Integration of COSMO-Based Methodologies Into Commercial Process Simulators: Separation and Purification of Reuterin

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The conceptual design of a new process is developed via computer-aided simulation for separating and purifying reuterin, an antimicrobial substance obtained by bacterial fermentation of glycerol, from its mixture with the nonfermented substrate, the main subproduct of the process (1,3-propanediol) and water. The nondatabank components included in the simulations are created by using the structures derived from quantum mechanical calculations and the properties (molecular weight, normal boiling point, and mass density) estimated by COSMO-RS method. The unknown remainder properties are estimated by the methods and models used by default in Aspen Plus (v7.3). The COSMOSAC property model, also implemented in Aspen Plus, is specified with the molecular volumes and sigma profiles obtained by COSMO-RS. The properties (boiling temperatures, densities, VL equilibria, etc.) predicted for glycerol, 1,3-propanediol, water, and their mixtures by COSMO-based methods agree reasonably well with experimental reported values, whereas those obtained for reuterin derivatives are consistent with the behavior of amphoteric compounds having strong capabilities to interact attractively with hydrogen donor and acceptor groups all together. The process consists of a two-stage distillation operation, the first of which removes the water and the second one separates reuterin as a 99.5 wt %-pure bottom product. The second column operates at low pressure (ca. 40 kPa) to avoid thermal decomposition of reuterin (over 280°C) and guaranties 99.9% recovery of the desired product. Water removing offers different heat integration and energy-saving opportunities considering that condenser pressure of the first column can be increased to ~15 bar preserving the thermal integrity of the reuterin. Dimensions of the equipments as well as capital and operating costs are evaluated. © 2012 American Institute of Chemical Engineers *AIChE J,* 58: 3404–3415, 2012

Keywords: design (process simulation), computational chemistry (quantum chemistry), bioprocess engineering, separation techniques, process synthesis

Introduction

Nowadays, process simulation plays an important role in the development of new processes. In correspondence, software packages such as Aspen Plus, Aspen HYSYS, ChemCad, Speedup, Promax, and UniSim are broadly used. However, the success of the process simulation depends largely on the accessibility and accuracy of physical and kinetic information for the chemicals involved.[1–4] Commercial simulators have large and even very large databases, however, new processes involving nondatabank components are being developed increasingly. This is a severe limitation and often hinders progress and the exploration of unconventional strategies.[5] Fulfilling the databases of the process simulators experimentally is a largely resource and time-consuming task. Thus, theoretical methods seem to be excellent candidates for achieving it.[2,3,5] In particular, the COSMO-based methods[6–14] such as COSMO-RS[6–10] and COSMO-SAC[11–14] have been established as a novel way to predict thermophysical data for liquid systems on the basis of quantum chemical calculations. In contrast to group contribution methods (GCMs), which depend on an extremely large number of experimental data, COSMO-based are *a priori* methods that predict thermodynamic properties by solely using the molecular surface polarity distributions of the individual compounds in the mixture.[9,12] COSMO-based methods have proven to be valuable tools for predicting vapor pressures, boiling and melting temperatures, densities, excess enthalpies, VL and LL equilibrium diagrams, etc.[6–25] This enables chemical and biochemical engineers to use the predictive power and broad applicability of modern quantum chemical methods for their needs. Many such engineers have taken up COSMO-based methods enthusiastically, resulting in a large number of publications reporting successful applications in many different areas, mostly by chemical engineering groups.[10] In fact, predictive thermodynamic models are in high demand in the current engineering practice. Their need is significant enough that engineers are willing to accept inaccuracies for their promised benefits such as time and cost savings.[14] Consequently, at the present, it is entirely possible to transit from molecular modeling to process simulation following, for example, the route: quantum chemical calculations → COSMO-based fluid properties estimation →

Additional Supporting Information may be found in the online version of this article.

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Aspen ONE process simulations. Therefore, the integration of COSMO-based methodologies into commercial process simulators for developing the conceptual design of new processes results a goal subject for many researchers and engineers.[26–31] Important success has been achieved in this field: (1) the COSMO-SAC method has been implemented in the Aspen Plus[26,27] process simulator as a method for property estimations, and further the COSMO-SAC sigma-profile database[12,14] has been incorporated into the database of this program,[27] and (2) the COSMO*logic* GmbH and Co. KG[32] has developed the COSMO*therm*CO,[33] a CAPE-OPEN[34,35] interface between the COSMO*therm*X[36] software and CAPE-OPEN compliant process simulators with the aim to apply thermodynamical data computed by COSMO*therm*X within process modeling and engineering simulations.[28,29] However, both the COSMO-based methods and the integration procedures exhibit some theoretical and practical (instrumental) limitations. Thus, for example, despite its broad applicability, the described limitations[10] clearly exclude COSMO-RS from many applications in process developments that require elevated accuracies. On the other hand, an intensive effort is needed to physically, confidently, and operatively integrate the COSMO-based methodologies into commercial process simulators. The integration procedures already need to be evaluated, developed, and improved, i.e., several theoretical and instrumental issues have to be overtaken to extensively use COSMO-based results in process engineering. This is especially remarkable when the components to be used in the simulations are not included in the databank of the simulator. To our knowledge, only a few attempts have explored[28–31] the use of COSMO-based outputs directly into process simulations. In this work, the integration of COSMO-RS methodology into Aspen Technology's commercial process simulators for designing a new process is considered. The process to be developed deals with the separation and purification of a potent antimicrobial substance termed reuterin, which is obtained by fermenting glycerol by the *Lactobacillus reuteri* bacteria.[37,38]

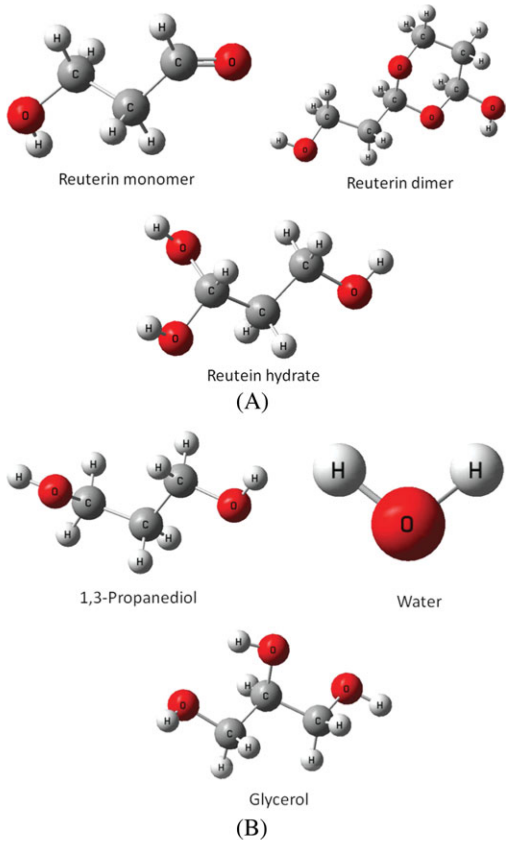


Figure 1. Optimized geometries of the three molecular forms of the reuterin (A) and the 1,3-propanediol, glycerol, and water (B).

