**First principles prediction of NRTL binary interaction parameters for furfural derivatives**

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**Abstract**

Biobased molecules constitute sustainable alternatives for fossil-based chemicals. However, to allow further valorisation, the complex product mixtures resulting from biomass processing typically require downstream separation. Although many (semi)empirical thermodynamic models, like NRTL, are available for separation process design, their application for biobased molecules is hampered due to the lack of the necessary data to determine the binary interaction parameters used in these models. Therefore, in this work a case study comprising a set of furfural derivates has been used to showcase a methodology to efficiently determine these parameters. Based on first principles, COSMO-RS is used to generate a dataset of thermodynamic activities, which is subsequently used to regress the NRTL model against. Comparison of NRTL-HOC simulated vapour-liquid equilibria (VLE’s) with experimental VLE’s showed excellent agreement, confirming that COSMO-RS can be used to extend the use of (semi)-empirical models towards applications involving biobased molecules of which limited experimental data is available.

**Thermodynamics and Molecular-Scale Phenomena**

**Keys words:** NRTL, COSMO-RS, vapour-liquid equilibria, furfural derivatives, bio-based components

# Introduction

The chemical industry transforms raw materials into a broad range of chemicals.1,2 Depending on their application, the required purity of these chemicals can strongly vary. For example, in case of building blocks for polymer production, lower purities are sufficient than when pharmaceutical or food applications are aimed at.3 Furthermore, the product streams exiting the chemical reactor are rarely pure components and usually multicomponent mixtures.4 As a result, subsequent purification or separation processes are often necessary. Most purification or separation processes are steered by thermodynamics, e.g., flash evaporation, distillation, liquid-liquid extraction and solid phase extraction. Hence, simulating and designing efficient separation trains requires detailed knowledge of the thermodynamic properties of all chemical species in the reactor effluent. Moreover, as chemical reactions are often impacted by thermodynamic non-idealities, having an adequate description of the thermodynamics of the reactants, intermediates and products is also critical for kinetic modelling of the involved reactions. Kinetic modelling in turn allows for reaction condition optimization or catalyst and/or reactor design.5–7

The thermodynamic non-ideality of mixtures can be described via several methods, i.e., activity coefficient models such as Wilson,8 NRTL (non-random two-liquid)9 or UNIQUAC (universal quasichemical),10 equations of states like Peng-Robinson11 or Hayden-O’Connell12 and group contribution methods such as UNIFAC (UNIQUAC functional-group activity coefficients)13 or GC-PC-SAFT (group-contribution perturbed-chain statistical associating fluid theory).14 Most of these methods are implemented in commercial software packages like Aspen Plus15 to allow straightforward process design. Activity coefficient models and equations of state make use of binary interactions between each pair of molecules within the considered mixture. This is a major disadvantage for these (semi)empirical models, as it implies that mixtures which have not yet been experimentally investigated cannot be described using these methods, as the binary interaction parameters are, typically, obtained via regression of these models against experimental data. Group contribution methods provide a solution for this, as they allow to predict the binary interactions based on the functional groups present in the different components, assuming group additivity. Thus, group contribution models can be used to simulate data without the explicit use of experimental data concerning the molecules of interest.16 However, these methods were originally developed for molecules and mixtures derived from the petrochemical industry. Thermodynamic properties of molecules that contain multiple functional groups and/or heteroatoms are, typically, not well described via the current group contribution methods, as potential neighbouring effects are rarely taken into account.17,18 However, biomass-derived components which are gaining in importance due to the transition from a fossil-based society towards a more sustainable one, belong to this class of highly functionalized molecules.19–21

Hence, to facilitate the transition to renewable feedstocks, it is crucial that the thermodynamic non-idealities of such biomass derivatives are elucidated and the thermodynamic models are fine-tuned accordingly. Some work has been published on the regression of different activity coefficient models, such as Wilson, NRTL or UNIQUAC, aiming at the prediction of, among others, vapour-liquid equilibria (VLE).22–24 However, the regressions are typically performed on a limited amount of experimental data, which are not representative for actual product pools obtained after conversion of the biomass. Moreover, since the estimated interaction parameters are specific for pairs of molecules, these regressed models cannot be extended towards mixtures which contain components that were not considered in the regressions. Similarly, Shang et al. regressed the Wilson, NRTL and UNIQUAC models as well as UNIFAC-DMD (Dortmund) model with experimental data and obtained new binary interaction parameters.25 However, although UNIFAC-DMD is a group contribution method, even these new parameters can only be used to describe a small number of mixtures of which the molecules contain the functional group they describe.

