I&EC research
Industrial & Engineering Chemistry Research

Article

pubs.acs.org/IECR

Selection of Solvents with A-UNIFAC Applied to Detoxification of Aqueous Solutions

José A. Scilipoti,[†] Martín Cismondi,[†] Alfonsina E. Andreatta,[†,‡] and Esteban A. Brignole*,[§]

[†]IDTQ–Grupo Vinculado PLAPIQUI–CONICET-FCEFyN, Universidad Nacional de Córdoba, X5016GCA, Av. Vélez Sarsfield 1611, Córdoba, Argentina

[‡]Facultad Regional San Francisco, Universidad Tecnológica Nacional, Av. de la Universidad 501, 2400, San Francisco, Córdoba, Argentina

[§]PLAPIQUI, Universidad Nacional del Sur–CONICET, Camino la Carrindanga km 7. 8000 Bahía Blanca, Argentina

Ⓢ *Supporting Information*

ABSTRACT: In this work, a molecular design of solvents program based on A-UNIFAC, a revised UNIFAC model where specific association interactions are taken into account, is applied to the removal of organic chemicals found in wood hydrolysates that are toxic for the fermentation of saccharified aqueous solutions to produce ethanol. The fundamentals of computer aided molecular design are discussed as well as the characterization and feasibility rules for the synthesis of feasible molecules. The detoxification process is analyzed from the point of view of solvent selection for liquid extraction and the primary solvent properties; the solvent-environmental properties and other solvent constraints to be applied in the computer aided molecular design are presented.

1. INTRODUCTION

Traditional agricultural products, like corn, wheat, and vegetable oils, have been used as the first choice for the production of liquid fuels. However, in the long run, these are not a sustainable alternative because they conflict with the production of food. This is due to the constraints of arable land and to the low yield of biofuel per hectare. The second generation biofuels are based on the use of biomass, mainly from lignocellulosic sources, as the raw materials for the production of biofuels and for the chemical and paper industry. Lignocellulosic resources have the potential of covering a significant fraction of the demand of liquid fuels for the transportation sector, without competing with food production.

Among the renewable fuels ethanol production and demand are growing strongly; therefore, the production of ethanol from lignocellulosic material is of great interest. The production of ethanol from biomass consists of several steps: feedstock pretreatment, production of hydrolysates, saccharification, fermentation, and ethanol recovery and dehydration.[1] Lignocellulosic derived sugar solutions contain also compounds derived from hemicellulose and lignin degradation. However, fermentation of cellulosic hydrolysates is hindered by compounds that have inhibitory effects on the fermentation process. These toxic compounds come mainly from the degradation of lignin and have to be removed to increase the fermentation yield. The selection of the separation technology for the detoxification process is a key decision, considering that this process step takes about 20% of the ethanol production cost.[2]

Liquid extraction is a feasible alternative for the detoxification process. In this separation problem the valuable product is the raffinate and not the extract. The extract will be a mixture of oxygenated paraffinic and aromatic compounds coming mainly from the degradation of lignin and hemicellulose. The solvent selection is complicated by the large number and variety of compounds that have to be removed and for the need of recovering the solvent from these products and from the raffinate. A large variety of solutes are critical for the detoxification process. Among other components, vanillin, acetic acid, levulinic acid, and 4-hydroxic benzoic acid were found to have inhibitory effects on the fermentation process.[2] The selection of a solvent for the detoxification of hydrolysates will be addressed in the present work by using a computer aided molecular design of solvents approach. In the present work the molecular design is based on a revised UNIFAC model where specific association interactions are taken into account.

