Supporting Information

Using Molecular Conformers in COSMO-RS to Predict Drug Solubility in Mixed Solvents

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Figures

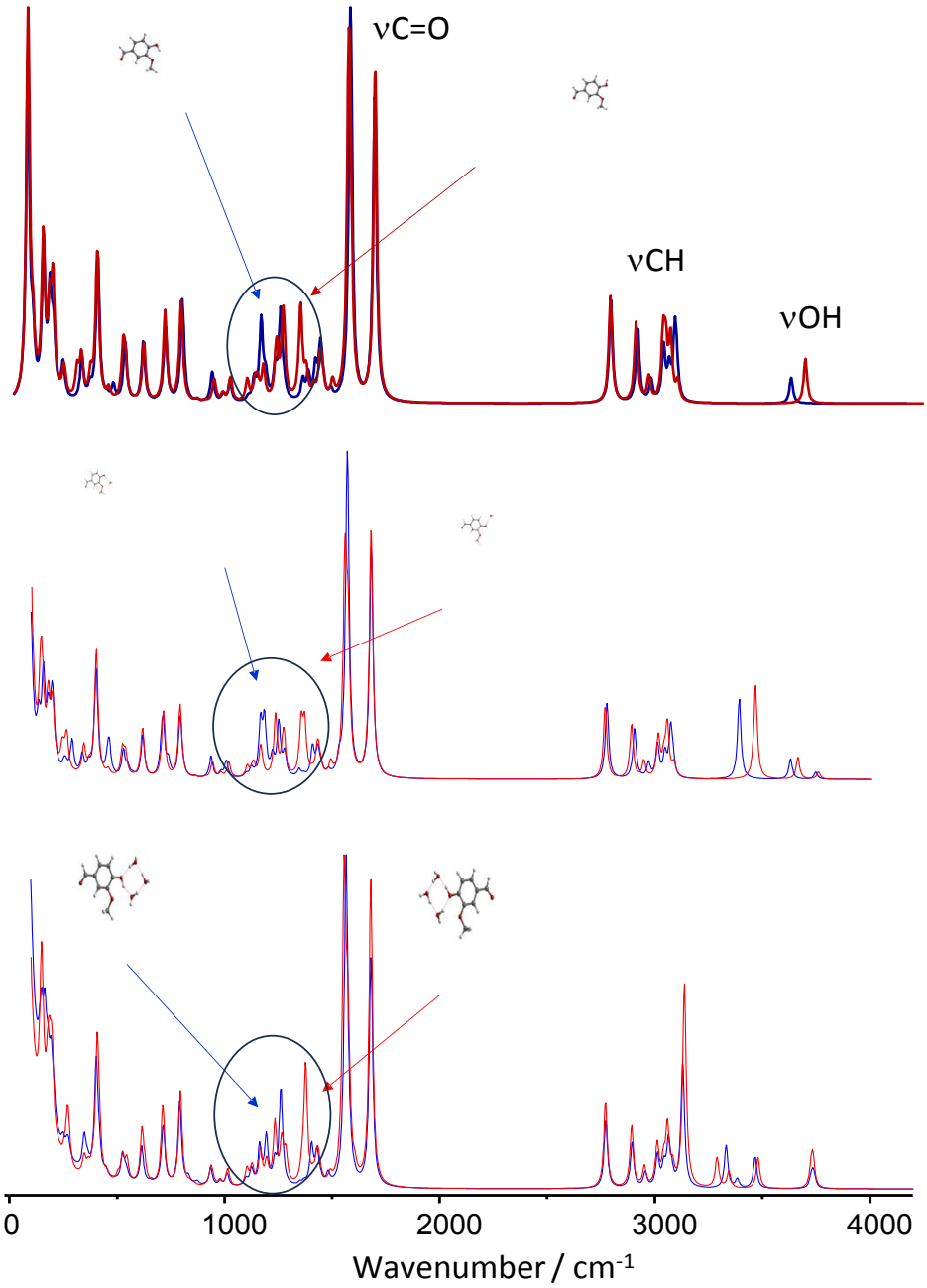

Figure S1. Comparison between calculated infrared spectra for vanillin protected (blue lines) and bare (red lines) conformers, as isolated molecules (top) and in cluster association with one water molecule (middle) and three water molecules (bottom). The ellipsoidal forms highlight the region where major differences are observed.