Although some progress has already been made, there is a lot of work yet to be done to capture the thermodynamics of biomass derivatives in these models. In fact, the main challenge in this research field is that it is very expensive and time consuming to experimentally collect all the data required to estimate every interaction parameter. It is, hence, practically unfeasible to model the thermodynamic non-idealities of bio-derivatives. In this regard, first principle-based methods, such as COSMO-RS (COnductor like Screening MOdel for Real Solvents),26 offer great potential. They allow the prediction of the chemical potential of components in a solution independent of experimental data and without having to assume group additivity. The general applicability of COSMO-RS has already been investigated.27-33 Spuhl and Arlt assessed the capability of COSMO-RS to predict VLE’s and activity coefficients for alkanes and various monofunctional components, including alkanes (e.g. n-pentane), alcohols (e.g. ethanol), alkenes and ethers (e.g. acetone). They found that, in comparison with experimental data, it performs well in predicting the activity coefficients of the considered components.27 Mambo-Lomba and Paricaud performed COSMO-RS and COSMO-SAC (Segment Activity Coefficient) calculations on mixtures of alkanes with hydrofluoroolefins or hydrochlorofluoroolefins. They proved that both methods’ predictions correspond well with experimental literature VLE data, thus perform well for various functional groups with different heteroatoms.28 Song et al. used COSMO-RS predictions to fill in the gaps present in a large experimental infinite dilution activity coefficients database of ionic liquid/solute mixtures, with solutes such as aromatics, alkanes and alcohols. They obtained 619 pairs of UNIFAC binary interaction parameters for ionic liquid solution systems via regression to the literature data, while filling in the gaps, i.e., 72 pairs missing interaction parameters, using COSMO-RS predictions.29 It is worth noting that COSMO-RS has also been used in many applications beyond the simulation of VLE data, among others, the prediction of polymerization kinetics,30-32 solvation Gibbs energies33 and excess enthalpies.34

In this work, instead of experimental data, COSMO-RS activity coefficient data are used to regress the NRTL binary interaction parameters. This is applied to a product pool of biobased components, of which the thermodynamics are little elucidated yet. As a case study a product-group of industrially relevant furfural (F) derivatives is analysed (Scheme 1).35,36 2-Methylfuran (MF), cyclopentanone (CP), furfuryl alcohol (FA), tetrahydrofurfuryl alcohol (THFA), 1,4-pentanediol (14PD), tetrahydrofuran (THF) and γ-valerolactone (GVL) can all be produced from furfural and additionally THF serves as a solvent as well.37–39 For each binary mixture the isobaric VLE was calculated in COSMO-RS both at atmospheric pressure and at 10.0 kPa. Furfural itself is one of the top value-added chemicals derived from biomass, more specifically hemicellulose.40 This component is used as an extractant for aromatics in the production of lubricating oils or as a solvent, but it is mainly considered to be a platform molecule, which can be converted in a broad range of biochemicals and biofuels. Furfuryl alcohol, as another example, is used in various applications ranging from the production of high quality cores and molds for metal casting, over wood protection to drug synthesis. Other important furfural derivatives are tetrahydrofurfuryl alcohol, which is used in printer inks, as an industrial cleaner or as paint-stripping agent, or 2-methylfuran, which is used as a solvent and for drug synthesis.17 The conversion of furfural gives rise to complex mixture comprised of several compounds from the product pool that is researched here (Scheme 1)35,36; since this mixture has to be separated to obtain the required product purities and because the binary interaction parameters of the involved components have not been reported before, this is a perfect mixture to assess the performance of the intended strategy.

In this work, NRTL-HOC has been selected as thermodynamic model to describe the phase equilibria, because NRTL9 performs well in predicting the thermodynamics of biomolecules.22-25 In this approach, the Hayden-O'Connell model (HOC) is used to describe the intermolecular interactions in the vapour phase.12 Some of the considered compounds are expected to exhibit relatively pronounced non-idealities in the liquid phase, however association and solvation are assumed to be negligible in the vapour phase. To verify this and to check their adequacy, the new NRTL-HOC predictions are validated with experimental vapour-liquid equilibria (VLE). Additionally, that check is used to confirm this methodology can be applied to this set of components*.* After validation, the obtained NRTL binary interaction parameters allow, among other things, straightforward separation train design for the considered components, using the NRTL-HOC model that is pre-implemented in many commercial software packages.

Scheme 1. Product-group of furfural (F) derivatives used in this work. All components can be obtained directly from F, the single arrows depict the conversion into other components within this product group. The double arrow from furfuryl alcohol to 1,4-pentanediol represents the multiple reaction steps required for this conversion.

# Procedures

## Generating activity coefficients using COSMO-RS

The activity coefficients of the components within binary mixtures at their boiling temperature were calculated with COSMO-RS26,41. First, molecular structures were optimized at the B3LYP/6-311+G(d,p) method and basis set using the Gaussian 16 C.01 package. All conformations were confirmed to have zero imaginary frequencies at the same level of theory. COSMO-RS theory was applied based on the single-point BP86/def2TZVP electronic structure to generate the σ-profiles for each structure (see S.I. section 1 for the σ-surfaces). Notably, in COSMO-RS all low-energy molecular geometries should be taken into account, since different conformers can exhibit different properties. Additionally, the conformer that maximizes attractive interactions in a binary solution, and hence minimizes the solution Gibbs energy, is often dependent on the composition of the solution. Therefore, only taking into account a limited set of conformers can result in unreliable results. Hence, for every component all possible conformers were included in the calculations, letting COSMO-RS account for multiple conformers. The contribution of different conformers is particularly notable for 1,4-pentanediol, which has two conformers that exhibit different properties due to difference in their polarity and availability of the hydroxy-groups (see S.I. Figure S6 for the σ-surfaces).