2. COMPUTER AIDED MOLECULAR DESIGN

Since the early work of Gani and Brignole[3] on computer aided molecular design of solvents, the field of computer aided solvent and product design has been a very active area of research and development. A thorough review of the subject is beyond the scope of this work, and the interested reader is referred to recent books or reviews on the subject.[4,5] The molecular design of solvents has its origin in the backward or inverse solvent selection problem, formulated as follows: "giving a set of property constraints and certain performance indexes, generate chemical structures with the desired set of physico-chemical and environmental properties". The building blocks for the synthesis of molecular structures are the functional fragments of group contribution methods. In the present work the functional groups are those of the UNIFAC

Special Issue: Jaime Cerdá Festschrift

Received: February 1, 2014
Revised: June 19, 2014
Accepted: July 23, 2014
Published: July 23, 2014

dx.doi.org/10.1021/ie500469f | *Ind. Eng. Chem. Res.* 2014, 53, 17051−17058

model for activity coefficients prediction[6,7] and the primary solvent properties: selectivity, solvent power, distribution coefficient, solvent loss, and relative volatility are predicted on the basis of UNIFAC groups. Correlations also based on UNIFAC groups have been developed to predict other physical properties like boiling point, density, and viscosity.[8]

2.1. Computer Aided Synthesis. For the computer aided generation and evaluation of molecular structures, a combinatorial-partition strategy was proposed by Brignole et al.[9] In this procedure linear molecules were built by using dual valence groups and were terminated by different combinations of single valence groups. Several molecular design procedures based on explicit optimization algorithms have also been proposed. Applications have been reported for the design of polymers,[10] refrigerants,[11,12] solvents,[13−16] etc. In many of the molecular synthesis approaches the stability or feasibility of the generated molecules, other than keeping the chemical neutrality (no free valences) is not taken into account. Pretel et al.[13] proposed chemical feasibility rules based on the electronegativity of the atoms of a given group. Later a revision of these feasibility rules was proposed by Cismondi and Brignole[17] for the synthesis of linear and branched chemical compounds. Two basic types of group valences were identified in aliphatic compounds: J (neutral) and K (electronegative). The methyl group ($-CH_3$), even though it is a J type group (CH_i), is identified as type M because of the different role it plays in the feasibility criteria analysis, with respect to the other J groups. The criteria to be satisfied for group combination in the molecular synthesis is a group valence of type K can be attached only to J or M groups in the synthesis process. On this basis a new combination characterization of the UNIFAC groups was made.[17] This characterization takes into account not only the group free valences but also the nature of the internal balances. In Table 1 some examples of the combination properties of UNIFAC groups are presented. A complete list of the combination properties of UNIFAC groups is given as Supporting Information.

Table 1. Group Characterization and Combination Properties[17]

UNIFAC group example	group valence	decomposed in subgroups	combination properties
CH_2Cl	1	$J_2 + K_1$	(K,1)(J,2)
CHCl	2	$J_3 + K_1$	(K,1)(J,3)
CCl	3	$J_4 + K_1$	(K,1)(J,4)
CH_2CO	2	$J_2 + K_2$	(K,2)(J,2)
CHNH	3	$J_3 + K_2$	(K,2)(J,3)
CH_2N	3	$J_2 + K_3$	(K,3)(J,2)

2.2. Chemical Feasibility. The "chemical" feasibility criteria are established to guarantee the following molecular attributes: (1) chemical stability, (2) avoid the generation of new functional groups, (3) avoid functional group proximity, and (4) preserve chemical neutrality. Using the new group characterization the main rule to comply with the above criteria is *Considering that there are only pure "K" and "J" groups, the synthesis concept that resumes the above combination rules is each J group cannot be attached to more than one K group*. And this concept leads to the fact that the building of feasible molecules requires the existence of a $J-J$ type bond for each K group incorporated into the molecule (after the first one, for not cyclic structures).[17] From this general criterion the rules listed in Table 2 are derived. The procedure for molecular design follows the algorithm proposed by Cismondi and Brignole.[17]

Table 2. Feasibility Criteria for Linear and Cyclic Branched Structures[17]

	$K \leq NJF$	$K > NJF$
noncyclic structures	$K \leq J$	$2K \leq J + NJF$
cyclic structures	$K \leq J$	$2K \leq J + NJF$
$J = 0$		$K \leq 1$

