Scientific paper

# Preferential Solvation of Ibuprofen and Naproxen in Aqueous 1,2-Propanediol

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*Received: 26-08-2008*

***Dedicated to Professor Josef Barthel on the occasion of his 80th birthday***

## Abstract

The recently published study of the solubility of ibuprofen (IBP) and naproxen (NAP) in aqueous 1,2-propanediol (PG) at several temperatures had as its purpose the modeling of the solubilities in terms of the solvent composition. It did not show how these drugs are preferentially solvated by water and by PG. The inverse Kirkwood-Buff integral (IKBI) and the quasi-lattice quasi-chemical (QLQC) approaches are here applied to this problem of the preferential solvation. The interactions involved are deduced from the results.

**Keywords**: Ibuprofen, naproxen, 1,2-propanediol, preferential solvation, inverse Kirkwood Buff integrals, quasi-lattice quasi chemical method.

## 1. Introduction

Most studies of the solubility of drugs in solvent mixtures have as their purpose the modeling of the solubilities in terms of the solvent composition, possibly also the prediction of the solubilities in the mixtures from those in the pure components. A very recent example is the study by Manrique et al.[1] of the solubility of ibuprofen (IBP, 2-[4-(2-methylpropyl)phenyl]propanoic acid, CAS reg. No. 15687-27-1) and naproxen (NAP, (+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid, CAS reg. No. 22204-53-1) in mixtures of water (W) and 1,2-propanediol (PG) at several temperatures. Thermodynamic functions of the solvation of the drugs were obtained, but not how they are preferentially solvated by water and by PG in the aqueous solvent mixtures. Such modeling of drug solubilities has been carried out over the years by means of various approaches, such as the 'nearly ideal binary solvent' (NIBS) approach of Acree and co-workers[2] or the model of Jouyban-Acree,[3] mobile order theory,[4] or Kirkwood-Buff integrals,[5] among others. More insight into the interactions of the drug molecules with those of the components of the mixed solvent would help in the choice of better co-solvents for the enhancement of drug solubilities in aqueous media, because these after all constitute the body fluids. Such insights should be obtainable from detailed information on how these drug molecules are preferentially solvated, since not only the direct drug-solvent interactions but also interactions between the components of the mixed solvent are involved.

The recent publication by Marcus[6] addressed this problem by means of two approaches: the inverse Kirkwood-Buff integral (IKBI) method and the quasi-lattice quasi-chemical (QLQC) one, each having its merits and drawbacks. The preferential solvation parameter $\delta x_{A,S}$ for the solute S by the component solvents A and B is defined as:

$$\delta x_{A,S} = x^{L}_{A,S} - x_A = -\delta x_{B,S} \quad (1)$$

where $x^{L}_{A,S}$ is the local mole fraction of A in the surroundings of the solute S and $x_A$ is its mole fraction in the bulk solvent mixture. S is preferentially solvated by A when $\delta x_{A,S} > 0$, otherwise by B. Negligible preferential solvation is indicated when $|\delta x_{A,S}| \leq 0.01$, but values $\delta x_{A,S} \approx x_B$ signify $x^{L}_{A,S} \approx 1$ or complete selective solvation of S by A. The magnitude and shape of the $\delta x_{A,S} = f(x_A)$ curve provide the desired information on the relative strength of the interactions of S with A and with B in their mixture.

In order to apply the IKBI and QLQC methods, the solubility data need to be transformed into standard molar Gibbs energies of transfer from one of the components,

say A, into the mixture A + B. If $s(x_A)$ is the solubility as a function of the solvent composition, then:

$$\Delta_t G^\infty(\mathrm{S, A \rightarrow A + B}) = -RT \ln[s(\mathrm{S\ in\ A + B})/s(\mathrm{S\ in\ A})] \quad (2)$$

provided that the solid that is at equilibrium with the saturated solutions is the same at all the solvent compositions and no solvates are formed. Another requirement is that the solute S is only sparingly soluble, so that an essentially infinite dilution quantity, $\Delta_t G^\infty$, results. Otherwise, activity coefficients of S at each solvent composition need to be employed. $\delta_t G^\infty$ implies that solute-solute interactions may be disregarded and the solute molecules are surrounded by solvent molecules only.