They are obtained at the BVP86/TZVP/DGA1 computational level considering solvent effects. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

By the end of 80s, it was found that *L. reuteri* converted glycerol into an antimicrobial substance termed reuterin, which inhibits the growth of Gram-positive and Gram-negative bacteria.[37,38] It was also observed that fermentation process produces large quantities of 1,3-propanediol and a little amount of β-hydroxypropionic acid. Reuterin is preferably produced using resting cells in a two-step fermentation process.[39] First, *L. reuteri* cells are grown anaerobically on glucose and reuterin is subsequently produced by washed cells resuspended and incubated in glycerol-containing media. Growing cells of *L. reuteri* also have the ability of producing reuterin during anaerobic glucose/glycerol cofermentation. However, the main product of that cofermentation is 1,3-propanediol.[40] Thus, glycerol can be converted to reuterin and 1,3-propanediol, both products with interesting applications. In 2008,[41,42] it was confirmed that *L. reuteri* is able to produce reuterin in the human intestinal tract. Separation and purification of reuterin are considered an attractive idea because of the possibility of its use as a direct drug in the manufacture of biocompatible implant, in food industry as biopreservative, and in other biotechnological productions.[43–48] On the other hand, 1,3-propanediol could potentially be used for many synthesis reactions, in particular as monomer for polycondensations to produce polyesters, polyethers, and polyurethanes.[49] 1,3-Propanediol is especially demanded for the manufacture of the aromatic polyester polytrimethylene terephthalate commercialized by Shell and DuPont.[50] This polymer exhibits properties desirable in carpets and textiles.[47] Nevertheless, large-scale separation processes of the reuterin could hardly be developed because of the lack of thermophysical and equilibrium information of the compound. Only structural information has been obtained, thanks to laboratory experiments in which the compound has been isolated, purified, and further structurally characterized by NMR techniques.[37,38,48,51] In agreement with the general aim of this work, a separation process based on VL operations is developed using process simulators with the only information obtained by quantum chemical calculations through COSMO-RS estimation of the thermophysical and equilibrium properties. Experimental studies[37,38,48,51] have revealed that reuterin is a mixture of three molecular structures in dynamical equilibrium: the 3-hydroxypropionaldehyde (HPA, reuterin monomer), its hydrate, and its dimer derivatives (Figure 1A). HPA dimer is the predominant molecular form at overall reuterin concentrations above 1.4 M, whereas at concentrations relevant for biological systems the hydrate is the most abundant, followed by the monomer form. Thus, for example, for ~0.05, 0.15, 1.20, and 7.50 M suspensions of reuterin, the molar ratios monomer:hydrate:dimer are 25:70:5, 20:65:15, 15:40:45, and 15:20:65, respectively.[51] Reuterin has been purified in laboratory by the following different steps.[38,51] Supernatant liquid obtained after cell separation by centrifugation is solidified and lyophilized at reduced pressure to eliminate water excess. Concentrate results a yellow-orange colored product. Colored substances are removed by sorption using organic solvent mixtures (acetone:ethyl acetate, 2:1, for example)[51] to elute the solute. To concentrate the desired product some other operations have been described. Finally, the solvents of the mixture are removed under low pressures (ca. 10^{-2} mbar) yielding a colorless, highly viscous HPA solution. Thermal decomposition of reuterin at 280°C was observed during gas chromatography experiments.[51]

This work is organized into three parts. First, the molecular geometries of the all reuterin species, together with the other components of reaction mixture, are optimized by the aims of density functional theory. Then, single-point calculations with solvent effects (COSMO) are carried out to characterize the electronic structure of all the considered compounds including the charge screening at the molecular surface. Second, their thermophysical properties are estimated by the COSMO-RS method. These properties are further used both to create a reuterin nondatabank hypothetical component in Aspen Plus and to specify the COSMOSAC property model used to calculate the activity coefficients of the components in the mixtures. COSMO-based property predictions are compared with UNIFAC calculations considering that molecular structures of the reuterin derivatives can be fully defined through well-parameterized UNIFAC groups. Unfortunately, experimental data on the thermophysical and equilibrium properties of these compounds are not still available. Finally, the study is devoted to conceptually design a separation process for obtaining the desired product including the corresponding economical analysis based on relative capital and operative costs. Here, the conversion among the different reuterin molecular forms occurring during the product concentration is reproduced by fixing different molar ratios of the reuterin molecular forms for the different stages of the separation process. This is certainly a limited way for modeling this phenomenon being the reactive distillation simulation the proper treatment. However, the lack of experimental information on the thermodynamic and kinetics of the possible reactions has determined the alternative approach described without explicit consideration of the chemical reaction.

Computational Details

Quantum chemical calculations

The compounds considered in this study are the three molecular forms of the reuterin (monomer, hydrate, and dimer), 1,3-propanediol, glycerol, and water. The optimized structures and the COSMO files of 1,3-propanediol, glycerol, and water are taken from the TZVP-parameterized C21-0107 database developed by the COSMO*logic*.[32] Geometries of the reuterin molecular species are optimized by BVP86/TZVP/DGA1 method considering solvent effects and using Gaussian03 software.[52] Solvent effects in geometry optimizations are incorporated through the conductor-like polarizable continuum model[6,53] method taking water as solvent and using the Klamt radii[7] for all the atoms. Harmonic vibrational frequency calculations are always carried out on the optimized structures to establish the nature of the stationary points. The ^{13}C NMR chemical shifts are calculated with GIAO method[54,55] at the same quantum chemical level used in this work. Tetramethylsilane isotropic nuclear shielding data are used as reference.

COSMO and COSMO-RS calculations

The charge screening on the molecular surface (COSMO) calculations are done with the density functional BVP86 using TZVP/DGA1 basis sets by the SCF COSMORS[7] method and also with Gaussian03 program package. Solvent-phase optimized geometries are used as inputs in these calculations in which a solvent with $\varepsilon \to \infty$ is assumed. In this way, all the compounds are computed at the same computational level used to create the COSMO*logic* TZVP database. Consequently, the thermophysical and phase equilibrium properties calculated for 1,3-propanediol, glycerol, and water are used to validate the current COSMO-RS estimations by comparison with the experimental data existing in the literature. A multivariate cluster analysis is performed to investigate possible conformers of molecular forms of the reuterin. However, calculated similarities between the σ-profiles for the possible conformers are always higher than 0.95. Therefore, the minimum energy structures are chosen to represent each compound of the reuterin. In case of 1,3-propanediol and glycerol, two and nine conformers are, respectively, considered as in the COSMO*logic* C21-0107 database. The conformer treatment implemented in the program package COSMO*therm*X (version C21-0111)[36] for estimating the thermophysical properties of the compounds is used. Both the σ-profile of the studied compounds and the COSMO-RS calculations are obtained by the COSMO*therm*X (version C21_0110) program.[36]