Based on the σ-profiles, using the COSMOthermX41 software package 19.0.4 the activity coefficients and corresponding boiling temperatures and dewpoints were generated as function of the mole fraction for the different binary mixtures considered. Experimental pure boiling temperatures were provided to COSMOThermX, as it is particularly proficient in predicting the relative interactions between components, however, lacks precision in predicting the absolute boiling temperatures for the pure components. Note that COSMO-RS is able to determine the boiling temperature of the binary mixture from the boiling temperature of the pure components (see section ‘Vapour pressure and VLE experiments’, and S.I. section 2). It should be noted that the boiling temperature at atmospheric pressure of some mixtures exceeds the limitations of the VLE apparatus used to obtain experimental data for model validation purposes (see section ‘Vapour pressure and VLE experiments’, and S.I. section 2). To also allow validation of these mixtures, the COSMO-RS calculations are performed both at atmospheric pressure and 10.0 kPa.

## Predicting the radii of gyration based upon first principle calculations

To calculate VLE’s, the fugacities of the components in the vapour phase need to be determined, see section ‘VLE simulations’. In order to calculate these, the radii of gyration of the components need to be known, which were determined as follows. First, using Gaussian 16, the principal moments of inertia were obtained based on the minimum-energy conformation. Subsequently, the radii of gyration were calculated according to equation 1.12 The results are listed in the supporting information section 2 table S1.

 (1)

## Parameter estimations

### NRTL binary interaction parameters

The binary interaction parameters were estimated via regression of the NRTL model against the activity coefficients generated by COSMO-RS, for a specific temperature, pressure and mole fraction. Hereto, the sum of squared residuals between the targeted activity coefficients and those calculated by the model was minimized using Athena Visual Studio.7,43

The NRTL equation is based on the two-liquid model of Scott and assumes a non-randomness in liquid mixtures, similar to the assumption used by Wilson to describe the distribution of components at the local molecular level.7–9 In a multicomponent mixture the activity coefficient of a component is calculated using equations 2 to 4. Multiplying the activity coefficient γi with the mole fraction of component *i* in the binary mixture, gives the thermodynamic activity ai of that component, which is, among other things, used to simulate VLE’s.

 (2)

 (3)

 (4)

The parameters aij and bij describe the binary interactions in the liquid and αij  is introduced to describe the non-randomness. As the effect of the non-randomness on the shape of the excess Gibbs energy curve is not very pronounced, it is usually not straightforward to estimate αij from experimental vapour-liquid data or even from COSMO-RS vapour-liquid data. Therefore, the value of this parameter has been fixed to 0.3 as recommended by Renon and Prausnitz, and only aij and bij are obtained from the regression.7,9 The regression was evaluated via the F-test for the 95% global significance of the regression, the 95% confidence interval for the statistical significance of the parameter estimates. Moreover, the binary correlation coefficients between the estimated parameters were calculated and evaluated.7

### Antoine constants

To be able to simulate vapour-liquid equilibria, the vapour pressures of the pure components as a function of temperature need to be known. Hereto the Antoine equation is typically applied. This equation, i.e., equation 5, derived from the Clausius-Clapeyron relation, describes the relation between the vapour pressure and the temperature of pure components.43 This equation was regressed against experimental vapour pressures which were obtained according to the procedure of these experiments as described in section ‘Vapour pressure and VLE experiments’. Similar to the procedure described in section ‘NRTL binary interaction parameters’, these regressions were performed using Athena Visual Studio7 and evaluated on a statistical basis. In order to balance the weight of every datapoint, these regressions were performed using the logarithms of the pressures as the model response. In this work, the Antoine constants are obtained for p in kPa and T in Kelvin.

 (5)

## Experimental vapour pressure and VLE measurements

### Chemicals

Furfural, furfuryl alcohol, 2-methylfuran, cyclopentanone and γ-valerolactone were supplied by Merck Life Science. Chemlab Analytical supplied tetrahydrofuran, Fischer scientific provided tetrahydrofurfuryl alcohol, and 1,4-pentandiol was supplied by Abcr. All chemicals had a purity of at least 99 mass%. However, furfural was found to be susceptible to slight oligomerization during storage, which affects its vapour pressure and binary vapour-liquid equilibria. Therefore, this component was distilled at 1.0 kPa before use.All other chemicals were used without further purification. The critical pressures and temperatures, radii of gyration, boiling temperatures at atmospheric pressure, densities, dipole moments and acentric factor for all chemicals are given the supporting information Table S1.

Figure 1. Schematic representation of the VLE apparatus : 1) Heating chamber with heater, 2) Cotrell pump, 3) thermocouple, 4) condensed vapour phase sampling port, 5) liquid phase sampling port, 6) mixing chamber, 7) condenser.

### Vapour pressure and VLE experiments

Both the vapour pressures of the pure components as well as the vapour-liquid equilibria of the binary mixtures were measured using the Pilodist VLE 110 (Figure 1). In these experiments, 90 cm³ of the considered pure component or binary mixture is added into the apparatus. Subsequently, the apparatus is closed and brought to the desired pressure, either by means of nitrogen gas or a vacuum pump. In the heating chamber (1), the liquid is heated to its boiling point and the heated liquid and the vapour starts to rise through the Cotrell pump (2). The boiling temperature is measured using a thermocouple (3) located at the top of the heating chamber. The vapour rises further and is condensed (7) to be recirculated to the mixing chamber (6), whereas the liquid is immediately recirculated to the mixing chamber. This process continues throughout the experiment.