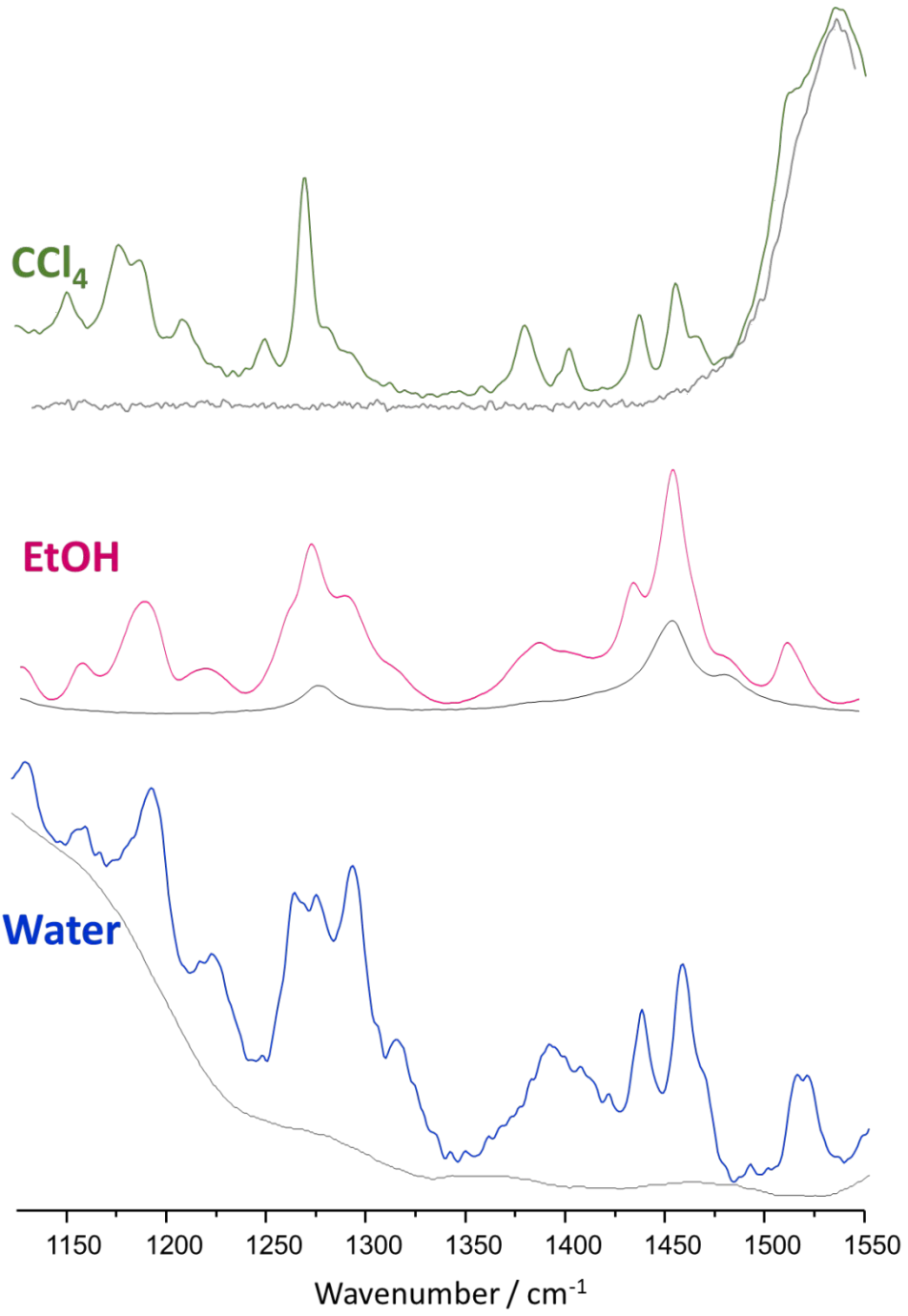

Figure S2. Raman spectra of vanillin solutions in carbon tetrachloride (green), ethanol (magenta), and water (blue), in the 1150-1550 cm-1 region, with the spectra of solvents in the same region

shown in grey. The corresponding difference spectra (solution minus solvent) are shown in Figure 4, main text.