Strategies for integrating COSMO-based results in Aspen Tech process simulators

Although COSMO-RS and COSMO-SAC are essentially similar in origin[11,56,57] they have had theoretical and computational developing trajectories rather different. Therefore, at present they offer two well-differentiated procedures to apply their results within process modeling and engineering simulations: (1) activity coefficients calculated by COSMO-RS[28,29] can be automatically exported through the COSMO*therm*CO interface[33] to the property packages created in a CAPE-OPEN compliant process simulator. This property package can be finally imported from Aspen Plus using its Import/Export CAPE-OPEN property package capabilities.[58] In the bridging role described before has been explored[28,29] the free-on-charge CAPE-OPEN compliant steady-state simulation environment COCO (CAPE-OPEN to CAPE-OPEN).[59] This procedure works well[28,29] if the components selected for the simulation are included in the COCO database; however, it exhibits some limitations when nondatabank components have to be created. (2) As mentioned in the Introduction, the COSMO-SAC model is implemented in the Aspen Plus since its version 12.0.[26] In the Aspen ONE v7.0 and further versions, the VT Sigma Profile Database created by the COSMO-SAC formalism[12,14,60] has been incorporated to the Aspen Plus database of PURE compounds.[27] Moreover, the COSMOSAC property model in Aspen Plus can be specified by the user giving both the molecular volume and the σ-profile of the individual components. The COSMO-SAC σ-profiles of compounds not included in the VT Sigma Profile Database can be generated by the open Fortran program ‘‘Sigma-average.exe’’ available at the homepage.[60] The computational support of the COSMO-SAC method already available for users in the web site[60]

Table 1. Experimental[51] and Calculated NMR ^{13}C Chemical Shifts (ppm) of the Reuterin Molecular Forms: Monomer, Hydrate, and Dimer

	Reuterin Monomer		Reuterin Hydrate		Reuterin Dimer	
Group	Calc.	Exper.	Calc.	Exper.	Calc.	Exper.
H—C=O	190	206	–	–	–	–
[OH]CH_2	49	55	52	58	52	57
[CC]CH_2	39	45	30	39	25	32
[OX]CH	–	–	82	89	87	94

also includes the "COSMOSAC-VT-2005.exe" code, a program that uses the sigma profiles of two pure components to calculate the liquid-phase activity coefficients in a solution. Hence, supplementary computational codes are needed to calculate thermophysical properties of individual compounds or equilibrium data, VLE for example, for mixtures. This is an instrumental limitation when trying to integrate the COSMO-SAC results to process simulators for extensive uses in process engineering, particularly when a set of properties should be collected for creating nondatabank compounds. On the contrary, the COSMO*therm*X[36] is a commercial program under continuous improvement that calculates, based on the COSMO-RS model, the σ-profiles and the σ-potentials of individual compounds as well as a complete set of thermophysical, equilibrium, and transport properties of pure compounds and mixtures, etc. Taking into account both circumstances, in this article, a hybrid approach is applied: the results of COSMO-RS calculations are used to create nondatabank components and to specify the COSMOSAC property package in Aspen Plus. This possibility is recognized by the developers of the Aspen Plus.[61] In fact, the primary version of the COSMOSAC property model as implemented in Aspen Plus is the model by Lin and Sandler,[11] but two other different versions under the same name (COSMOSAC) are also available including the COSMO-RS[8] model. Finally, the strategy adopted in this work is consistent with the methodological basis of our research group[23,62–64] consisting of the systematic use of the COSMO-RS method for designing new materials with specific properties, predicting the properties of new compounds, etc.

Creating property packages

Nondatabank components for reuterin derivatives are created in Aspen Plus specifying their molecular structures as UNIFAC-DMD groups (see Supporting Information), molecular weights, normal boiling temperatures, and mass densities. In addition, the three-dimensional optimized structure of the compounds is given in mol format. Once the basic specifications are fulfilled the remainder properties of the individual compounds are predicted by the corresponding methods, models, and calculation routes implemented as default in Aspen Plus (v7.3). Reuterin product is represented in process simulations through either one or all its three individual molecular forms. The dimer is particularly interesting to represent the reuterin product taking into account that it turns the predominant molecular form resulting from the transformation among the three species under concentration.[51] Therefore, it represents a limit situation respect to the cases where other molecular forms of the reuterin are considered. In some cases reuterin product is alternatively represented by a pseudo-component (reuterin-N, with $N = 1$–4) consisting of mixtures with molar ratios monomer: hydrate:dimer 25:70:5, 20:65:15, 15:40:45, and 15:20:65[51] experimentally studied (see Introduction). The properties (including the σ-profiles) of reuterin-N pseudo-components are calculated as linear combinations of the corresponding properties in the individual species using these molar ratios as coefficients of the individual properties in the regressions. Components 1,3-propanediol, glycerol, and water are selected from the PURE-25 database of the Aspen Plus (v7.3) including their COSMO-SAC parameters. The COSMOSAC model is used simultaneously in process simulations to calculate the activity coefficients in the liquid phase and to model the vapor phase. Both the properties used for creating nondatabank compounds (reuterin species) and the parameters used for specifying their COSMOSAC models are computed by COSMO-RS method. Molecular volumes and σ-profiles used for specifying COSMOSAC model for reuterin species are collected in the Supporting Information. In some VLE

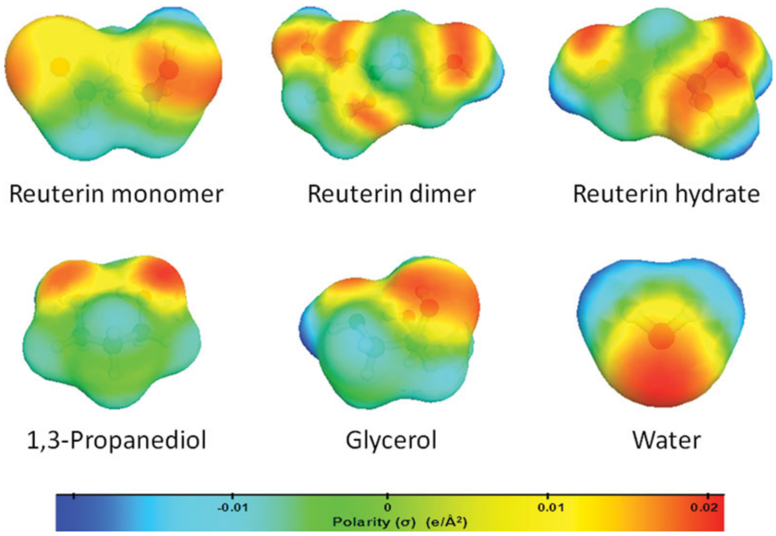


Figure 2. Screening of the polarized charge distribution on the molecular surface for the studied compounds given by COSMO-RS.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