3. COMPUTER AIDED MOLECULAR DESIGN WITH A-UNIFAC

Mengarelli et al.[18] introduced an associating term to the UNIFAC model in addition to the combinatorial and residual contributions of UNIFAC. This contribution is based on the Wertheim's statistical association fluid theory (SAFT)[19−22] and uses the group contribution approach of the associating term proposed by Zabaloy et al.[23] and Gros et al.[24] for the group contribution with association equation of state (GCA-EOS). In the Wertheim theory the association interaction is determined by the number of bonding sites assigned to each associating molecule. Similarly in a group contribution model the number of bonding sites in each functional group of the molecules determine the way the molecules interact (see the Appendix).

The search of solvents for the detoxification of lignocellulosic hydrolysates requires a thermodynamic model that takes into account association effects. This is due to the fact that many toxic compounds present associating groups; therefore the A-UNIFAC model is more reliable to obtain estimates of the primary solvent properties: distribution coefficients, solvent loss, selectivity as well as the pure component solvent properties.[25] Therefore, a revision of the molecular design of solvents algorithm is needed to deal with associating and non associating groups in the synthesis of solvents procedure. The main task of the new algorithm is to identify in an automatic way the type of interactions that will take place between the functional groups of the molecules in the heavy or light phase solution mixtures.

3.1. Characterization of Association Sites. In the A-UNIFAC model the first task is to identify the association types and sites in a given molecule or functional group and the determination of the interaction parameters between associating groups. Ferreira et al.[26] define four types of associating groups with their specific association sites to apply the model to mixtures of alcohols, water, carboxylic acids, esters, aromatic hydrocarbons, and alkanes.

A carboxylic group (COOH) has a single associating site that can self-and cross-associate.

A hydroxyl group (OH) has two associating sites: one electropositive and the other electronegative.

An ester group (COO) has a single associating electronegative site that cannot self-associate but can cross-associate.

An aromatic ring group (A_{ring}) has a electronegative site that cannot self-associate but can cross-associate with electropositive sites.

The UNIFAC model has other associating groups, which have not been parametrized at this moment such as amine, ketone, aldehyde, etc.

With the aim of implementing previous definitions in the context of solvent molecular design, three different types of sites were identified and characterized:

I Positive/Negative (±): characteristic of group COOH. This site is able to associate with the other two sites II and III and exhibit self-association.

II Negative (−): cannot self-associate. It can associate with the other two sites: I and III.

III Positive (+): cannot self-associate. It can associate with the other two sites: I and II.

Table 3 summarizes the associating groups identified and characterized in the present work.

Table 3. Characterization of Associating Groups

group	number of sites	type of association site
COOH	1	I
OH	2	II–III
H_2O	2	II–III
COOR	1	II
A_{ring}	1	II

3.2. Algorithm for the Associating Contribution Calculation.

3.2. Algorithm for the Associating Contribution Calculation. Examining eq 7 in the Appendix, we can see that the main difficulty for the automatic calculation of the associating contribution is found in the construction of the matrix of association strengths, for which it is necessary to prepare the matrixes of the groups association energy and volume parameters. The algorithm must first identify those groups capable of associating, its associative sites, and, then, the type of association between them. Identification of associating groups, and their association sites, is carried out as described in the previous section, through the analysis of all the groups that compose each component in the mixture and recognizing which are able to associate with the groups listed in Table 3. Characterization of the association sites of each group determines the interactions between them and the association energy and volume parameters arrays. For this purpose the algorithm examines all possible interactions and determines, based on the following three conditions, whether there is interaction between site A of group k and site B of group j:

- If site A is of type I or site B is of type I, $\varepsilon^{A_kB_j} \neq 0$ and $\kappa^{A_kB_j} \neq 0$.
- If sites A and B are not the same type, $\varepsilon^{A_kB_j} \neq 0$ and $\kappa^{A_kB_j} \neq 0$.
- If sites A and B are the same type and different from type I, $\varepsilon^{A_kB_j} = 0$ and $\kappa^{A_kB_j} = 0$.