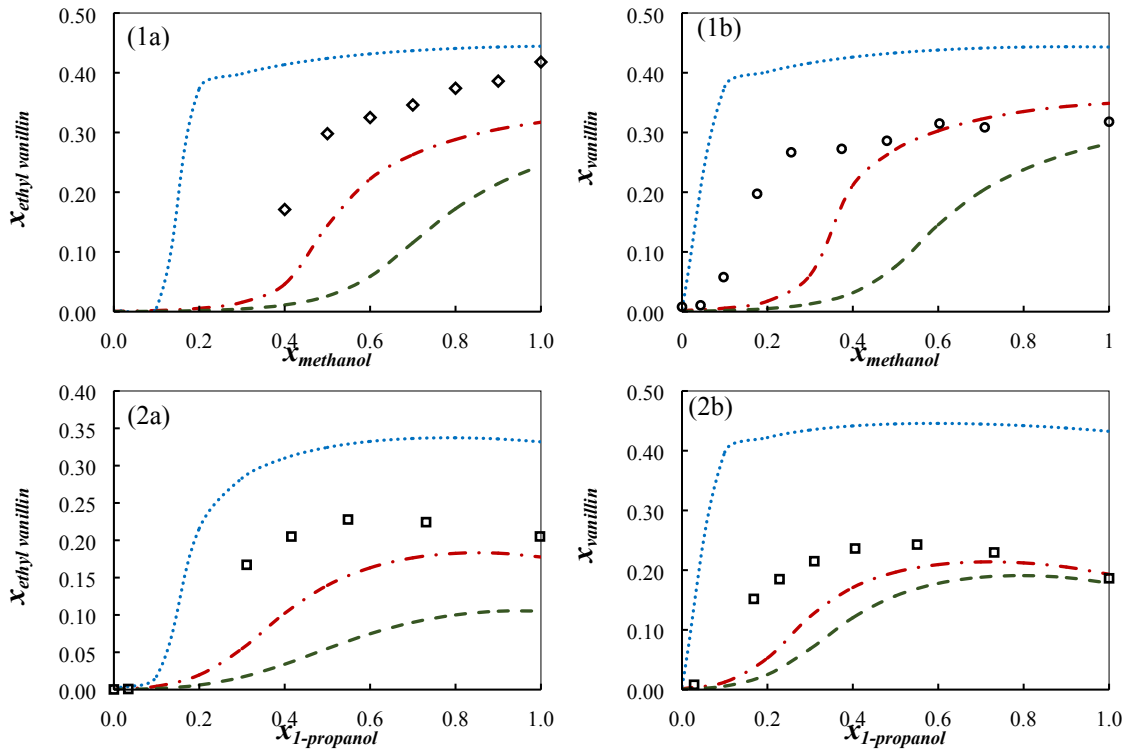

Figure S3. Predicted and experimental mole fraction solubility of EVA (a) and VA (b) in methanol + water (1) at 303.15 K and EVA (a) and VA (b) 1-propanol + water (2) mixtures at 303.15 K and 313.15 K, respectively. The COSMO-RS predictions were calculated using the default conformer set distribution (red dashed-dotted lines), "bare" conformer (blue dotted lines) and "protected" conformer (green dashed lines). Symbols represent experimental data taken from literature: □ [1], ◇ [2] and ○ [3].