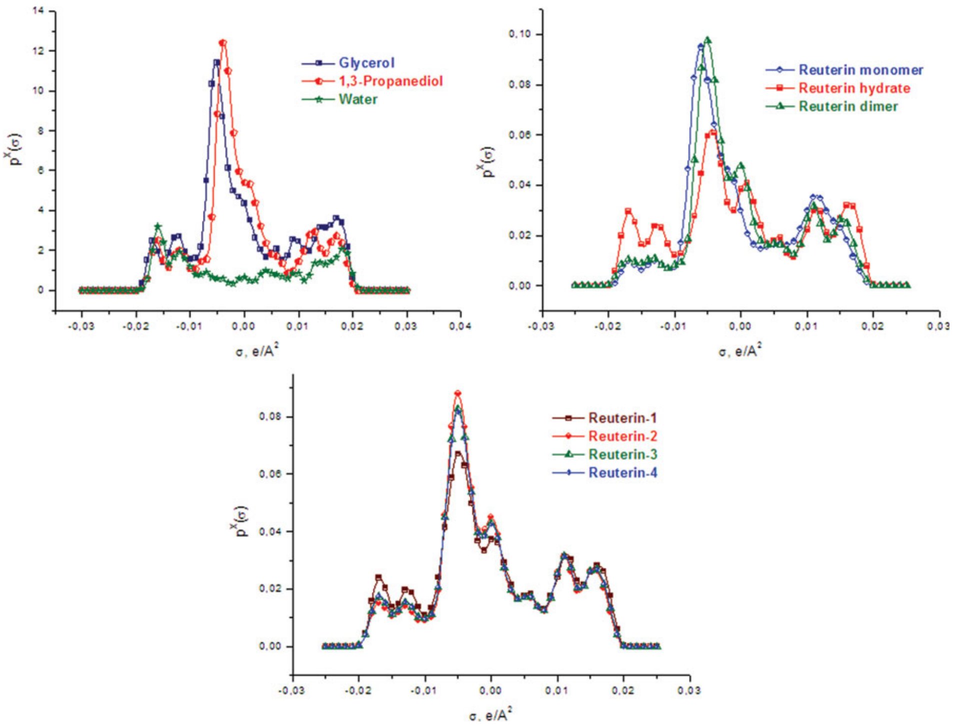


Figure 3. σ-Profiles of the studied components and the reuterin-N pseudo-components (see Computational Details) given by COSMO-RS.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

calculations, for comparison, nondatabank 1,3-propanediol, glycerol, and water components are also created and UNIQUAC and/or UNIFAC activity models are used to calculate the activity coefficients. For identifying the property package used in the simulations, the following nomenclature is used in this work: compound source/thermodynamic model.

Process simulation calculations

Process simulations (including phase equilibrium calculation, azeotrope search, and conceptual design) are performed with Aspen Plus (v7.3). The results of the Aspen Plus property predictions for individual compounds as well as VLE calculations for binary mixtures are compared when possible with experimental data to validate the integration procedure altogether. The experimental property data (for pure compounds and binary mixtures) are taken through the dynamic data evaluation developed at the Thermodynamics Research Center (NIST) and implemented in the Aspen Plus.[27] A preliminary conceptual design is first performed to define the column sequence and operating pressures needed to reach the desired separation. Initial specifications of distillation columns are derived using the DSTWU shortcut model. The following design specifications are set: (1) to remove 99.9 mol % of the water from the mixture and (2) to obtain a 99.5 wt %-pure reuterin component. Rigorous column calculations are performed using the RadFrac model assuming ideal equilibrium stages. A partial condenser with only vapor distillate is selected for the first column, whereas a total condenser is the choice for the second one. The design is carried out for a fermentation broth feed with a composition of 8 wt % 1,3-propanediol, 10 wt % glycerol, 2 wt % reuterin, and 80 wt % water. A total of 100 kmol/h (~2140 kg/h) of the feed is considered in simulations. Sensitivity analyses are carried out to rudimentarily optimize the reuterin recovery and energy consumptions with respect to the feed-to-column temperature, reflux ratio, column number of stages, and feed stage to the columns. Shortcut and sensitivity analyses calculations are carried out using the reuterin dimer to represent the overall product.

Sizing and economics

Colum sizing calculations considering sieve trays and the remainder default specifications of the Tray sizing utility in Aspen Plus are done. Economic evaluations by using the Aspen Process Economic Analyzer (APEA) v7.3 integrated into

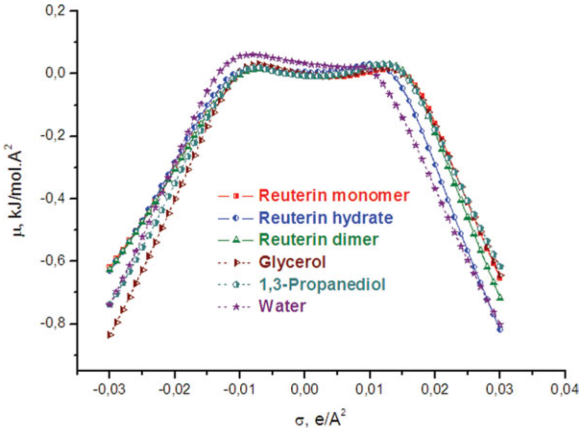


Figure 4. σ-Potentials of the three molecular forms of the reuterin, glycerol, 1,3-propanediol, and water, calculated by COSMO-RS for the corresponding pure components at room temperature.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 2. Boiling Temperatures and Mass Densities Calculated by COSMO-Based Methods for the Pure Compounds and Reuterin-N Mixtures Studied in This Work

		Calculated Values	
Component	Experimental*	COSMO-RS	COSMO-SAC[†]
Boiling Temperature (°C)			
Water	100.0	103.9	100.0
1,3-Propanediol	213.8/178.2[‡]	193.4/154.4[‡]	214.4/175.6[‡,§]
Glycerol	286.9/182.1	218.4/180.1	288.0/181.9[§],
Reuterin-monomer	–	187.0	–
Reuterin-hydrate	–	317.2	–
Reuterin-dimer	–	366.6	–
Reuterin-1 mixture	–	287,1	–
Reuterin-2 mixture	–	298,6	–
Reuterin-3 mixture	–	319,9	–
Reuterin-4 mixture	–	329,8	–
Density (kg/m^3)			
Water	997	995	–
1,3-Propanediol	1050**	1019	–
Glycerol	1255	1218	–
Reuterin-monomer	–	1032	–
Reuterin-hydrate	–	1272	–
Reuterin-dimer	–	1307	–
Reuterin-1 mixture	–	1214	–
Reuterin-2 mixture	–	1229	–
Reuterin-3 mixture	–	1252	–
Reuterin-4 mixture	–	1259	–

Experimental values for comparison are also included when available.
*Unless otherwise is indicated the boiling temperatures correspond to 1 atm and the densities are taken to 20–25°C and 1 atm.
[†] From Refs. 20 and 60.
[‡] Left value is the NBT, right value is the equilibrium temperature to 30 kPa.
[§] Calculations were performed using Aspen Plus (v7.3) and the COSMOSAC information of the program databank.
Left value is the NBT, right value is the equilibrium temperature to 0.027 bar.
**Taken from Ref. 67.

