively:

$$\overline{V}_D = V + x_W \frac{dV}{dx_D} \quad , \qquad (14)$$

Table 6. Physicochemical properties of the 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	*Q* / kJ mol^{-1}	$RT\kappa_T$ / cm^3 mol^{-1}	$\overline{V}_D^0$ / cm^3 mol^{-1}	$\overline{V}_W^0$ / cm^3 mol^{-1}
0.00	2.479	1.133	81.01	18.06
0.10	2.424	1.202	82.66	17.97
0.20	1.968	1.272	83.90	17.75
0.30	1.351	1.342	84.79	17.46
0.40	0.765	1.411	85.39	17.15
0.50	0.351	1.481	85.74	16.86
0.60	0.204	1.551	85.90	16.67
0.70	0.371	1.620	85.93	16.62
0.80	0.847	1.690	85.88	16.77
0.90	1.583	1.760	85.82	17.17
1.00	2.479	1.829	85.78	17.88

$$\overline{V}_W = V + x_D \frac{dV}{dx_D} \quad . \qquad (15)$$

Partial molar volumes of non-electrolyte drugs are not frequently reported in the literature, which is explained by the big uncertainty surrounding its determination due to the low solubilities exhibited, particularly in aqueous media. For this reason, in a first approach, the molar volume of these sulfonamides was considered here as independent of co-solvent composition, and calculated according to the groups contribution method proposed by **Fedors, R.F.** (1974) and exemplified by **Barton, A.F.M.** (1991). Table 7 shows the number of functional groups present in all the sulfonamides, as well as the respective individual contribution to internal energy (U / kJ mol^{-1}) and molar volume (V / cm^3 mol^{-1}). Table 8 shows the U and V values for every sulfonamide calculated as additive properties. From volume values, the radiuses of the drug molecules (required for equation 9) were calculated by using equation (10), values which are also shown in Table 8.

Tables 9 and 10 show that the $G_{D,S}$ values were negative in all cases, whereas $G_{W,S}$ was negative in water-rich mixtures but positive in 1,4-dioxane-rich mixtures.

In order to use the IKBI method, the correlation volumes were iterated three times by using the equations (2), (8) and (9) to obtain the values reported in Table 11.

The values of $\delta x_{D,S}$ varied non-linearly with the 1,4-dioxane concentration in the aqueous mixtures at 298.15 K (Fig 2). The addition of 1,4-dioxane to water tends to make negative the $\delta x_{D,S}$ values of all these sulfonamides from the pure water up to the mixture 0.18 in mole fraction of 1,4-dioxane reaching minimum values in x_D = 0.05. Possibly the structuring of water molecules around the non-polar groups

Table 7. Contribution to internal energy and molar volume by every functional group and number of groups present in the sulfonamides according to the Fedors method (**Fedors, R.F.** 1974; **Barton, A.F.M.** 1991)

Group	U / kJ mol^{-1}	V / cm^3 mol^{-1}	SA	SP	SD	SSM	SMP	SMZ	SMX
–O–	3.4	3.8	–	–	–	–	1	–	1
–NH_2	12.6	19.2	2	1	1	1	1	1	1
–NH–	8.4	4.5	–	1	1	1	1	1	1
=N–	11.7	5.0	–	1	2	2	2	2	1
–S–	14.2	12.0	–	–	–	–	–	1	–
–SO_2–	25.6	19.5	1	1	1	1	1	1	1
>C=	4.3	–5.5	–	1	1	3	2	2	2
–CH=	4.3	13.5	–	4	3	1	2	–	1
–CH_3	4.7	33.5	–	–	–	2	1	1	1
Phenylene	31.9	52.4	1	1	1	1	1	1	1
Ring closure	1.1	16.0	–	1	1	1	1	1	1
Conj. bond	1.7	–2.2	–	3	3	3	3	2	2