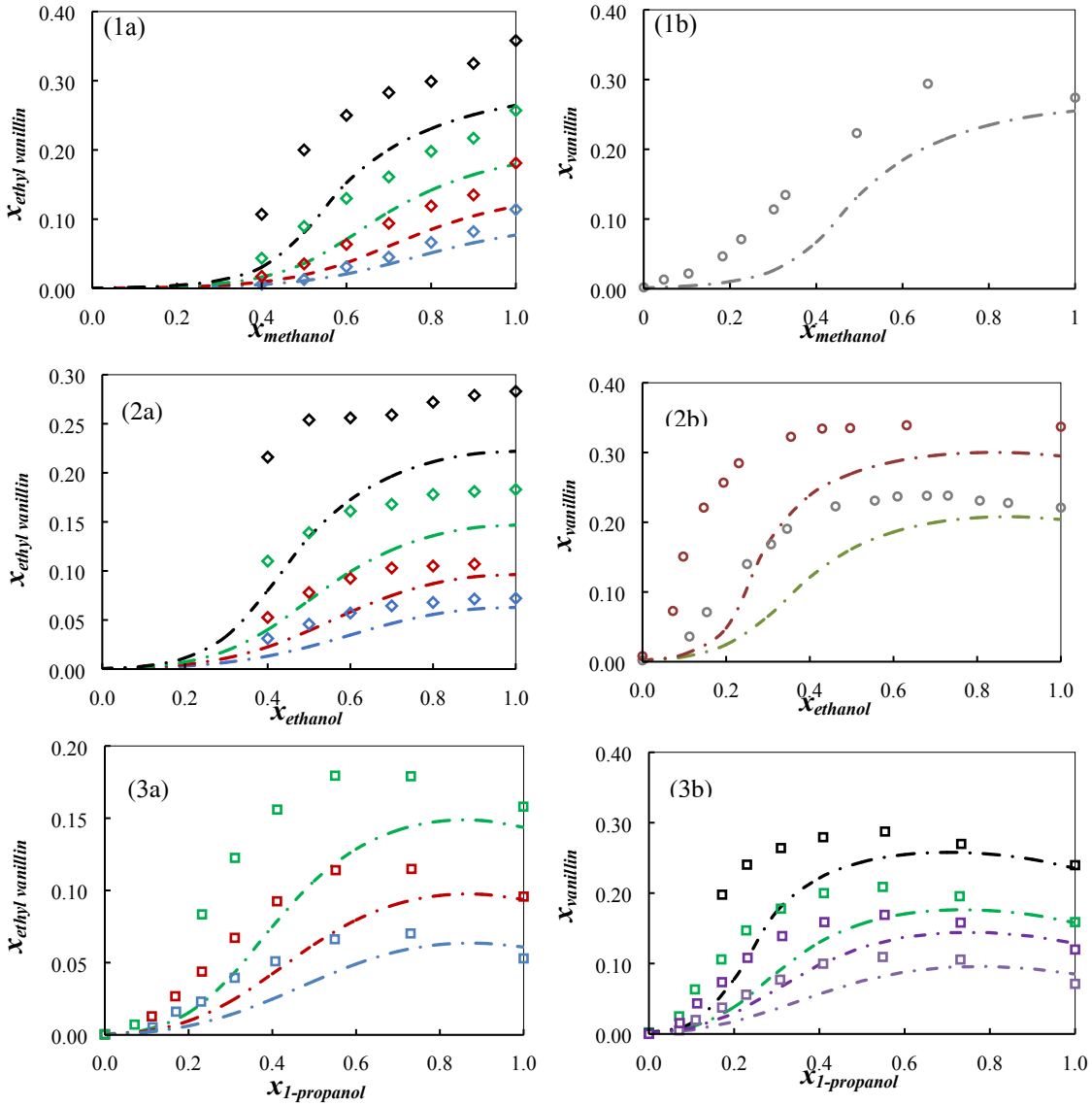

Figure S4. Predicted and experimental mole fraction solubility of EVA (a) and VA (b) in (1) methanol + water, ethanol + water (2) and 1-propanol + water (3) mixtures at different temperatures (dashed-dotted lines). Different colours represent different temperatures: □ 313.15 K ,□ 308.15 K, □ 303.15 K, □ 298.15 K, □ 288.15 K □ 283.15 K and □ 278.15 K. Symbols represent experimental data taken from literature: □ [1], ◇ [2] and ○ [3].