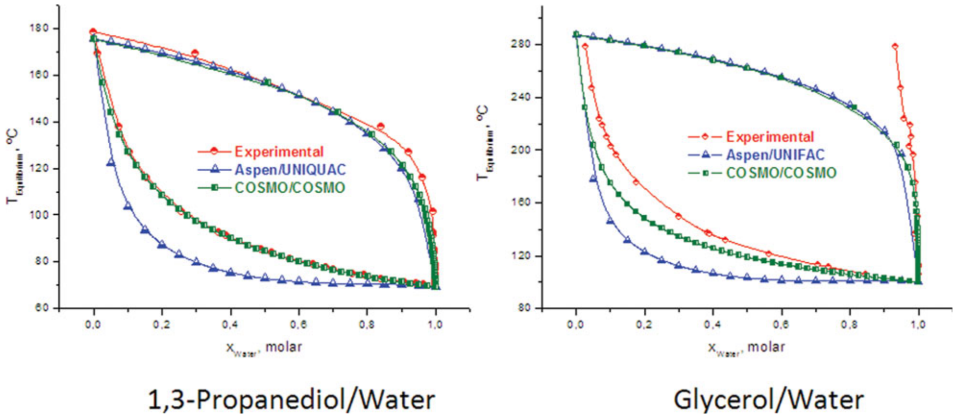
Aspen Plus are accomplished. The economic analysis is based on relative capital and operating costs calculated for the equipment mapping, computational methods, and specifications used by default in APEA v7.3. No customizing is introduced in APEA calculations. The column is mapped as a single-diameter tray section, U-tube keetle-type reboiler, fixed head shell and tube condenser, centrifugal reflux pump, and horizontal condenser drum. Floating head shell and tube heat exchanger are selected as process heater and cooler. Carbon steel is accepted as material for cost estimations. The utility costs include medium, high, and very high pressure vapor, cooling water, and electricity.

Results and Discussion

Molecular electronic structure and charge screening

Geometry optimization of the reuterin molecular species (monomer, hydrate, and dimer) gives the molecular structures shown in Figure 1. The values obtained for some selected geometrical, electronic, and energetic parameters as well as the Cartesian coordinates of the optimized geometries are attached as Supporting Information to this article. The three reuterin species were experimentally identified by NMR spectroscopy by analyzing the changes in intensity of ^{13}C NMR signals with sample concentrations.[51] Table 1 compares the experimental assignments by Vollenweider et al.[51] with the calculated ^{13}C NMR chemical shifts of the optimized molecular structures for each reuterin specie. As can be seen, the monomer is easily identified by the signal of carbon atom in carbonyl group. Dimer and hydrate species are more difficult to distinguish; however, both experimental and calculated ^{13}C chemical shift values for [CC]CH$_2$ and [OX]CH groups are, respectively, lower and higher in dimer than in hydrate. Therefore, the reasonable agreement between experimental and calculated NMR spectra (Table 1) for reuterin species supports the assignments by Vollenweider et al.,[51] validating the optimized molecular geometries in this work.

The differences in the polarities of the molecular forms of the reuterin are not so important. The dipole moments of the optimized geometries of the monomer, the hydrate, and the dimer specie of reuterin are, respectively, 4.7, 5.5, and 5.4 Debye. Moreover, the oxygen heteroatoms responsible for the polar character of these compounds and consequently for their interactions in solution have similar Mülliken charges. Those of the OH groups are the most negative in all the reuterin derivatives with charges in the range from −0.35 to −0.42. The O-atom of the carbonyl group in the monomer exhibits a negative charge of −0.34, and finally, the ring O-atom in the dimer has a charge of −0.22. The screening charge distribution on the molecular surface of the



1,3-Propanediol/Water

Glycerol/Water

Figure 5. Experimental (○) and calculated VLE diagrams for the 1,3-propanediol/water (at 30 kPa) and glycerol/water (at 101.3 kPa) binary mixtures.

(△) Using Aspen Plus (v7.3) databanks compounds and activity coefficient models. (□) Using COSMO-based methods. Experimental VLE data for 1,3-propanediol and glycerol binary mixtures with water are taken, respectively, from Refs. [67] and [65]. VLE dataset for glycerol/water binary mixture used in this article passed the Herington test of thermodynamic consistency but passed neither the van Ness nor the infinite dilution test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

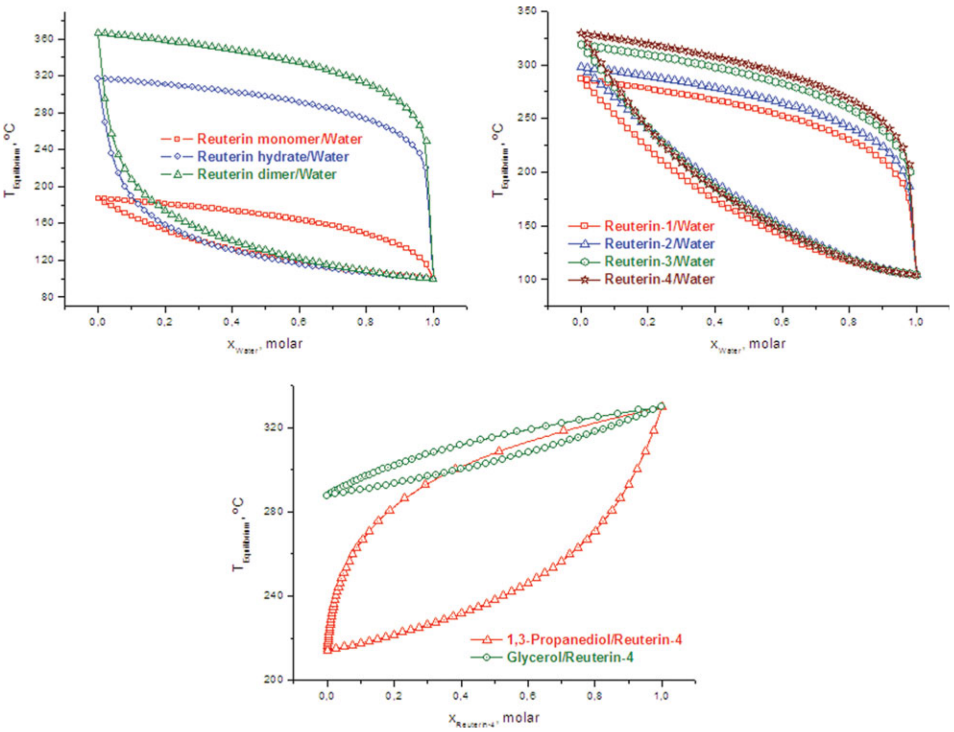


Figure 6. Calculated (COSMO/COSMO property packages) VLE diagrams of the binary mixtures reuterin derivatives/water, reuterin-N/water, and hydrate, glycerol/reuterin-4.

***P* = 1 atm in all calculations. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]**

compounds (Figure 2), given by COSMO-RS, shows the simultaneous presence of both negatively and positively polarized surface segments, as correspond to amphoteric compounds having strong capabilities to interact attractively with hydrogen donor and acceptor groups all together. This information is properly reflected in the σ-profiles (Figure 3) and the σ-potentials (Figure 4) of the compounds. The σ-profiles display maximum values for: (1) $\sigma < -0.01$ e/Å^2, which belongs to strongly acid segments having donors character in H bond (protons of —OH, for example) interactions, (2) $\sigma > 0.01$ e/Å^2 corresponding to strongly basic atomic segments that exhibit acceptor nature in H bond (oxygen in —OH and —CHO groups as well as ether oxygen in cyclic group of reuterin dimer) interactions, and (3) the region -0.005 e/Å^2 $< \sigma < 0.005$ e/Å^2, which is determined by nonpolar surface segments (corresponding mainly to —CH and —CH_2 groups). The σ-potentials computed for the pure compounds at room temperature are highly symmetric, indicating attractive interactions with both proton donor and proton acceptor polar groups. This picture suggests the studied compounds trend to form strongly hydrogen bonds in solution. As can be seen in Figures 2 and 3, the polarized charge distribution on the molecular surface and the σ-profiles of the reuterin molecular forms are similar. This chemical similarity of all the compounds of the mixture reveals that it is difficult to find an extracting solvent to separate them. Thus, in this work, the possibility to separate the reuterin from its mixture with glycerol, 1,3-propanediol, and water by rectification is evaluated.