Since the associative site of the type I can both self-associate and cross-associate with either of the other two types of sites, the association parameters will always be nonzero when such site is present. Furthermore, according to the sites characterization and their ability to associate, sites of different types always can associate and therefore their association parameter will be nonzero. Only when both sites are of the same type (except the type I site) will the association parameters will be zero. Figure 1 shows a flowchart summarizing what is explained here.

For example, in a mixture with a paraffinic acid and water, the associative groups are COOH (1) and H_2O (2) with the following association energy and volume matrix:

$$\chi^{(l,k,m,n)} = \begin{bmatrix} \chi^{(1,1,1,1)} & \chi^{(1,2,1,1)} & \chi^{(2,1,1,1)} & \chi^{(2,2,1,1)} \\ \chi^{(1,1,1,2)} & \chi^{(1,2,1,2)} & \chi^{(2,1,1,2)} & \chi^{(2,2,1,2)} \\ \chi^{(1,1,2,1)} & \chi^{(1,2,2,1)} & \chi^{(2,1,2,1)} & \chi^{(2,2,2,1)} \\ \chi^{(1,1,2,2)} & \chi^{(1,2,2,2)} & \chi^{(2,1,2,2)} & \chi^{(2,2,2,2)} \end{bmatrix}$$

$$= \begin{bmatrix} \neq 0 & \neq 0 & - & \neq 0 \\ \neq 0 & =0 & - & \neq 0 \\ - & - & - & - \\ \neq 0 & \neq 0 & - & =0 \end{bmatrix}$$

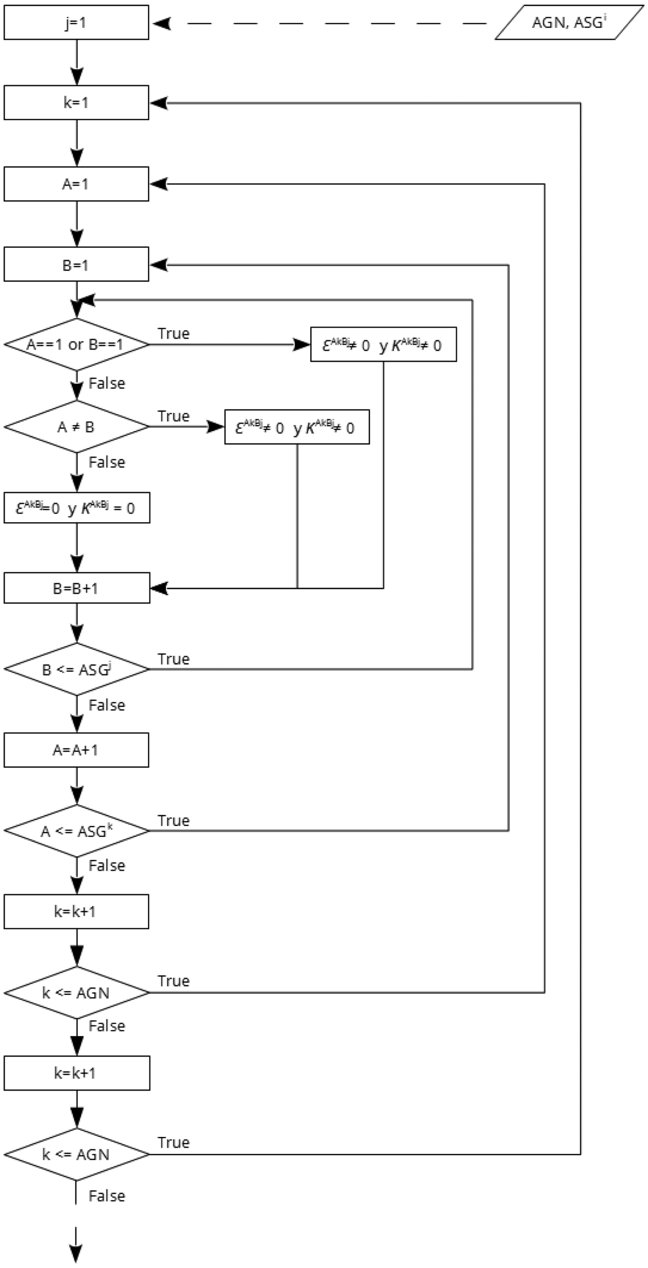

Figure 1. Algorithm for the associative contribution calculation. AGN and ASG^i are input variables. AGN = number of associative groups; ASG^i = number of sites in each associative group, with $i = k$ or j.