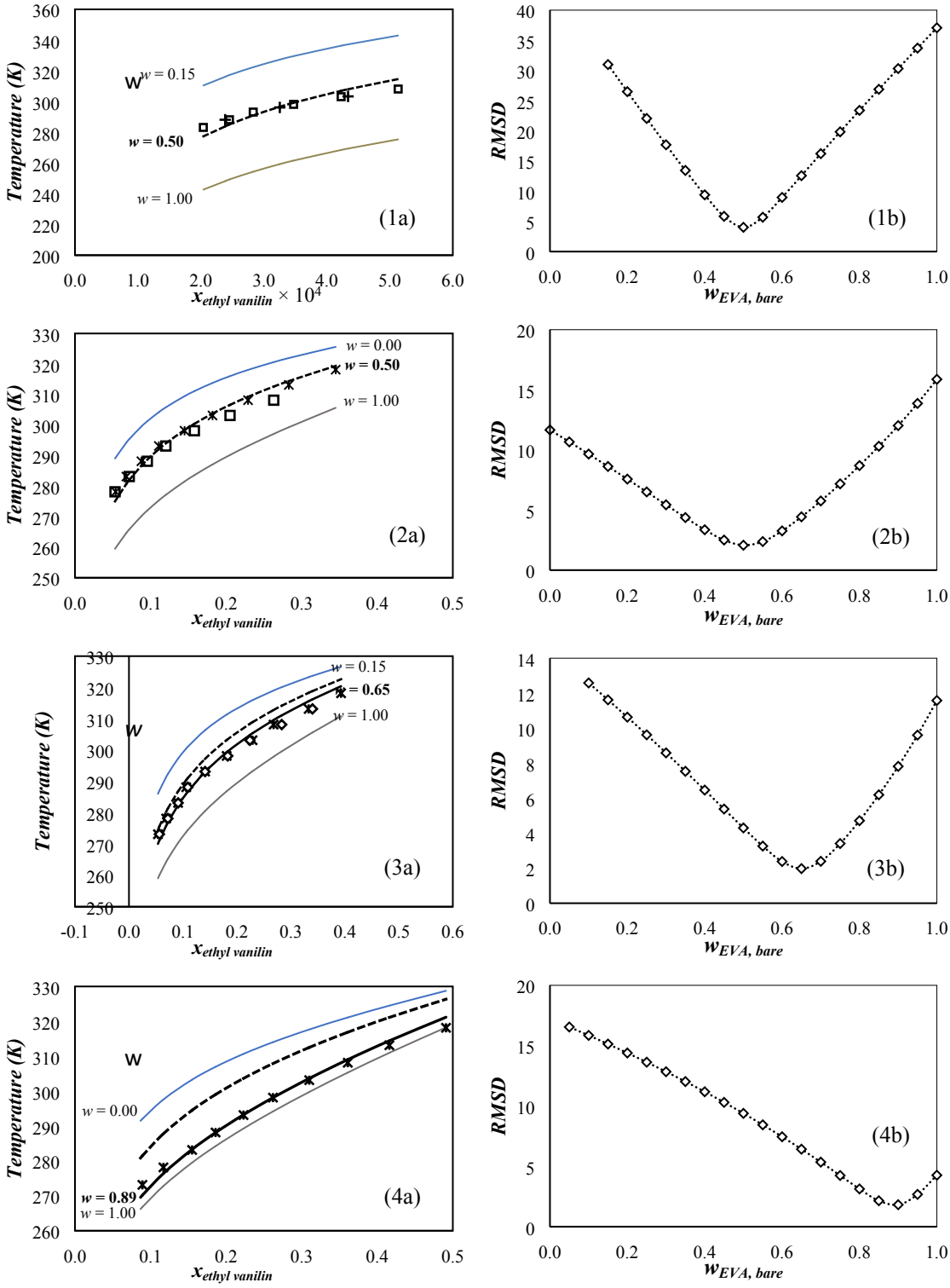

Figure S5. Fitting of the "bare" conformer prefactor (a) of ethyl vanillin at several temperatures and corresponding RMSD value (b) in water (1), 1-propanol (2), ethanol (3), methanol (4). The

dashed-dotted line corresponds to the predictions using default conformer set distribution (w_{bare} = 0.5) and the blue and grey solid lines represent the upper and lower limits of the tested conformer prefactor, respectively. Symbols represent experimental data taken from literature: □ [1], ✱ [4], + [5] and ◇ [2].