In order to measure the vapour pressure of a pure component as a function of temperature, this specific pure component is added into the Pilodist VLE 110 and the liquid is heated to its boiling temperature at the considered pressure. During these experiments, the condensed vapour and liquid recirculate continuously. At first, the pressure and temperature fluctuates a little bit. Once they are stabilized, the pressure and temperature are noted and the pressure is changed to a new setpoint, continuing this process gradually increasing the pressure. This was done in several steps, not exceeding the working range of the apparatus: between 0.25 – 300.0 kPa and up to 523.15 K.

The VLE experiments for binary mixtures were started using a binary mixture containing a high mole fraction of the lowest boiling component. After measuring a tie line, the mole fraction of the highest boiling component is gradually increased allowing to measure a next tie line. As with the vapour pressure experiments, the liquid and condensed vapour are continuously recirculated during such an experiment. Each time the liquid and vapour passes through the Cotrell pump (2), they are intensively mixed. After 30 minutes of recirculation at a constant temperature, the system stabilizes and the vapour-liquid equilibrium is reached. Both the condensed vapour and the liquid phase were sampled from the respective ports (4) and (5). After sampling, the removed liquid volume was replaced by adding an equal amount of the highest boiling component in order to gradually change the composition of the mixture and to be able to investigate the entire composition range.

### Sample analysis

The compositions of the samples collected during the VLE measurements were determined via density measurements or gas chromatography (GC). When the difference in density between the two components was sufficiently large (>100 kg/m³), the samples were analysed with an Anton Paar DMA 4500 density meter*.* For the gas chromatography analysis a Shimadzu GC2010-pro with a flame ionization detector (FID) was employed. Nitrogen was used as the carrier gas, the stationary phase was a SH-Stabilwax column (30 m x 0.32 mm x 0.50 μm). The following temperature program was used: first the temperature is held constant for 1 minute at 313.15 K. Then the temperature is gradually increased at a rate for which a clear separation between peaks takes place. Finally, the temperature is increased to 403.15 K and maintained there for 1 minute, to ensure no contamination would remain on the column.

### Thermodynamic consistency assessment

The Redlich-Kister test (area test)45 and the Fredenslund test (point test)46 were performed to assess the thermodynamic consistency of the experimental VLE data. The Redlich-Kister test is based on the general Gibbs-Duhem equation, i.e., equation 6. At a constant pressure and constant temperature, this equation simplifies to equation 7. Hence, for thermodynamically consistent data obtained under such conditions, plotting ln(γ1/γ2) against x1 should result in areas above and below the x-axis which are equal to each other. However, considering small experimental errors and inaccuracies during the determination of the areas, the two areas are considered equal when their difference is less than or equal to 2% of the total area, see equation 8.

 (6)

 (7)

 (8)

However, for isobaric non-isotherm datasets, i.e., constant pressure but varying temperature, the heat effect caused by the mixing process cannot be neglected and equation 6 simplifies to equation 9. Unfortunately, determining the heat effect is very hard as the heat of mixing at various temperatures and compositions is unavailable for most binary mixtures. Moreover, it is almost impossible to measure at the bubble point of a set of mixtures having different compositions.47 Furthermore, numerically the right-hand side of equation 9 is typically of the same order of magnitude as the admissible limit value of D. Hence, except for rare cases when very strong thermal effects are at play, it is very likely that a dataset is thermodynamically inconsistent when the numerical value of D is greater than 10. Therefore, the allowed limit value of equation 8 is raised from 2 to 10% for isobaric datasets, see equation 10.47 In practice, a polynomial (equation 11) is fitted against the experimental data, after which the value of D is determined through integration of this function.45

 (9)

 (10)

 (11)

The second test, i.e., the Fredenslund test, makes use of the fact that experimental VLE-data are over-dimensioned.According to the phase rule of Gibbs48, there are only 2 independent variables for a binary system at equilibrium, while experimentally the composition of both the vapour and liquid phases as well as the temperature are measured at a constant pressure. Hence, in principle the vapour phase composition can be predicted from the values obtained for the other variables using equation 12. The fugacity of component *i* at the standard state, , and the fugacity coefficient in the vapour phase, , appearing in equation 12, are both calculated using the HOC equation of state (equation 13),49 while assuming that association and solvation are negligible in the vapour phase. In other words, the HOC binary interaction parameters are set equal to 0. Finally, according to the Fredenslund test, a dataset is declared thermodynamically consistent if the absolute average deviation between the calculated, yi,cal, and the experimentally observed vapour fractions, yi,exp, is smaller than or equal to 0.01, see equation 14.47

 (12)

 (13)

 (14)

## Vapour-liquid equilibria simulations and model validation

### VLE simulations

When at a given temperature and pressure, thermodynamic equilibrium is reached, the chemical potential of each component in the vapour phase is equal to its chemical potential in the liquid phase. If the same standard state is used to describe the chemical potentials in both phases and no peculiar phenomena occur, e.g. additional work done on one of the phases, this condition simplifies to the equality of fugacities, see equation 15.7,50 The fugacity of a component in a gas phase can be calculated from its partial pressure, , and a fugacity coefficient,, while that of a liquid phase component can be found by multiplying its activity, , with a standard state fugacity,, see equation 16. Applying Dalton’s law, a components partial pressure is calculated from its mole fraction in the gas phase, , and the total pressure, . The liquid phase activity of the component is obtained from its activity coefficient, , determined using NRTL (see section ‘NRTL binary interaction parameters’) and its mole fraction in the liquid phase, . The standard state fugacity relates the liquid phase standard state to the gas phase standard state. It is calculated from the saturation pressure of the component, , the fugacity coefficient of the gaseous pure component at its saturation pressure, , and the Poynting factor accounting for the pressure dependence of the liquid activity. As a result, equation 15 can be rewritten as equation 17.