## 2. Methods and Data

The IKBI approach depends on obtaining the Kirkwood-Buff integrals[6] as follows.

$$G_{A,S} = RT\kappa_T - V_S + x_B V_B D/Q \quad (3)$$

$$G_{B,S} = RT\kappa_T - V_S + x_A V_A D/Q \quad (3a)$$

Here $G_{A,S}$ and $G_{B,S}$ are the Kirkwood-Buff integrals (in $\mathrm{cm^3\ mol^{-1}}$) as obtained from the thermodynamic data: the isothermal compressibility of the mixtures, $\kappa_T$ (in $\mathrm{GPa^{-1}}$), and the partial molar volume of the solute, $V_S$, and those of the solvents, $V_A$ and $V_B$ (in $\mathrm{cm^3\ mol^{-1}}$). The functions $D$ and $Q$ (in $\mathrm{kJ\ mol^{-1}}$, as is $RT$) are given in eqs. (4) and (5), and depend on the first derivative of standard molar Gibbs energies of transfer, $\Delta_t G^\infty$, and the second derivative of the excess Gibbs energy of mixing of the two solvents, $G^E_{A,B}$, with respect to the composition.

$$D = \mathrm{d}\Delta_t G^\infty(\mathrm{S, A \rightarrow A + B})/\mathrm{d}x_B \quad (4)$$

$$Q = RT + x_A x_B\, \mathrm{d}^2 G^E{}_{A,B}/\mathrm{d}x_B{}^2 \quad (5)$$

A final quantity that is required is the correlation volume around S, $V_{cor}$, within which preferential solvation takes place and the local mole fraction, $x^L{}_{A,S}$, is defined.

$$V_{cor} = 2522.5[r_S + 0.1363\{x_A{}^L V_A + (1-x_A{}^L)V_B\}^{1/3} - 0.085]^3 \quad (6)$$

This volume involves one solvation shell and depends on the size of the solute molecule (its radius, $r_S$ in nm) plus a distance of one mean solvent diameter from the surface of the solute. The resulting correlation volume, in $\mathrm{cm^3\ mol^{-1}}$, the numerical coefficients of which relate sizes to volumes,[6] requires iteration, since it involves the local mole fractions of the two solvents.

The resulting preferential solvation parameter is then:[6]

$$\delta x_{A,S} = x_A x_B (G_{A,S} - G_{B,S}) / [x_A G_{A,S} + x_B G_{B,S} + V_{cor}] \quad (7)$$

The QLQC approach counts the pairs of adjacent molecules on the quasi lattice of the solution, that has a lattice parameter $Z$ (coordination number), the neighboring pairs being so arranged because of the interactions involved in the quasi-chemical model. At infinite dilution of the solute, the fraction of A-A contacts in a mixture of $N_A + N_B$ solvent molecules is $N_{AA}/Z(N_A + N_B) = x_A - N_{AB}/Z(N_A + N_B)$ and similarly for B-B contacts. The fraction of A-B contacts depends on the interaction energy between these molecules, $\Delta E_{AB}$ according to the quasi-chemical aspect:

$$N_{AB}/Z(N_A + N_B) = [1-\{1-4x_A x_B (1-\exp(-\Delta E_{AB}/RT))\}^{1/2}]/[2(1-\exp(-\Delta E_{AB}/RT))] \quad (8)$$

The interaction energy $\Delta E_{AB}$ is obtained from the excess Gibbs energy at the equimolar composition:

$$\exp(\Delta E_{AB}/RT) = [\{2\exp(-G^E_{AB\ (x = 0.5)}/ZRT)\} - 1]^2 \quad (9)$$

When the solute S is introduced at infinite dilution it interacts with the two solvents, with the difference in the interaction energy given by its standard molar Gibbs energy of transfer:

$$\Delta E_{AB,S} = \Delta_t G^\infty(\mathrm{S, A \rightarrow B})/Z \quad (10)$$

Finally, the local mole fraction of solvent component A in the surroundings of S is given by the quasi-chemical expression:

$$x_A{}^L = 1/[1 + (N_{BB}/N_{AA})^{1/2}\exp(\Delta E_{AB,S}/2RT] \quad (11)$$

The derivation of the expressions employed here is described in the references given in the previous publication[6] as are also the relative merits of the two methods (the IKBI has fewer unverifiable assumptions) and their drawbacks (the need for derivative functions for IKBI implying highly accurate data).