where χ represents ε and κ. The positions [2,2] and [4,4] are the interactions between the same sites of group 2, which are type II and III, they do not self-associate, and their association energy and volume are equal to zero. There is no element in the third row and column because group I just has one associative site. From ε and κ matrixes, eq 6 allows the calculation of the association strength matrix.

4. SOLVENT SELECTION IN AQUEOUS SOLUTION DETOXIFICATION PROCESSES WITH ECOFAS

4.1. Detoxification Separation Problem. Lignocellulosic hydrolysates are dilute aqueous sugars solution accompanied by other compounds derived mainly from the decomposition of lignin. The detoxification of hydrolysates by liquid extraction differs from a typical extraction problem in many ways.

The number of compounds to be extracted is very large,[27] the extracted products are of secondary interest, and the main product is a purified raffinate. From hemicellulose degradation are obtained furfural derivatives and levulinic acid, acetic, and formic acid. Phenolic compounds, like vanillic acid and vanillin, are generated from partial breakdown of lignin. Other compounds are hydroxybenzoic acids, polyphenols, etc. The solvents should exhibit the classical primary solvent properties and meet additional physical constraints. The solvent should be recovered from the extract in the distillate and also easily stripped from the raffinate aqueous phase. The main families of fermentation inhibitors are aliphatic acids, furanyl derivatives and phenolic compounds (vanillin, phenol, p-hydroxybenzoic acid, etc.). Also the fermentation inhibitors can be classified in two types: volatile and not volatile organic chemicals, the former can be removed by steam stripping previous to liquid extraction. All these properties can be predicted by group contribution methods on the basis of activity coefficients at infinite dilution predictions. A detoxification by liquid extraction process scheme is given in Figure 2. In this figure key solvent properties for each separation unit are shown. Table 4 indicates how primary solvent properties (mass basis) are estimated.

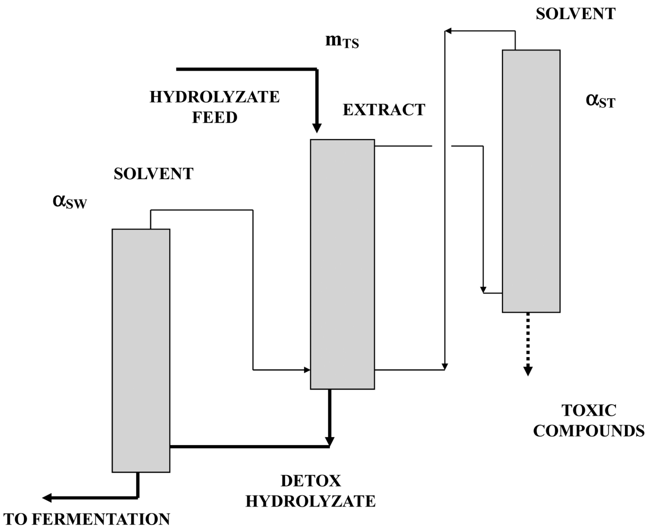

Figure 2. Process scheme for hydrolysate detoxification by solvent extraction: ($\mathbf{m_{TS}}$) toxic compound distribution coefficient, ($\boldsymbol{\alpha}_{\mathbf{ST}}$) solvent/toxic relative volatility, ($\boldsymbol{\alpha}_{\mathbf{SW}}$) solvent/water relative volatility.