 (15)

 (16)

 (17)

Since the vapour pressures are acquired with the Antoine equation (see section ‘Antoine constants’), all data except the fugacity coefficients are available to calculate the mole fractions (equation 17). The fugacity coefficient are obtained using the HOC equation of state (equation 13),12 assuming that in the vapour phase of the considered mixtures, association and solvation are negligible. The HOC-calculations require the critical pressure and temperature, dipole moment and acentric factor of the pure components, which are listed in Table S1 of the supporting information. The obtained fugacity coefficients range from 0.9 to 1.0, which confirms no strong deviations from the ideal gas law. Finally, the vapour liquid equilibria of the binary mixtures are calculated using equation 17. In practice, an iterative search is performed to determine for every liquid phase mole fraction, a corresponding temperature and vapour phase mole fraction.

### Validation of the VLE simulations with experimental data

The agreement of the VLE’s simulated using NRTL-HOC with the experimentally observed ones is assessed by means of their mean percentage deviation (MPD) of the temperature for given mole fractions of the liquid and vapour phase (equation 18) and of the liquid and vapour phase mole fractions for a given temperature (equation 19). In order to take into account potential errors on both the liquid as well as the vapour phase, the temperature deviation for both phases is considered in the calculation of MPD(T). Similarly, the deviation of both mole fractions in function of the temperature is accounted for in MPD(x,y). The model simulations are considered to be in good agreement with the experimental data when the MPD is less than or equal to 5%.

 (18)

 (19)

In equation 18, Tx,i and Ty,i represent the corresponding boiling and dew temperatures for a given liquid and vapour mole fraction, respectively. ΔTExtr is the difference between the maximum and minimum temperatures measured during the experiments, thus corresponding to the pure component boiling points, except for azeotropic mixtures. Analogously, in equation 19, Δx,yExtr are the maximum and minimum mole fractions determined in the experiment. Since the mole fractions are always varied from 0 to 1, Δx,y is always equal to 1 in this work.

# Results and discussion

First, the activity coefficient dataset generated using COSMO-RS and the estimation of the binary interaction parameters of the NRTL model via regression against the generated data is discussed. Additionally, the Antoine equation is regressed against experimental pure component vapour pressure data. Subsequently, the estimated NRTL-parameters and the Antoine constants are used to simulate the vapour liquid equilibria using the NRTL-HOC model. Finally, these model simulations are validated by comparing them to a selection of experimental VLE’s, which are first assessed for their thermodynamic consistency.

## Assessment of the thermodynamic activities generated by COSMO-RS

Based on first principles, using COSMO-RS (see S.I. section 1 for the σ-surfaces), an activity coefficient dataset was generated, regarding all possible binary mixtures that can be formed from the product pool depicted in Scheme 1. The activity coefficients, corresponding liquid phase mole fraction and boiling temperatures at 10.0 and 101.3 kPa are listed in S.I. section 3, tables S2-S29. The activities for four representative binary mixtures are shown in Figure 2. All activity plots are depicted in the supporting information section 4.

Most activity coefficients are close to 1, as a result most thermodynamic activities follow clear linear trends with the mole fractions, with only minor deviations from the bisector and the perpendicular bisector, an example of which is given in Figure 2.a. For the majority of the binary mixtures only minor deviations from Raoult’s law are observed.51

However, there are a few binary mixtures within the dataset, which exhibit more pronounced deviations from Raoult’s law. Here, interactions between different molecules are called unlike interactions, whereas like-like is used to appoint interactions between same components. The THF/MF mixture shows a small negative deviation from Raoult’s law (Figure 2.b), indicating stronger unlike interactions and the components are less volatile than in a thermodynamically ideal mixture.51 Compared to the other components in the investigated product pool, THF and MF are smallest and least polar. However, THF has a high electron density around the oxygen atom and since MF has a less strong negatively charged ring and a slightly positively charged methyl group, it is likely that the two components interact stronger with each other than with themselves, resulting in a negative deviation.