Property estimation

Table 2 shows the calculated values of both the boiling temperatures and the densities for the pure compounds and reuterin-N pseudo-components using COSMO-based

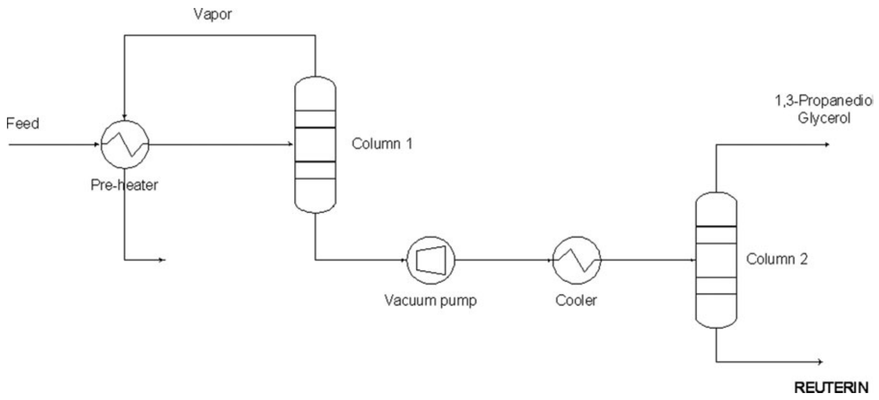


Figure 7. Scheme of the two-column process design for separating 99.9%-pure reuterin product from the mixture with glycerol, 1,3-propanediol, and water.

Table 3. Sensitivity Analysis for Individual Columns: Explored and Optimized conditions

	Manipulated Variables			
	Column 1		Column 2	
Variables	Explored Conditions	Optimized Conditions	Explored Conditions	Optimized Conditions
Number of stages, n	5–10	5	8–20	20
Feed stage	2 (n − 1)	4	2 (n − 1)	16
Feed temperature (°C)	50.0–102.3*	102.3	50.0–216.7†	50.0
Molar reflux ratio	0.05–3.0	0.05	0.3–5.0	5.0
Objective Variables				
Variables	Column		Optimized value	
Reboiler duty (MJ/kg h)‡	Column 1		0.97	
Reuterin recovery (%)	Column 2		99.9	

*$T_{\text{Bubble point}}$ at 100 kPa = 101.0°C.
†$T_{\text{Bubble point}}$ at 40 kPa = 142.8°C.
‡Per kilogram fed to column.

methods. Normal Boiling Temperatures (NBT) calculated for 1,3-propanediol, glycerol, and water are in reasonable agreement with the experimental values. These results match well with the conclusions of systematic studies on the application of COSMO-RS[66] and COSMO-SAC[17,20] to NBT estimation of organic compounds with different functionalities. The referred studies reveal that COSMO-based methods are in general valuable for estimating normal boiling temperatures of organic conventional compounds and substances having larger and more complex molecules than the former like pollutants, herbicides, insecticides, and drugs.[20] Density calculation for 1,3-propanediol, glycerol, and water gave relative errors of about 2.0%, coinciding with the accuracies obtained in previous density studies by COSMO-RS method.[23] Reuterin compounds exhibit high boiling temperatures and densities as correspond to compounds with high bond hydrogen-interacting capacities. In particular, the reuterin dimer and reuterin hydrate, the major components of mixtures having moderate and high global molar concentrations of reuterin,[51] have the highest boiling temperatures and densities of the mixture. In correspondence, they should be the final product of a continuous sequence of VL separations as observed in laboratory experiments. The reuterin monomer has boiling temperatures lower than 1,3-propanediol and glycerol but higher than water. As a consequence, any reuterin molecular form (or mixture of them) could represent the global product in the first stage of the separation process devoted to remove water from the mixture without affecting the separation scheme (see below). The normal boiling temperatures and densities of the reuterin-N pseudo components trend to the corresponding values of the reuterin dimer when the dimer concentration increases (Table 2). The results shown in Table 2 meet well the laboratory experiments carried out to isolate and purify the reuterin in the sense that reuterin was obtained as a dense and viscous product after a continuous VL separation process.[38,51] The shape of the dependence between the boiling temperature and the equilibrium pressure of the reuterin derivatives is similar to the one observed in conventional organic compounds. Besides, the hydrate and the dimer exhibit boiling temperatures higher than the decomposition temperature of the reuterin for pressures higher than ~40 kPa.

Azeotrope search reproduces the absence of azeotropes experimentally proved[67] in mixtures 1,3-propanediol/water and glycerol/water (Figure 5). No azeotropes are found in the pressure interval from 10 to 150 kPa in any binary mixture of the all considered compounds including the reuterin-N pseudo-components (Figure 6). Figure 5 shows a reasonable agreement between experimental and calculated VLE diagrams for the binary mixtures 1,3-propanediol/water (at 30 kPa) and glycerol/water (at 101.3 kPa) confirming that COSMO-based methods are a valid alternative to activity models and GCMs for evaluating VLE properties of mixtures. VLE diagrams calculated for binary mixtures of the individual species of the reuterin (monomer, hydrate, and dimer)/water and the reuterin-N pseudo-components/water are similar as well as the VLE diagrams of the binary mixtures of 1,3-propanediol and glycerol with reuterin-4 (Figure 6). This suggests that no significant changes would be expected in process simulations as a consequence of the component used to represent the reuterin product. Consequently, thus so, no great implications in their VL equilibrium distribution under different concentrations resulting from the transformation among the three reuterin species should be expected. Thus, the only changes guess when the more volatile monomer is substituted by the less volatile hydrate and dimer in the mixture are as follows: (1) the vapor and liquid curves are more separated as correspond to binary mixtures composed by species more and more different in volatilities, and (2) the VLE are displaced to the higher equilibrium temperatures in correspondence with the decreasing of the volatilities of the reuterin compounds.

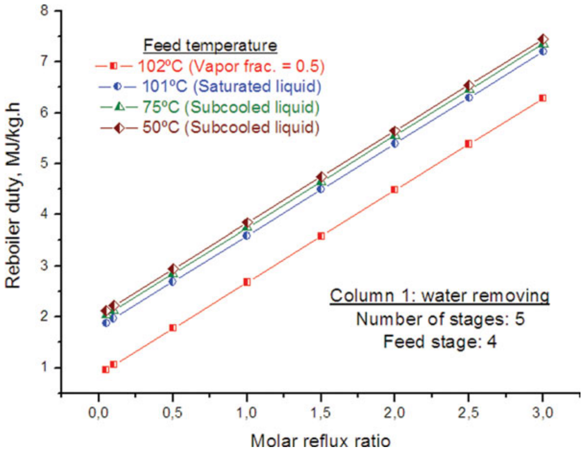


Figure 8. Sensitivity analysis for column 1 that removes water from the mixture with 1,3-propanediol, glycerol, and reuterin.