Table 8. Some physicochemical properties of the sulfonamides

Property	SA	SP	SD	SSM	SMP	SMZ	SMX
V_S[a]/ cm^3 mol^{-1}	110.3	158.5	150.0	179.0	168.3	151.7	152.0
U[a]/ kJ mol^{-1}	82.7	117.8	125.2	134.6	133.2	133.8	115.6
δ_S[b]/ MPa$^{1/2}$	27.4	27.3	28.9	27.4	28.1	29.7	27.6
r_S[c]/ nm	0.352	0.398	0.390	0.414	0.406	0.392	0.392
Acidic sites [d]	4	3	3	3	3	3	3
Basic sites [e]	5	6	7	7	9	9	8

[a] V_S and U correspond to total molar volume and internal energy calculated according to **Fedors, R.F.** (1974) and **Barton, A.F.M.** (1991).
[b] δ_S is the Hildebrand solubility parameter calculated as $(1000U// V_S)^{1/2}$.
[c] r_S is the molecular radius calculated with equation (10).
[d] Acidic sites were assigned as: two for H_2N– and one for –NH–.
[e] Basic sites were assigned as: one for H_2N–, four for –SO_2–, one for =N–, two for –O–, and two for –S–.

Table 9. $G_{D,S}$ values ($cm^3\ mol^{-1}$) for the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	–1521	–805	–1603	–1475	–1725	–1237	–1904
0.10	–429	–378	–486	–456	–585	–444	–574
0.20	–256	–296	–305	–297	–386	–310	–359
0.30	–190	–260	–233	–234	–303	–254	–278
0.40	–164	–240	–198	–202	–262	–222	–250
0.50	–153	–212	–168	–169	–227	–175	–250
0.60	–123	–129	–110	–111	–152	–59	–220
0.70	–91	–106	–101	–119	–127	–57	–150
0.80	–92	–130	–121	–146	–144	–103	–137
0.90	–99	–146	–135	–163	–156	–130	–141
1.00	–108	–157	–148	–177	–166	–150	–150

Table 10. $G_{W,S}$ values ($cm^3\ mol^{-1}$) for the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	–109	–157	–149	–178	–167	–151	–151
0.10	–273	–270	–321	–320	–381	–301	–367
0.20	–283	–321	–333	–319	–426	–339	–397
0.30	–278	–370	–325	–295	–451	–366	–416
0.40	–291	–431	–314	–259	–481	–388	–480
0.50	–335	–438	–249	–135	–472	–274	–659
0.60	–219	63	152	339	–54	557	–692
0.70	106	455	424	528	312	978	–144
0.80	229	383	414	468	300	819	117
0.90	312	318	434	475	290	736	252
1.00	413	297	507	548	324	745	380

Table 11. Correlation volume ($cm^3\ mol^{-1}$) of the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	615	759	735	816	787	740	741
0.10	694	874	829	931	873	842	817
0.20	856	1032	1003	1101	1071	1010	1014
0.30	985	1182	1144	1241	1232	1157	1168
0.40	1102	1325	1267	1364	1372	1289	1312
0.50	1216	1443	1369	1463	1490	1381	1470
0.60	1290	1463	1411	1509	1524	1362	1576
0.70	1338	1528	1493	1612	1591	1437	1578
0.80	1431	1664	1620	1753	1719	1591	1658
0.90	1537	1797	1747	1890	1847	1740	1767
1.00	1652	1924	1879	2030	1975	1888	1889

of these drugs (aromatic rings and/or methyl groups), *i.e.* hydrophobic hydration, contributed to lowering the net $\delta x_{D,S}$ to negative values in these water-rich mixtures (Table 12).

Sulfonamides act in solution as a Lewis acid due to the hydrogen atoms in its $–NH_2$ and –NH– groups (Table 1) in order to establish hydrogen bonds with proton-acceptor functional groups in the solvents (oxygen atoms in –OH and –O– groups). In addition, these drugs could act as a Lewis base due to free electron pairs in either, i) oxygen atoms of $–SO_2–$ and –O– groups, ii) nitrogen atoms of $–NH_2$, and =N– groups, or iii) sulfur atom of –S– groups, to interact with hydrogen atoms in water. Table 8 shows the respective numbers of acidic and basic sites in the sulfonamides considered.