However, in this product pool mostly positive deviations from Raoult’s law were observed, indicating that like-like interactions are stronger and the components are more volatile than in a thermodynamically ideal mixture. In the case of the 14PD/F, CP/THF, F/MF (Figure 2.c), F/THF, F/THFA, GVL/THF and THFA/MF mixtures, small positive deviations from Raoult’s law are observed. These deviations from ideality can be explained by the polarity of the involved components. In all of these binary mixtures, one component is more polar than the other one, thus like-like interactions are preferred. A clear example is the F/MF mixture, although structurally very similar F is more polar due to the aldehyde group. Therefore, like-like interactions are stronger in this mixture. Similarly, CP/THF, F/THF and GVL/THF show positive deviations from Raoult’s law, due to the difference in polarity of the two components. Another reason positive deviations are observed, is the possibility for one component to form hydrogen bridges with itself, having both hydrogen bond donor and acceptor atoms. In some cases this only accounts for small deviations from Raoult’s law, since the second component in the mixture has a hydrogen bridge acceptor atom, allowing for hydrogen bridge formation as well. Notably, this is only observed for the 14PD/F and F/THFA mixtures. The F/FA mixture could be expected to have similar behaviour, but the molecular structures of F and FA differ very little, enhancing unlike interactions. The mixtures of THFA/MF, 14PD/MF (Figure 2.d) and FA/MF show positive deviations from Raoult’s law as well, since THFA, 14PD and FA are prone to hydrogen bridge formation. However, since the oxygen of MF is shielded by the ring and the methyl group, it is less accessible for hydrogen bonding. Hence, like-like interaction is preferred over unlike interaction in these mixtures. The deviation is less pronounced in the THFA/MF mixture than in the 14PD/MF and FA/MF mixtures, since the hydrogen bond donor and acceptor groups of 14PD and FA are more accessible than in THFA. In case of the 14PD/MF mixture, this deviation is most pronounced, due to the presence of a linear conformer of 14PD. In the COSMO-RS calculations, 14PD is present as a linear conformer, which can form 2 hydrogen bonds with other compounds, and a ‘cyclic’ conformer forming an intramolecular hydrogen bond between the hydroxyl groups, which allows for only 1 hydrogen that can form hydrogen bonds with other compounds. If only the ‘cyclic’ conformer would be present, only small deviations would be observed due to the lower polarity. However, the linear form of 14PD is highly polar due to the two hydrogen bonds it can form, which results in high activities at low concentrations of 14PD, explaining the strong positive deviation from Raoult’s law.

## Determination of new NRTL binary interaction parameter values via regression against the COSMO-RS activity coefficients

To obtain the binary interaction parameters, aij,ji and bij,ji, NRTL was regressed against the COSMO-RS activity coefficient data (see section ‘Assessment of the thermodynamic activities generated by COSMO-RS’). Typically, the binary interaction parameter aij has a value between -5 and +5 and the binary interaction parameter bij is mostly in between -3000 and +3000, αij was fixed at a value of 0.3.22,25,52 This applies to all parameters obtained here as well. The obtained NRTL-parameters, with their 95% confidence intervals, are listed in Table 1. The obtained F values for the global significance of the regression all exceed the tabulated value by at least 3 orders of magnitude, both models are thus considered statistically significant. The good fit between the models is reflected in the activity plots (Figure 2, S.I. section 4) as well. It can be concluded that the regressed binary interaction parameters provide a good correspondence between the NRTL and the COSMO-RS simulations and can be considered statistically significant, given their 95% confidence intervals.

Figure 2. Thermodynamic activities at the boiling point of the binary mixture for (a) cyclopentanone (yellow)/tetrahydrofuran (orange) at 101.3 kPa, (b) tetrahydrofuran (orange)/ 2-methylfuran (red) at 101.3 kPa showing a small negative deviation from Raoult’s law, (c) furfural (light green))/2-methylfuran (red) at 101.3 kPa, showing a small positive deviation from Raoult’s law and (d) 1,4-pentanediol (pink)/2-methylfuran(red) at 101.3 kPa, showing a strong positive deviation from Raoult’s law calculated using COSMO-RS (full lines) and the NRTL model, which was regressed against the COSMO-RS dataset (dotted lines). The full grey line are the bisector and perpendicular bisector as reference for ideal behaviour according to Raoult’s law.

## Pure vapour pressures and Antoine constants

For all components, the pure vapour pressure as function of the temperature was experimentally mapped. The full experimental data are listed in section 5 of the supporting information and visualized in Figure 3. Afterwards, the Antoine equation (equation 5) was regressed against this experimental data and the estimated values of the parameters associated with this equation, i.e., the Antoine parameters, with their 95% confidence intervals are listed in Table *2*. In all cases, the obtained parameters provide a satisfying agreement between the Antoine equation and the experimental results. The obtained F values for the 95% global significance of the regression all exceed the tabulated value by at least 3 orders of magnitude, the model is hence considered statistically significant.

MF (S.I. section 1 figure S3) and THF (S.I. section 1 figure S7) have the highest vapour pressure, whereas the vapour pressure of F (S.I. section 1 figure S1) and THFA (S.I. section 1 figure S4) are lower. 14PD (S.I. section 1 figure S6) has an even lower vapour pressure. This aligns with the expected trend that the most polar components have a lower vapour pressure, especially when hydrogen bond formation is possible.

Figure 3. Experimental vapour pressures (dotted lines) and the Antoine curves (full lines) of 2-methylfuran (red), tetrahydrofuran (orange), cyclopentanone (yellow), furfural (light green), furfuryl alcohol (dark green), tetrahydrofurfuryl alcohol (turquoise), GVL (blue) and 1,4-pentanediol (pink).

Table 1. Binary interaction parameters of the NRTL model with their 95% confidence interval, obtained via regression of the NRTL model against the activity coefficient dataset as generated using COSMO-RS; the first component is represented by i, while the second one is represented by j. The listed F values of 95% global significance have to be compared to the table value of 3.8.