The data required for the application of the IKBI and QLQC methods in the present instance are first of all the solubilities $s$ of the IBP and NAP in the solvent mixtures, water (W) + PG. These were provided by Manrique et al.[1] at 5 temperatures between 20 and 40 °C at 6 solvent compositions. The latter were at 20 mass % steps from neat W to neat PG, and when transformed to $x_{PG}$: 0, 0.0588, 0.1363, 0.2621, 0.4864, 1, they show a gap beyond the equimolar composition. The solubility of NAP in neat PG is still sufficiently low permitting the disregard of solute-solute interactions, but that of IBP, at the higher temperatures, is considerable. For the lack of activity coefficient data (*not* the quantities so designated by Manrique et al.[1] but those relating to solute-solute interac-

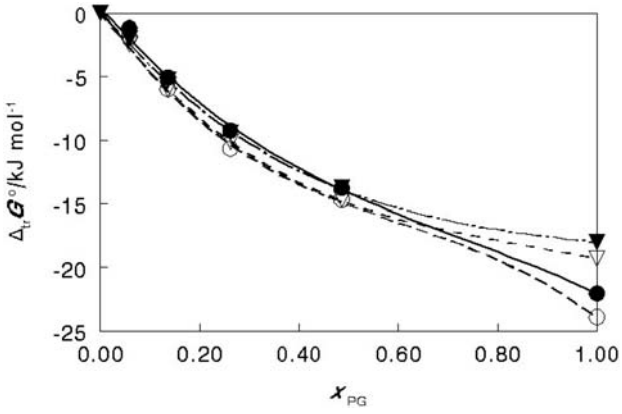


**Fig. 1.** The standard molar Gibbs energies of transfer, $\Delta_{tr}G^{\infty}$/kJ mol$^{-1}$, of IBP (circles) and NAP (triangles) from W to W + PG as a function of the PG content, $x_{PG}$, at 25 °C (filled symbols) and 40 °C (empty symbols). The curves are 3rd degree polynomials fitted to the data.

tions), eq. (2) must still be applied. The resulting values at 25 and 40 °C are shown in Fig. 1, third degree polynomials being fitted to them.

No excess Gibbs energies of mixing have been reported for the W + PG system, but such values can be derived from published data. Water activities at 80 °F (26.67 °C) were reported by Curme and Johnston,[7] from which the excess chemical potential of water, $\mu_W^E$, is readily obtained. Its derivative with respect to $x_{PG}$ can be used in lieu of $d^2G^E_{A,B}/dx_B^2$ in eq. (5), and when expressed as a Redlich-Kister expression $\mu_W^E$ is readily transformed into $G^E_{W,PG}$ for use in eq. (9). Subsequently, Sloan and Labuza[8] reported water activity data at 23 °C that can be treated similarly, although the resulting curve appears to be rather wave-like. It is deduced from these two sources that $G^E_{W,PG} < 0$ at these two temperatures, although Verlinde et al. [9] considered that $G^E_{W,PG} \approx 0$ at 15 to 50 °C from vapor pressure data. Application of the UNIQUAC method by Jonsdottir and Klein[10] to W + PG at 80 °C, however, yielded positive values of $G^E_{W,PG}$, and larger positive values were provided from UNIQUAC calculations (albeit with different group contributions) by Lancia et al.[11] at 98 °C. These results are summarized in Fig. 2. The vapor pressures and compositions reported by Chu et al.[12] at 80 and 110 °C lead to still positive but smaller $G^E_{W,PG}$ values than obtained from the UNIQUAC calculations, but the non-availability of the 2nd virial coefficients at the high temperatures and considerable vapor pressures does not permit the accurate calculation of $G^E_{W,PG}$.

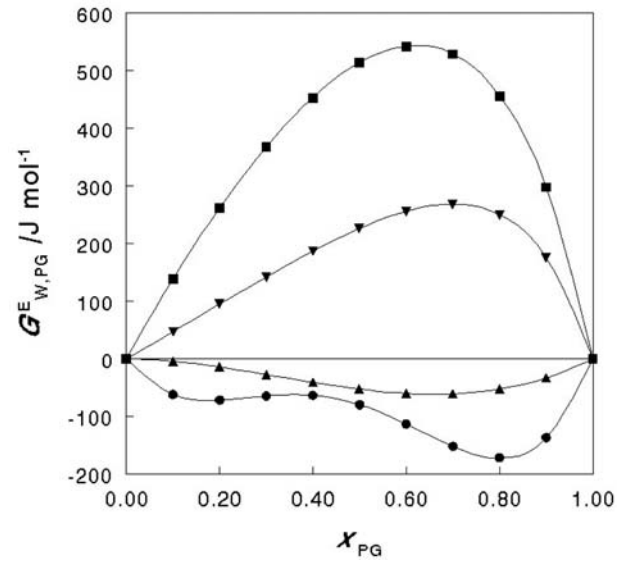


**Fig. 2.** The excess Gibbs energy of mixing, $G^E_{W,PG}$/J mol$^{-1}$, of W and PG as a function of the PG content, $x_{PG}$, at several temperatures: ● 23 °C,[8] ▲ 26.67 °C,[7] ▼ 80 °C,[10] and ■ 98 °C.[11]