Reboiler duty is optimized as a function of the feed conditions and reflux ratio for a column with five theoretical stages fed by stage 4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

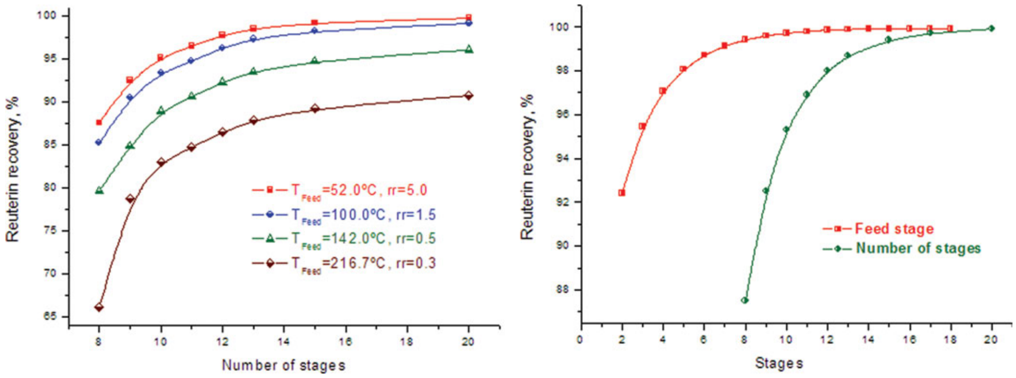


Figure 9. Sensitivity analysis for column 2 that separates reuterin from the mixture with 1,3-propanediol and glycerol.

Reuterin recovery is optimized as a function of: (left) feed conditions for different numbers of theoretical stages. In these experiments, feed stream is introduced by the middle-column stage in all the cases; (right) the number of stages and the feed stage. In all these experiments, $T_{\text{Feed Stream}} = 50.0^{\circ}$C and reflux ratio = 5.0. For studying the feed stage effect, 20-stage column is considered. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The present COSMO-based property predictions yield very similar results to those computed by using UNIFAC property model as implemented in Aspen Plus. This result can be taken as a support of the COSMO-based calculations if considered that molecular structures of the reuterin derivatives and the remainder components of the system studied in this work can be fully defined through well-parameterized UNIFAC groups. Unfortunately, experimental data on the thermophysical and equilibrium properties of these compounds are not still available.

Conceptual process for separating reuterin

Preliminary simulations (using reuterin-4 pseudo-component to represent the reuterin product) show that separation processes with one, two, or three rectification columns lead to separate 99.5 wt %-pure reuterin product from the mixture with glycerol, 1,3-propanediol, and water, reuterin being always the bottom product as correspond to the boiling temperatures of the components (Table 2). Considering an unique pressure for all the process suggests that the most economic design consist of two columns (Figure 7) for the pressure interval in which the reuterin is thermally stable (ca. 40 kPa). The first column removes the water from the mixture, whereas the second one separates reuterin from both 1,3-propanediol and glycerol. Furthermore, two-column configuration allows reducing costs if the columns are operated at different pressures. In fact, the two-column design where columns operate at 100 and 40 kPa, respectively, is about 6.5% less expensive than that where both columns operate at the reduced pressure (Figure 7). The complete

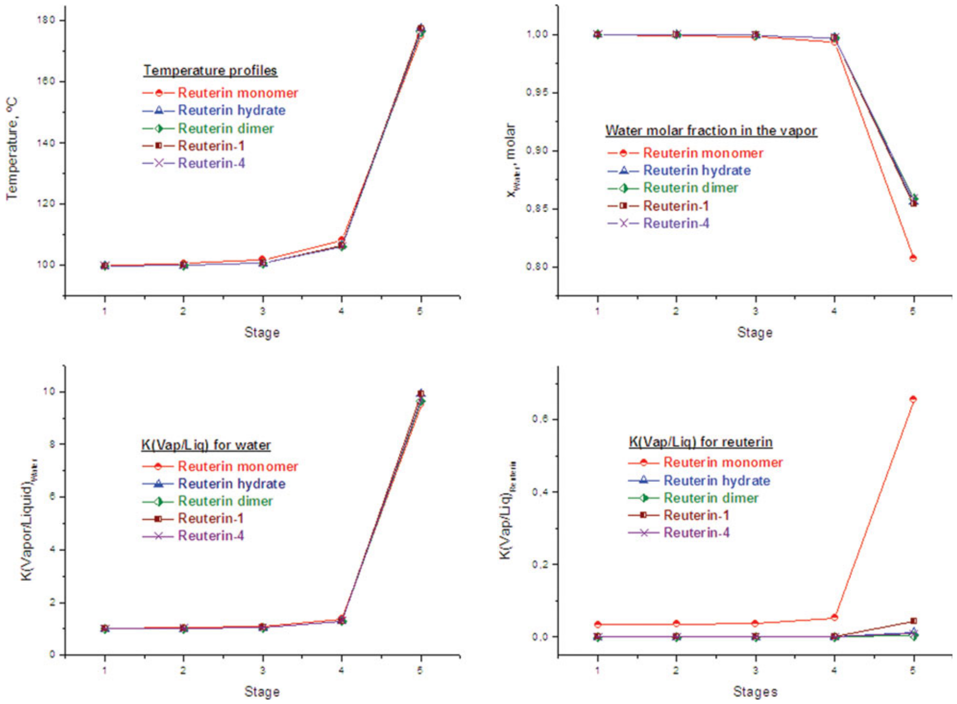


Figure 10. Temperature, composition, and *K* (vapor-to-liquid) profiles for the optimized column 1 (water removing phase).

Different (pseudo)compounds are used to represent the reuterin product. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