Table 2. Antoine constants with their 95% confidence intervals, regressed against experimental vapour pressures (S.I. section 5). The units in the Antoine equation are kPa for the pressures and K for the temperatures, see equation 5. Depending on the number of experimental measurements, the table value to which the listed F values of 95% global significance have to be compared, varied between 3.96 and 4.00.

Table 3. Mean percentage deviations (MPD) for T and x,y, between the simulated and the experimental VLE’s.

## VLE simulations using NRTL-HOC

Given the Antoine constants and newly obtained binary interaction parameters, all input is at hand to simulate the VLE’s. Thereto NRTL-HOC is applied, assuming that association and solvation in the vapour phase are negligible. The generally observed trends are as expected, couples of aromatic, polar components interact stronger, thus have smaller tie lines, than couples of components with dissimilar structures. All VLE plots are depicted in the Supporting Information section 6, while the ones of the mixtures that were studied experimentally as well are also depicted in Figure 4.

In section ‘Assessment if the thermodynamic activities generated by COSMO-RS’, the thermodynamic activities of the components within the binary mixtures are described. As expected, the non-idealities observed there are also reflected in the VLE’s. For instance, when no or similar deviations from Raoult’s law are observed, THF and MF behave similar in interaction with other components in this product group due to their similar boiling points. This is the case for the F/MF and F/THF mixtures (Figure 4 a and b), the VLE’s have very similar sized tie-tines. However, in combination with FA, MF shows a positive deviation of Raoult’s law, whereas THF behaves almost ideally. The FA/MF mixture shows broader tie lines than the FA/THF mixture (S.I. section 6 figures S11 panels k and l and S12 panels k and l). Similarly, in combination with THFA, MF and THF behave differently, THF shows no significant deviation while MF shows small positive deviations from Raoult’s law. Comparing these VLE’s it is clear that the tie lines of the THFA/MF mixture are indeed broader than the tie lines of the THFA/THF mixture (S.I. section 6. figures S11 panels z and α and S12 panels z and α). Last, 14PD interacts differently with MF and THF as well. As a result of the positive deviation from Raoult’s law, the VLE’s of the 14PD/MF mixture show broader tie lines than the 14PD/THF mixture (S.I. section 6. figures S11 panels e and f and S12 panels e and f), which does not deviate significantly from Raoult’s law, as is reflected in the activities.

Although no strong deviations from Raoult’s law were observed in the activities of the THF/MF mixtures, their VLE’s show a significant deviation from ideality. They form a negative azeotrope (S.I. section 6. figures S11. β and S12. β), which is sign of a negative deviation. Likely, because their boiling points are that similar, even small deviations that do not strongly affect the activities, are visible in the VLE’s.

## Model validation

To validate the NRTL-HOC VLE simulations, the results are compared to experimental data. Since it is very costly and time consuming and, in some cases even not practically feasible, to perform VLE measurements of the binary mixtures, the experimental study was limited to 10 mixtures. These mixtures are considered to be sufficiently representative for the entire set of mixtures considered in this work. Based on the characteristics of the components the following mixtures were selected: F/MF, F/THF, F/THFA, F/FA, MF/1,4-PD, FA/GVL, FA/CP, CP/THF, GVL/THFA and GVL/MF. The mixtures of F/FA, F/THFA and FA/GVL were analysed at 10.0 kPa, since for these mixtures experiments at atmospheric pressure would cause issues related to the reactivity of these components at the high temperatures that would have to be applied. All other VLE experiments were carried out at atmospheric pressure.

### Thermodynamic consistency of the experimental data

Since small experimental errors are inevitable, each experimental dataset was subjected to both the Redlich-Kister and the Fredenslund test to assess their thermodynamic consistency and to ensure the data is sufficiently reliable.

The D-values for the Redlich-Kister test and the average absolute deviation for the Fredenslund test are listed in table S48 of the Supporting Information. Since all D-values were lower than 10, all datasets passed the Redlich-Kister test (equation 10). For the mixtures that were measured at 10.0 kPa, the test results are much lower than for the other mixtures. This is because at lower pressures, lower boiling temperatures are obtained, thus the molecules show exhibit less experimental difficulties or deviations.

All experimental datasets passed the Fredenslund test (equation 13) as well. Notably, for the MF/1,4-PD mixture, the error calculated by the test is much lower than for the other mixtures. As for this mixture, the tie lines could only be measured for temperatures below 355 K. In this region only small differences in the molar composition of the vapour phase are observed. Therefore, the vapour phase mole fractions calculated by the Fredenslund test did not deviate much, thus a small average absolute deviation was obtained. Based on the two test results, it is concluded that all experimental datasets are thermodynamically consistent.

### Validation of the simulated VLE

The experimental data are used to validate the NRTL-HOC simulated data, obtained using the newly obtained NRTL binary interaction parameters. Thereto, the MPD’s of the temperature and the liquid and vapour mole fractions were calculated, these results are listed in Table 3. All MPD-values are lower than 5 %, hence, it can be concluded that the simulated VLE’s agree well with the experimental data. Moreover, a visual comparison as can be found in Figure 4, also shows that both data sets agree well.