The isothermal compressibility, $\kappa_T$, and partial molar volumes, $V_W$ and $V_{PG}$ of the W + PG mixtures, required in eq. (3), were calculated from the densities and excess molar volumes at ambient and at elevated pressures at several temperatures reported by Geyer et al.[13] The partial molar volumes $V_{IBP}$ and $V_{NAP}$, also needed for eqs. (3), are assumed equal to the molar volumes of the liquid drugs, but neither these nor the densities of the solid drugs were found. However, the molecular volumes $v_m$ were reported as 0.2816 nm$^3$ for IBP[14] and 144.50 (without units!) for NAP.[15] Since phenobarbital appeared in both lists[14,15], the NAP value was converted by the same ratio as for this drug to 0.3226 nm$^3$, some 15% larger than that for IBP, in view also of the larger molar mass,[1] 230.26 (NAP) and 206.28 (IBP) g mol$^{-1}$. The molar volume of the (assumed liquid solute) is obtained from the molecular volume and the assumed packing fraction of molecules in liquids of 58%.[6] The radius required in eq. (6) is calculated as $r_S = (3\ v_m/4\pi)^{1/3}$. The approximations so incurred in the values of $V_S$ and $r_S$ have only slight (±5%) effects on the results of the IKBI calculation.

## 3. Results and Discussion

For the application of the IKBI method, the derivatives of the fitted 3rd degree polynomial of $\Delta_t G^{\infty}$(IBP or NAP, W→ W + PG) = f($x_{PG}$) were obtained. In view of the scarcity of the experimental points (Fig. 1) and their absence at $x_{PG} > 0.5$ except for $x_{PG} = 1$, the accuracy of these derivatives leave much to be wanted. No $G^E_{W,PG}$ data for 40 °C are available nor could be estimated, but for 25 °C the $\mu^E_W$ at 26.67 °C[7] could serve. In fact, the first derivative $d\mu^E_W/dx_{PG}$ can with advantage replace the second derivative $d^2G^E_{W,PG}/dx_{PG}^2$. The results of the application of the IKBI method with the solubility data at 25 °C are shown in Fig. 3.

For the application of the QLQC method, the solubility data at both 25 and 40 °C could be used. The $\Delta_t G^{\infty}$(IBP or NAP, W→W + PG) = f($x_{PG}$) values were fitted with values of $Z$ between 8 and 12 and were found not

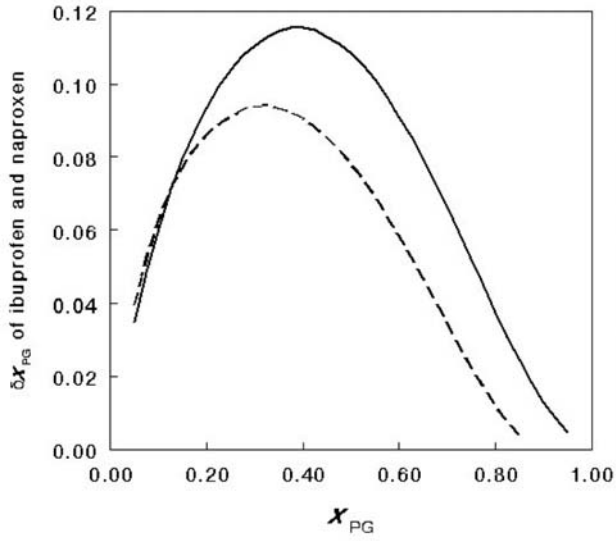


**Fig. 3.** The preferential solvation parameter, $\delta x_{PG} = f(x_{PG})$ obtained by the IKBI method: for IBP (—) and NAP (- - - -) at 25 °C.

to be very sensitive to them, so that $Z = 10$ was employed. The excess Gibbs energies of mixing W + PG at the equimolar composition and at various temperatures were interpolated from Fig. 2. The results of the application of the QLQC method are shown in Fig. 4. They are seen to be in general agreement with those from the IKBI method (Fig. 3), though not with regard to the detailed shapes of the curves: the IKBI values of $\delta x_{A,S} = f(x_{PG})$ peak at a somewhat lower PG content than the QLQC ones. This is to be expected in view of the lack of solubility data at $0.5 \leq x_{PG} < 1$ on the one hand (with regard to the IKBI method) and