A suitable solvent for detoxification should have high relative volatility with respect to water, moderate solvent loss, and relatively low molecular weight with respect to the extracted product. These constraints reduce the number of solvent candidates for this separation. However, the number of compounds to be extracted is quite large considering the products derived from the decomposition of lignin and hemicellulose. This feature allows a different formulation of the solvent evaluation problem: "given a particular solvent, evaluate the solvent performance for the removal of solutes that can be synthesized from a set of selected groups that are present in toxic hydrolysates compounds".

4.2. Solvent Selection for the Detoxification Problem.

In the present work the computer aided molecular design (CAMD) of solvents is carried out with an upgraded program of MOLDES[17] where the automatic calculation of the associating contributions using the A-UNIFAC thermodynamic model has been added. This program is called ECOFAS because it is applied to the separation problems involved in the biofuel production from lignocellulosic biomass and the computation of environmental properties, like the octanol–water partition coefficients and VOCs solubilities in water. The results obtained are compared with UNIFAC, the model implemented in the MOLDES program to calculate phase equilibrium properties in molecular design of solvents.

Table 4. UNIFAC and A-UNIFAC Evaluation of Primary Solvent Properties for Detoxification by Liquid Extraction

property (mass basis)	estimate
solvent selectivity	$\beta = \dfrac{\gamma^{\infty}_{B,S}\mathrm{MW}_A}{\gamma^{\infty}_{A,S}\mathrm{MW}_B}$
solute distribution coefficient	$m = \dfrac{\gamma^{\infty}_{A,B}}{\gamma^{\infty}_{A,S}}\dfrac{\mathrm{MW}_B}{\mathrm{MW}_S}$
solvent lost	$\mathrm{Sl} = \dfrac{1}{\gamma^{\infty}_{S,B}}\dfrac{\mathrm{MW}_S}{\mathrm{MW}_B}$
solvent power	$\mathrm{Sp} = \dfrac{1}{\gamma^{\infty}_{A,S}}\dfrac{\mathrm{MW}_A}{\mathrm{MW}_S}$
relative volatility solvent/water	$\alpha_{S,B} = \gamma^{\infty}_{S,B}\dfrac{P^S_S}{P^S_B}$
relative volatility solvent/solute	$\alpha_{S,A} = \gamma^{\infty}_{S,A}\dfrac{P^S_S}{P^S_A}$

Examining the types of fermentation inhibitory compounds, generally presented in hydrolyzed lignocelluloses,[27] a wide variety of groups can be found with the capability of association.

ECOFAS calculates the primary solvent properties from activity coefficients at infinite dilution calculated with the UNIFAC or A-UNIFAC model, according to Table 4. The A-UNIFAC model predictions are based on the revised and extended original UNIFAC VLE parameter tables.[28−32] In the case of associating groups the revised VLE parameters reported by Mengarelli et al.[18] and Ferreira et al.[26] were used. The toxic compounds to be removed are assumed to be in a dilute aqueous solution. The concentration of sugars in the hydrolysates is less than 10 wt % that is approximately a 0.011 glucose molar solution. The thermodynamic properties of sugars in aqueous and alcohol solutions were studied by Ferreira et al.[33] From this work it is possible to predict the effect of this level of glucose concentration on the solvent extraction properties. Table 5 shows the liquid–liquid equilibria predictions with A-UNIFAC of the binary system *n*-pentanol–water and ternary system of *n*-pentanol–water–glucose. From these results we can see that the activity coefficients of water in both phases are only slightly modified by the presence of glucose. In the case of *n*-pentanol, a low solubility in water (solvent loss), is predicted in both cases. On the basis of these results and the low molar concentration of sugar in the hydrolysates water solution, the effect of sugar is neglected in the calculation of the process separation variables during the computer aided molecular evaluation of solvents.