However, when looking at the figures in great detail, two types of deviations between the VLE’s simulated using NRTL-HOC and the experimental data can be observed, namely a narrowing or broadening of the tie lines or a shift in the data towards lower or higher mole fractions and/or temperatures. The first type of deviations is sign of a small divergence of the interactions. If the simulated VLE shows a narrowing of the data, NRTL-HOC predicted slightly stronger unlike interactions than were observed experimentally. Vice versa a broadening of the simulated tie lines compared to the experimental ones indicates that the simulation forecast the like-like interactions to be little stronger than observed experimentally. In case of the shift in the data, it is not possible to unambiguously link this to a deviation in temperature or mole fractions. However, these visual deviations are all very minimalistic. As mentioned above, all MPD values are below 5%, which demonstrates that the methodology used to simulate VLE is reliable and accurate for the investigated furfural derivatives. Furthermore, since COSMO-RS activity coefficients were used for the regression of NRTL, it is concluded that COSMO-RS can be used as an alternative to gather data and to adapt the (semi)empirical models, which are often used to simulate and design separation trains.

Figure 4. T-x/y phase diagrams, both experimental (dotted lines) and NRTL-HOC simulated (full lines) a)-b) 101.3 kPa, c)-d) 10.0 kPa, e) 101.3 kPa, f) 10.0 kPa, g)-j) 101.3 kPa.

# Conclusions

Since it is costly and time consuming to acquire the necessary experimental data to regress (semi-)empirical models used for the design of separation trains for biobased products, in this work, an efficient alternative strategy is presented. The methodology allows to determine the binary interaction parameters of activity coefficient models, such as NRTL, based upon first principles, i.e., via regression of the considered model against activity coefficient data generated using COSMO-RS. Where other thermodynamic models rely on experimental data, COSMO-RS does not, hence its potential for elucidating the thermodynamics of biobased components within the liquid phase. Thus, provided that the vapour phase is not highly non-ideal, this methodology allows the simulation of VLE’s without the need for experimental data. As a proof of concept, in this work, the VLE’s of 28 binary mixtures were mapped in this way, which showed that the different interactions exhibited by the investigated furfural derivatives could be predicted.

Additionally, the VLE’s of 10 binary mixtures were also experimentally acquired, aiming at model validation. The obtained experimental data were found to be thermodynamically consistent and, hence, a reliable benchmark to validate the simulations. Since in the vapour phase, the considered furfural derivatives do not show highly non-ideal behaviour, NRTL-HOC could be used to simulate their VLE’s, setting the HOC binary parameters to 0. Therefore, the NRTL is regressed against the data generated by COSMO-RS and new binary interaction parameters are obtained. Applying the obtained NRTL parameters, NRTL-HOC is confirmed to simulate the VLE’s of the studied furfural derivatives well as the results align well with the experimental data. Thus solely with the chemical structures as an input for COSMO-RS and pure component vapour pressures, the critical pressure and temperature, dipole moment and acentric factor, reliable NRTL-HOC-simulations were obtained. Nevertheless, it remains important to validate these simulations with a limited set of experimental data, to ensure the methodology is applicable to the considered mixtures of components. Furthermore, in future work, it would be interesting to extend this research to other component families, as well as other phase equilibria, such as LLE’s, and other thermodynamic properties, such as excess enthalpies.

In addition to proposing a novel methodology, the study also delivers 28 sets of binary parameters, which can be used for various applications, e.g., separation train design or kinetic modelling concerning the considered molecules, using NRTL.

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**Data availability statement**

The data that supports the findings of this study are available in the supplementary material of this article.

|  |  |  |
| --- | --- | --- |
| **Nomenclature** |  |  |
| aij,ji | Interaction parameter 1 in the NRTL model | R’ | Radius of gyration in m  |
| ai | Activity of component *i* | ΔTExtr | Difference between the maximum and minimum temperature of a VLE experiment |
| AAnt | Antoine constant for p in kPa and T in K | Tb | Boiling temperature at atmospheric pressure in K |
| bij,ji | Interaction parameter 2 in the NRTL model | Tc | Critical temperature in K |
| B | Second virial coefficient in cm³/mol | Ti0 | Boiling point of pure component *I* in K |
| BAnt | Antoine constant for p in kPa and T in K | *viL* | Liquid molar volume of component *i* m³/mol |
| Bij | Second virial coefficient characterizing pair interactions between molecule *i* and *j* in cm³/mol | Δx,yExtr | Difference between the maximum and minimum mole fraction of a VLE experiment |
| CAnt | Antoine constant for p in kPa and T in K | xi | Mole fraction of component *i* in the liquid phase |
| D | Variable described in the Redlich-Kister test | yi | Mole fraction of component *i* in the vapour phase |
| fio | Fugacity of component *i* at the standard state in kPa | αij | Non-randomness factor in the NRTL model |
| IA,B,C | Principal moments of inertia in kg·m²  | γi | Activity coefficient of component *i* |
| Gij | Binary interaction as described in the NRTL model | *ρ* | Density in kg/m³ |
| *h*E | Molar excess enthalpy in J/mol | µ | Dipole moment in D |
| m | Molecular mass in g | φi | Fugacity coefficient of component *i* in the vapour phase |
| n | Number of experimental points | τij | Binary interaction as described in the NRTL model |
| pc | Critical pressure in MPa | *υ*E | Molar excess volume in m³/mol |
| pi0 | Vapour pressure of pure component *i* kPa | ω | Acentric factor |
| R | Universal gas constant in J/mol·K |  |  |

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