In the mixtures with composition varying from $0.18 < x_D < 0.47$ for sulfisomidine and $0.18 < x_D < 0.70$ for sulfamethoxazole, the local mole fractions of 1,4-dioxane were greater than those for water. In this way, the co-solvent action may be related to the breaking of the ordered structure of water (hydrogen bonds) around the non-polar moieties of the drugs, which increases the solvation of these sulfonamides having maximum values in different co-solvent compositions according to each sulfonamide. Ultimately, from these 1,4-dioxane proportions up to neat 1,4-dioxane, the local mole fractions of co-solvent decreased, being the $\delta x_{D,S}$ values negative, as they are in water-rich mixtures.

According to the preferential solvation results, it is possible that in intermediate composition mixtures, the sulfonamides could have acted as a Lewis acid with 1,4-dioxane molecules to some extent because this co-solvent has a basicity near to the one for water, *i.e.*, the Kamlet-Taft hydrogen bond acceptor parameters are $\beta = 0.37$ for 1,4-dioxane and 0.47 for water (**Kamlet, M.J. & Taft, R.W.** 1976). Otherwise, non-specific interactions such as London forces could have

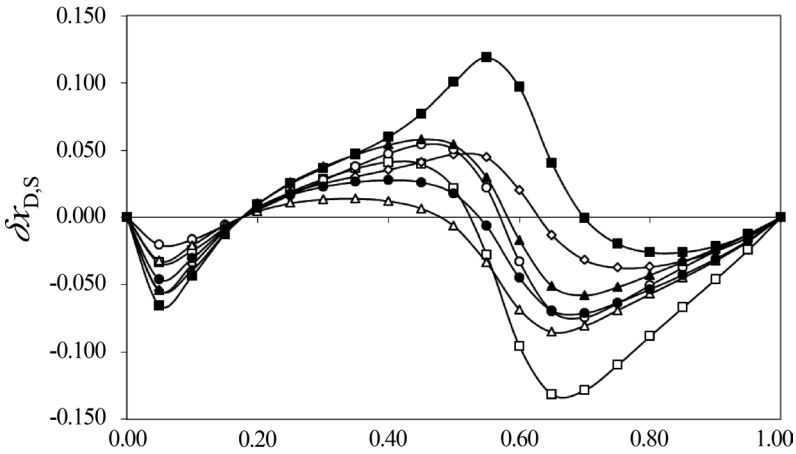


Figure 2. $\delta x_{D,S}$ values for the sulfonamides under study in 1,4-dioxane + water co-solvent mixtures at 298.15 K. (◊): SA; (○): SP; (●): SD; (Δ): SSM; (▲): SMP; (□): SMZ; (■): SMX.

Table 12. $\delta x_{D,S}$ values for the sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K

x_D	SA	SP	SD	SSM	SMP	SMZ	SMX
0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.10	–0.0348	–0.0164	–0.0301	–0.0205	–0.0390	–0.0245	–0.0434
0.20	0.0074	0.0056	0.0067	0.0044	0.0098	0.0068	0.0097
0.30	0.0252	0.0275	0.0227	0.0133	0.0376	0.0285	0.0366
0.40	0.0353	0.0474	0.0277	0.0120	0.0538	0.0411	0.0598
0.50	0.0468	0.0505	0.0175	–0.0065	0.0538	0.0216	0.1004
0.60	0.0204	–0.0326	–0.0447	–0.0683	–0.0167	–0.0954	0.0970
0.70	–0.0316	–0.0741	–0.0711	–0.0806	–0.0578	–0.1285	–0.0009
0.80	–0.0367	–0.0503	–0.0533	–0.0568	–0.0427	–0.0882	–0.0258
0.90	–0.0250	–0.0246	–0.0307	–0.0321	–0.0232	–0.0460	–0.0212
1.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