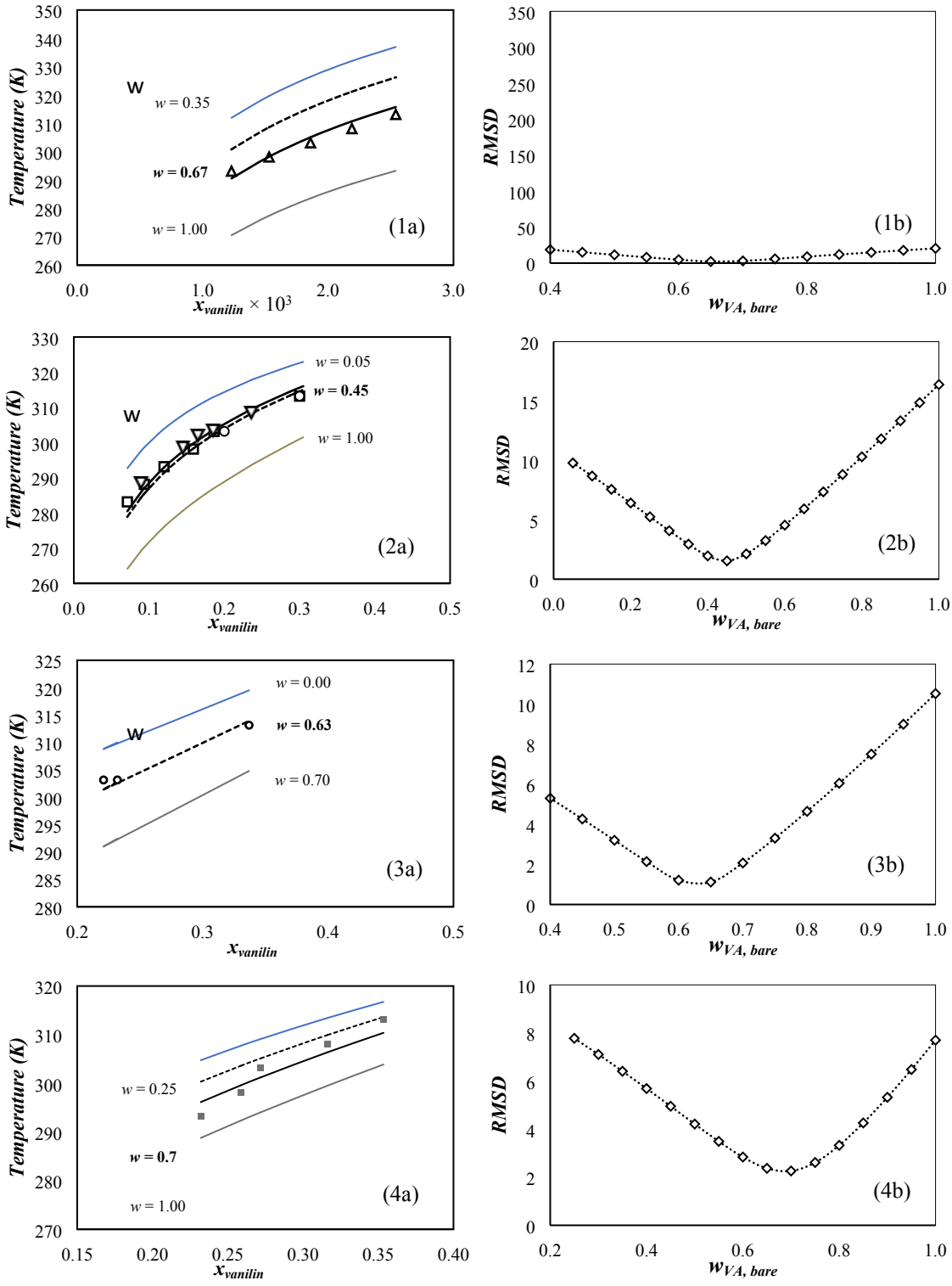

Figure S6. Fitting of the "bare" conformer prefactor (a) of vanillin at several temperatures and corresponding RMSD value (b) in water (1), 1-propanol (2), ethanol (3), methanol (4). The dashed-

dotted line corresponds to the predictions using default conformer set distribution (w_{bare} = 0.5) and the blue and grey solid lines represent the upper and lower limits of the tested conformer prefactor, respectively. Symbols represent experimental data taken from literature: △ [6], □ [1], ▽ [7], * [4], + [5] ◇ [2], ○ [3] and ▯ obtained in this work.