5. RESULTS

5.1. Extraction of Vanillin by Computer Aided Molecular Design.

A typical solvent design result is given in Table 6, where a solvent search is made for the removal of vanillin from an aqueous solution, allowing up to 10% of solvent loss, selectivity greater than 4 and distribution coefficient higher

Table 5. Liquid−Liquid Equilibria at 298 K of the Binary *n*-Pentanol−Water and *n*-Pentanol−Water−Glucose Predicted by A-UNIFAC

n-Pentanol (1)−Water (2)			
n-pentanol rich phase		water rich phase	
x_1	x_2	x_1	x_2
0.740	0.260	0.003	0.997
γ_1	γ_2	γ_1	γ_2
1.049	3.596	197.945	1.000

n-Pentanol (1)−Water (2)−Glucose (3)					
n-pentanol rich phase			water rich phase		
x_1	x_2	x_3	x_1	x_2	x_3
0.704	0.295	0.001	0.014	0.971	0.015
γ_1	γ_2	γ_3	γ_1	γ_2	γ_3
1.070	3.414	8.190	94.980	1.007	0.227

Table 6. Case of Solvent Design: Separation of Vanillin from Aqueous Solution

component to be recovered	$(ACH)_3$ $(AC)_2$ $(ACOH)_1$ $(CHO)_1$ $(CH_3O)_1$
boiling point (K)	558
groups participating in the synthesis:	(CH_2), $(CH{=}CH)$, (CH_2CO), (CH_2COO), (CH_2O), (FCH_2O), (CH_3), (OH), (CHO)

name	B.P. (K)	selectivity	solvent loss (%)	distribution coefficient
1-butanol	390.8	18.74	8.60	10.31
valeraldehyde	376.1	17.13	6.40	7.47
1-pentanol	410.9	17.86	3.90	7.26
1-hexanol	430.1	16.97	1.70	5.34
1-hexanal	401.4	14.49	2.70	4.44
1-heptanol	449.4	16.14	0.72	4.06
1-octanol	468.4	15.38	0.30	3.18
ethyl acetate	343.4	17.45	6.48	1.15
methylbutirate	375.9	8.10	1.80	0.88
Solvents with Two Functional Groups				
2-butoxyethanol	444.5	4.48	7.00	9.86
Heptanediol	539.0	11.76	6.24	6.82

than 0.4. The solvent behavior of normal alcohols is good for this separation; however, the use of n-butanol should be avoided due to the formation of an azeotropic mixture with water. The solvents are presented in decreasing order of distribution coefficient which is the chosen performance index. Among alcohols there is a trade-off between distribution coefficient and solvent loss: the larger the paraffinic chain the lower the solvent loss, but also the lower the distribution coefficient. Aldehydes should also be discarded due to chemical stability reasons. A reasonable solvent in this example seems to be *n*-pentanol because it has a reasonable value of the distribution coefficient, is a low boiling alcohol and can be easily stripped from the aqueous raffinate. Other solvent option is ethyl acetate. It has been reported that ethyl acetate is a good solvent for removal of toxic compounds present in the hydrolysates such as acetic acid, furfural, vanillinic acid and 4-hydroxybenzoic acid.[34,35] Based on these considerations, we choose 1-pentanol and ethyl acetate to assess their performances with an inverted strategy that is discussed in the next section. In addition, in this example potential solvents with two functional groups are also indicated. However, in this case, even though the distribution coefficients are attractive, their boiling points are too high for the solvent to be recovered in the extract distillate. In this example 10 groups were selected for the synthesis process, 1427 solvent structures were generated, and 239 solvents comply with the solvent requirements.

5.2. Inverted Strategy. The next example shows the results of using the inverted strategy discussed in section 4.1: "given a particular solvent, evaluate its solvent performance for the removal of solutes that can be synthesized from a set of selected groups that are present in toxic hydrolysates compounds". As it was already justified in the previous example, we choose 1-pentanol and ethyl acetate to compare their performance in the extraction of toxic compounds. Table 7 shows the evaluation of both solvents for the extraction of typical fermentation inhibitors that were synthesized by molecular design. In this table the UNIFAC and A-UNIFAC model results are compared in the computation of distribution coefficients and solvent losses.