been also involved here. On the other hand, in 1,4-dioxane-rich mixtures, where the drugs are preferentially solvated by water, they could have acted mainly as a Lewis base in the presence of water because the Kamlet-Taft hydrogen bond donor parameters are $\alpha = 1.17$ for water and 0.00 for 1,4-dioxane, respectively (**Taft, R.W. & Kamlet, M.J.** 1976). In this way, the specific and nonspecific interactions between sulfonamides and this co-solvent decreased in these final mixtures (**Ruidíaz, M.A., *et al.*,** 2010; **Ruckenstein, E. & Shulgin, I.** 2001).

Finally, it is interesting to make some comparisons according to the molecular similarities among the sulfonamides. Figure 3 shows the comparison between: i) sulfapyridine and sulfadiazine (difference in one nitrogen atom in the heterocyclic moiety), ii) sulfadiazine and sulfisomidine (difference in two methyl groups and in the position of the two nitrogen atoms in the heterocyclic moiety), and iii) sulfamethizole and sulfamethoxazole (difference in one nitrogen atom and the change of a sulfur atom by oxygen atom in the heterocyclic moiety).

In the first case (SP vs. SD), sulfadiazine exhibited more affinity for water than sulfapyridine, *i.e.*, in water-rich mixtures because $\delta x_{D,S}$ minimum values are –0.046 and –0.020 for SD and SP, respectively. The 1,4-dioxane preferred region was greater for SP than for SD and the maximum $\delta x_{D,S}$ values were 0.054 and 0.028 for SP and SD, respectively. Finally, in the 1,4-dioxane-rich region the behaviors were almost similar. If this behavior were to be considered as a criterion of drug polarity, then sulfadiazine would be a more polar compound than sulfapyridine. This is in agreement with other polarity parameters as the Hildebrand solubility parameter δ_S values reported in Table 8 (27.7 vs. 28.9 $MPa^{1/2}$ for SP and SD, respectively), and the reported molar octanol-water partition coefficients (0.995 and 0.826 at 298.15 K for SP and SD, respectively) (**Martínez, F. & Gómez, A.** 2002).

In the second case (SD vs. SSM), sulfadiazine exhibited more affinity for water than sulfisomidine only in water-rich mixtures because $\delta x_{D,S}$ minimum values were –0.046 and –0.020 for SD and SSM, respectively. Otherwise, the 1,4-dioxane-preferred region was greater for SD than for