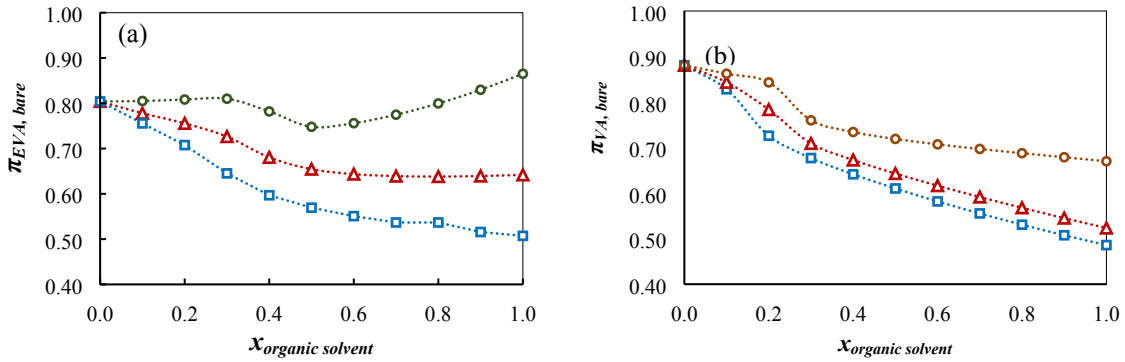

Figure S7. Distribution of the "bare" conformer of EVA (a) and VA (b) in organic solvent + water mixtures at 313.15 K using the adjusted conformer prefactor. Symbols represent different solvent systems: □ 1-propanol + water, Δ ethanol + water and ○ methanol + water.

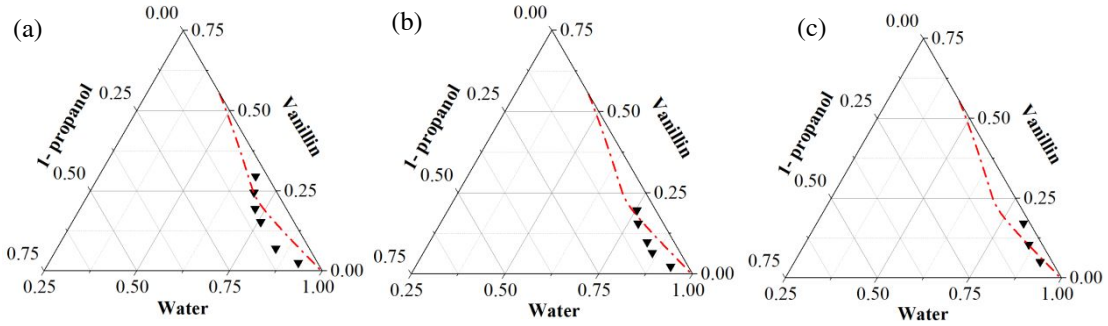

Figure S8. Predicted and experimental liquid-liquid equilibria of vanillin in 1-propanol + water mixtures at 303.15 K (a), 308.15 K (b) and 313.15 K (c) in molar fraction using COSMO-BP-TZVP template. The COSMO-RS predictions were calculated using the default conformer set distribution (dashed-dotted lines). Triangles represent experimental data taken from [7].

Tables

The solubility of vanillin was measured by the analytical isothermal shake-flask method, previously described in detail elsewhere [8]. Briefly, vanillin was added in excess in methanol to insure saturation of the solution. The samples were shaken under constant stirring (950 rpm) and temperature during 72 h, using an Eppendorf Thermomixer Comfort equipment.

After equilibrium was reached, two to three samples were collected from the supernatant solution, using pre-heated plastic syringes coupled to a poly-propylene filter (0.45 mm pore size). Then, the samples were diluted in a mixture of water and ethanol (50:50 by wt.%) and the vanillin was quantified by UV-spectroscopy using a SHIMADZU UV-1700, Pharma-Spec spectrometer at 281 nm. At least two individual samples were quantified for each system.

Table S1. Experimental solubility of vanillin in methanol at five temperatures measured in this work.

Temperature (K)	Solubility in molar fraction
293.15	0.23 ± 0.05
298.15	0.26 ± 0.04

303.15	0.27 ± 0.01
308.15	0.32 ± 0.01
313.15	0.35 ± 0.01

Table S2. Root mean squared relative error (RMSRE) of the solubility predictions of the ternary systems.[a]

Ternary system	Fitter weight prefactor	Default distribution
1-propanol + water + VA	0.41	0.57
ethanol + water + VA	0.45	0.55
methanol + water + VA	0.57	0.46
1-propanol + water + EVA	-	0.54
ethanol + water + EVA	0.30	0.38
methanol + water + EVA	0.41	0.38

[a] RMSRE is obtained by the normalized residual between the experimental and predicted solubility.

References

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