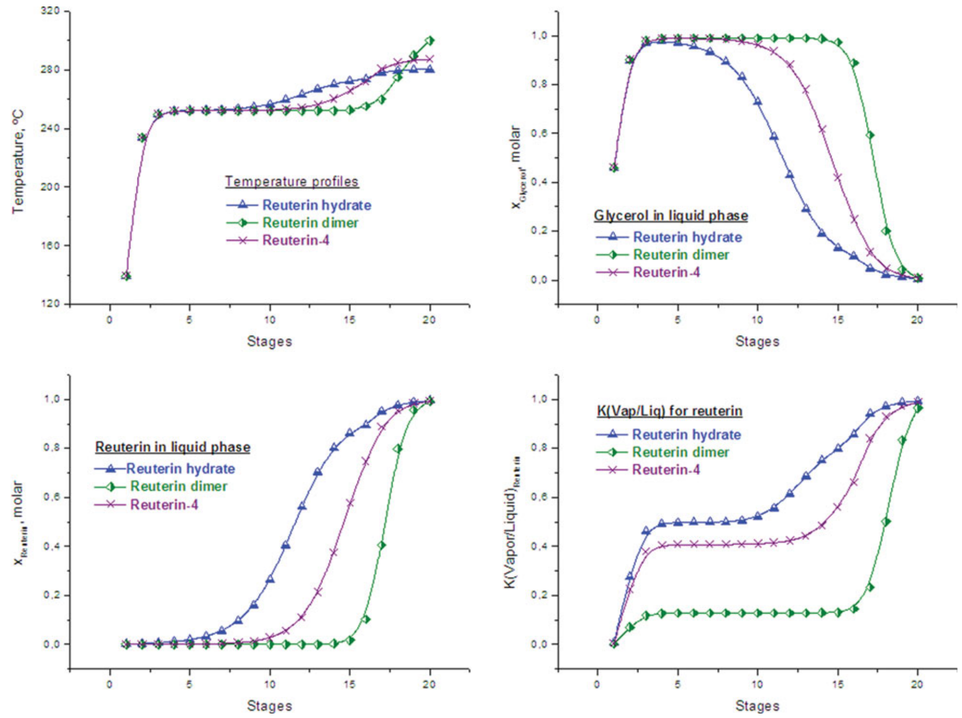


Figure 11. Temperature, composition, and *K* (vapor-to-liquid) profiles for the optimized column 2 (reuterin separation from the mixture with 1,3-propanediol and glycerol).

Different (pseudo)compounds are used to represent the reuterin product. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

separation of all the four components (1,3-propanediol, glycerol, reuterin, and water) as individual products is possible with a three-column process.

Shortcut calculations suggest that specified separations in columns 1 and 2 require minimum molar reflux ratios 0.01 and 0.15 and minimum number of stages 3 and 7, respectively. Sensitivity analysis for column 1 (Table 3 and Figure 8) demonstrates that the lowest reboiler duties are attained when fermentation broth is fed as a vapor–liquid mixture, the reflux ratio is low, and the feed stage guaranties a large rectification zone. On the other hand, a near-to-room temperature feed and a large reflux ratio favor the reuterin recovery at the second column (Table 3 and Figure 9). Total capital costs of columns 1 and 2 increase 3.9 and 4.9%, respectively, for the conditions explored in sensitivity analyses the tower representing 45–50% of the installed cost of the column. The column diameters calculated for the optimized conditions are about 0.7 m in both cases with maximum flooding factors always lower than 70%. Temperature, composition, and *K* (vapor-to-liquid) profiles for the optimized column 1 (Figure 10) are quite identical irrespective of the compound used to represent the reuterin product. Moreover, the recovery of the reuterin in the bottom product is 100% for any of the compounds with the exception of the monomer, which yields slightly lower recovery (95.0%) due to its higher volatility (Figure 10). However, the complete recovery of the monomer in the first column is guaranteed when its molar reflux ratio is increased to ~0.12, preserving the remainder conditions unchanged. Molar concentration of reuterin in the feed mixture to column 2 is ~0.9 M increasing to ~9.8 M at the bottom of the column. For these concentrations, the predominant molecular forms of the reuterin are the hydrate and the dimer[51] representing more than 85.0 mol % of the total amount of the reuterin product. Temperature, composition, and *K* (vapor-to-liquid) profiles for the optimized column 2 (Figure 11) show moderate differences depending on the (pseudo)compound used for representing the reuterin product but achieving anyway the process goal. The more complex scenario for column 2 consists of an equilibrium mixture for reuterin product where its three individual molecular forms coexist. This mixture could be represented, for instance, by molar ratios monomer:hydrate:dimer 15:20:65[51] (considering an overall reuterin molar fraction 0.1). The composition profile obtained in this case for the optimized column 2 (Figure 12) demonstrates that multiple conceptual solutions are possible to obtain a reuterin product with the design specifications previously established. It is

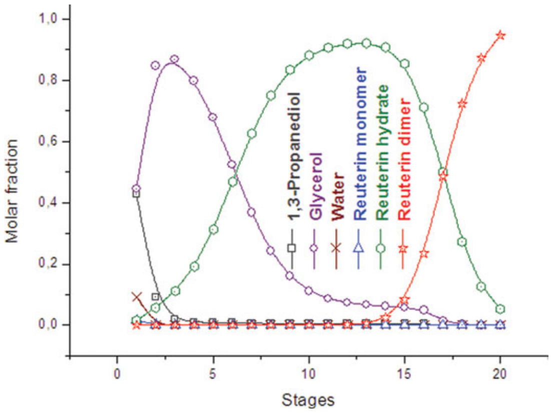


Figure 12. Composition profile for the optimized column 2 taking the reuterin product as a mixture of its individual molecular forms.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

noticeable that the major components of the reuterin mixture (hydrate and dimer) can be easily drawn by the lower part of the column.

The total capital cost estimated for the designed process (Figure 7) is ~5.3 millions USD, representing the total installed cost of the equipments the 21.5% of this capital. The columns represent ~85.0% of the total installed cost of the equipments. The energy balance of the overall process (Figure 7) suggests that heating requirements of the feed stream to column 1 can be satisfied whether the water vapor generated by the own column is used as preheating fluid. This can be attained if condenser pressure is slightly superior to atmospheric (1.2 bar, for example). This alternative reduces the total utilities cost 58.0% with respect to the base case where the preheating of the feed broth is guaranteed by auxiliary vapor service. In the alternative case shown in Figure 7, the water removing consumes ~71.6% of the total utilities cost as medium–high pressure vapor to feed the column reboiler. Consequently, combining distillation with other techniques to eliminate water could substantially reduce the operating costs of the process. Moreover, medium pressure steam could also be obtained even preserving the thermal integrity of the desired product if condenser pressure of the first column is further increased up to 15 bar.

Concluding Remarks

The conceptual design of a process to separate and purify reuterin from its mixture with glycerol, 1,3-propanediol, and water is developed. For this, the structural information of the individual molecules derived from quantum chemical calculations and COSMO-based methods is adequately integrated to process simulators to gain access to all its simulation, design, sizing, and economic evaluation capabilities.

Reuterin, existing as three molecular forms in equilibrium, shows strong capabilities to form hydrogen bonds either in pure state or in the mixtures with the main components of the fermentation broth in which is obtained. This is correspondingly reflected in COSMO-based predictions of both the boiling temperatures and densities of the pure compounds and the VL properties of the mixture to be separated. COSMO-based methods probe their competence to adequately describe the main properties of the studied compounds and mixtures comparing the predicted properties with experimental data. Chemical similarity among all the compounds of the fermentation broth suggests that extractive techniques are not adequate to separate reuterin from the mixture and consequently puts attention to VL operations. Because of the relative high boiling temperatures respect to the remainder components of the mixture, it has been demonstrated the possibility of obtaining reuterin as the bottom product of a distillation sequence.

The process consists of two-stage distillation process, the first of which removes 99.9 mol % of the water and the second one separates reuterin as a 99.5 wt %-pure bottom product. Column 2 operates at low pressure (ca. 40 kPa) to avoid thermal decomposition of reuterin (over 280°C) and guaranties 99.9% recovery of the desired product. Specified separations and recoveries are met with 5- and 20-stages columns and reflux ratios 0.01 and 5.0, respectively. Columns diameters are ~0.7 m in both cases. Water removing offers different heat integration and energy-saving opportunities considering that condenser pressure of the first column can be increased to ~15 bar preserving the thermal integrity of the reuterin.

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