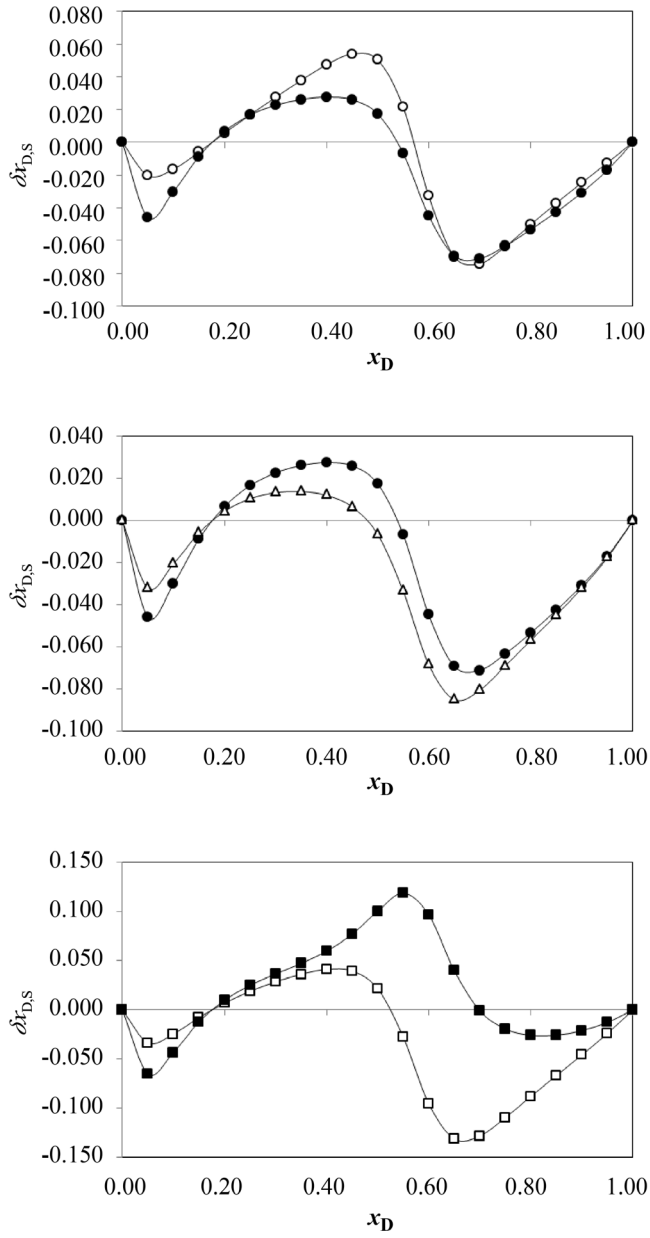


Figure 3. Comparison of preferential solvation between similar sulfonamides in 1,4-dioxane + water co-solvent mixtures at 298.15 K. Top graph: (○): SP vs. (●): SD; Middle graph: (●): SD vs. (Δ): SSM; Bottom graph: (□): SMZ vs. (■): SMX.

SSM and the maximum $\delta x_{D,S}$ values were 0.028 and 0.014 for SD and SSM, respectively. Finally, in the 1,4-dioxane-rich region sulfisomidine was preferentially solvated by water more than sulfadiazine because the $\delta x_{D,S}$ minimum values were –0.071 and –0.085 for SD and SSM, respectively. In this case, there was no agreement with solubility parameters because the δ_S value for SSM was 27.4 $MPa^{1/2}$, which was lower than the one for SD (Table 8).

Finally, in the third case (SMZ vs. SMX), in water-rich mixtures, sulfamethizole was preferentially solvated by water less than sulfamethoxazole ($\delta x_{D,S}$ values were –0.034 and –0.065, for SMZ and SMX, respectively). Otherwise, the 1,4-dioxane-preferred region was far greater for SMX than for SMZ and the maximum $\delta x_{D,S}$ values were 0.119 and 0.041 for SMX and SMZ, respectively. Finally, in the 1,4-dioxane-rich region, sulfamethizole was preferentially solvated by water much more than sulfamethoxazole because the $\delta x_{D,S}$ minimum values were –0.131 and –0.026 for SMZ and SMX, respectively. In this case, there was good agreement with solubility parameters because the respective δ_S values for SMZ and SMX were 29.7 and 27.6 $MPa^{1/2}$ (Table 8). It is important to note that sulfamethoxazole exhibits a molar octanol-water partition coefficient of 8.222 compared to 1.101 (both at 298.15 K) exhibited by sulfathiazole, a sulfonamide structurally related to sulfamethizole (**Martínez, F. & Gómez, A.** 2002).

Conclusions

Explicit expressions for local mole fractions of 1,4-dioxane and water around the selected sulfonamides were derived on the basis of the IKBI method applied to equilibrium solubility values of these drugs in 1,4-dioxane + water mixtures. Thus, all these drugs were preferentially solvated by water in water-rich and 1,4-dioxane-rich mixtures, but preferentially solvated by 1,4-dioxane in mixtures with intermediate composition at 298.15 K. Nevertheless, the molecular reasons for these results are not clear given the complexity of these compounds with several acidic and basic sites, and, therefore, it is not easy to propose the respective molecular interactions involved.

Disclosure

Authors report no conflicts of interest in this work.

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