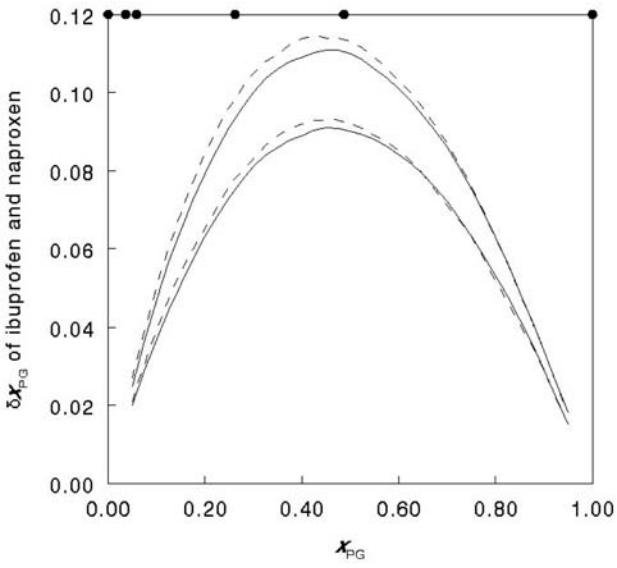


**Fig. 4.** The preferential solvation parameter, $\delta x_{PG} = f(x_{PG})$ obtained by the QLQC method: for IBP (upper curves) and NAP (lower curves), — for 25 °C and - - - - for 40 °C. The dots at the top denote the solvent mole fractions of the experimental data.

the use of only $\Delta_t G^{\infty}$(IBP or NAP, W→ PG) rather than the full curve (for the QLQC method).

Both methods indicate that PG is preferred over W in the surroundings of both drug molecules, of IBP more than of NAP, although the preference is not large, the maximal $\delta x_{A,S}$ being ≤0.12 and ≤0.09 respectively. The temperature dependence for both drugs (Fig. 4) is a small increase of the preferences with increasing temperatures. Ibuprofen (2-[4-(2-methylpropyl)phenyl]propanoic acid) has a hydrophilic head, the carboxylic group, and a hydrophobic tail. Naproxen ((+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid) has in addition to the hydrophilic head also a methoxy group in the, albeit more bulky, hydrophobic tail. Neat PG solvated both drugs many times better than W (at 30 °C, $\Delta_{solv}G°$/kJ mol$^{-1}$ are –38.03 in PG vs. –15.27 in W for IBP and –45.38 in PG vs 26.95 in W for NAP).[1] The neat solvents have a network of hydrogen bonds, more pronounced and stiff for water than for PG, so that the formation of a cavity in the solvents to accommodate the bulky solutes is an endoergic process, more in W than in PG. This is compensated by the exoergic solvation of the polar groups of the drug molecules. It stands to reason that the water component of the mixed solvent clusters around the carboxylic group, but not exclusively, because PG has two hydroxyl groups that can donate hydrogen bonds to and accept them from the carboxylic group. However, such hydrogen bond donation by PG can, in the case of NAP, also take place with the oxygen atom of the methoxy group, so that the preferential solvation by W should be smaller than for IBP. The hydrocarbon part of PG can interact by means of dispersion forces with the aromatic hydrophobic part of the drug molecules that W can do much less effectively (by dipole–polarizable aromatic ring interaction, mainly).

In the mixtures, the interactions between PG and W moderate the difference in the solvation abilities of the neat solvents. The negative $G^{E}_{W,PG}$ values at room temperature shows that the molecules of the solvent components interact more strongly with each other than with their own kind. This interaction loosens the tight hydrogen bond network of the water and facilitates the inclusion of the drug molecules, in addition to the direct solvation of the polar groups. The result is a preferential solvation of both drug molecules by PG at all compositions, but not as much as would have been suggested by the differences in the solvation abilities of the neat solvent components. The results are compatible with the thermodynamic analysis of the solubilities by Manrique et al.,[1] but provide additional information.

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## Povzetek

Delo obravnava preferenčno solvatacijo na osnovi podatkov o temperaturni odvisnosti topnosti ibuprofena (IBP) in naproksena (NAP) v mešanicah vode in 1,2-propandiola (PG) z uporabo inverznega Kirkwood-Buffovega integrala (IKBI) ter "quasi-lattice quasi-chemical" (QLQC) metode.