Table 7. Two Inverted Strategies to Evaluate the Yield of Ethyl Acetate and 1-Pentanol As Solvents for the Detoxification Problem: Comparison of the Distribution Coefficients Obtained with UNIFAC and A-UNIFAC

groups participating in the synthesis: (CH_2), $(CH{=}CH)$, (CH_2CO), (CH_2COO), (CH_2O), (FCH_2O), (CH_3), (OH), (COOH), (CHO), (ACH), (AC), (ACOH)

	UNIFAC		A-UNIFAC	
solute	ethyl acetate (6.48)[a]	1-pentanol (3.88)[a]	ethyl acetate (6.22)[a]	1-pentanol (2.34)[a]
acetic acid	0.33	0.81	0.22	0.39
p-hydroxybenzoic acid	1.97	4.93	6.34	2.48
vanillic acid	1.15	1.98	13.43	2.13
3,4-dihydroxybenzoic acid	0.12	0.73	0.92	0.15
ferulic acid	10.81	10.34	29.92	28.21
methylpropanedioic acid	0.09	0.43	0.05	0.095
phenol	24.51	24.52	101.93	29.34

[a] Solvent loss (%).

There is a lack of experimental phase equilibrium data of mixtures from lignocellulosic biomass hydrolysates. The results of Table 7 can be compared with experimental data for the following ternary systems: water−acetic acid−ethyl acetate,[36] water−acetic acid−*n*-pentanol,[37] and water−phenol−ethyl acetate.[38] The partition coefficients based on these data are 1.73, 3.56, and 170.75, respectively. The predictions of ECOFAS are based on activity coefficient at infinite dilution in the different solvents and water, while the experimental data are measured at diluted but finite solute concentrations. It is important to remark that the distribution coefficients of solutes with association vary significantly with the concentration in the diluted area. Although the predictions should be confirmed by experimental data, we can see that ethyl acetate shows better solvent properties for the removal of toxic components than 1-pentanol. In accordance to these predictions, the liquid extraction with ethyl acetate improved the performance on fermentation of *P. stipites*,[37] since it would remove the 56% of acetic acid and the complete removal of furfural, vanillic acid and 4-hidroxybenzoic acid. Also, it has been reported that the extraction with ethyl acetate increases by a factor of 12 the rate of glucose consumption of hydrolysates from pine.[38] In another study 84% of phenolic compounds has been removed from the hydrolysis of woods of *Eucalyptus* after liquid extraction with ethyl acetate.[39] The low molecular weight phenolic compounds have been pointed out as the stronger fermentation inhibitors.[40]

5.3. Octanol−Water Partition Coefficient. The logarithm of the partition coefficient of a component in a mixture of octanol and water (log P_{ow}) is an indicator of the environmental impact of the compound. Also log P_{ow} is used as a general rule to select organic solvents from the biocompatibility point of view. In general, the solvents with log P_{ow} values higher than 4 are considered biocompatible.[41] Table 8 shows the ECOFAS predictions for the series of alkanes and alcohols studied by Zautsen et al.,[42] as possible solvents in the liquid extraction of inhibitor compounds during the fermentation process. In these examples, fermentation and extraction process are simultaneous, therefore the solvent must be biocompatible. Zautsen et al. have found an increase of the biocompatibility of these organic solvents when log P_{ow} increases (Figure 3).

Table 8. Values of log P_{ow} Estimated with UNIFAC and A-UNIFAC and Experimental Values

	log P_{ow}		
solvent	UNIFAC	A-UNIFAC	experimental
hexane	2.72	3.35	3.90
octane	3.59	4.42	4.27
decane	4.46	5.49	5.25
dodecane	5.33	6.56	6.10
tetradecane	6.20	7.64	7.20
hexadecane	7.07	8.71	8.20
pentanol	1.34	1.58	1.51
hexanol	1.78	2.12	1.82
octanol	2.65	3.19	2.82
decanol	3.52	4.26	4.57
oleyl alcohol	6.13	7.90	7.50
oleic acid	6.53	8.59	7.73

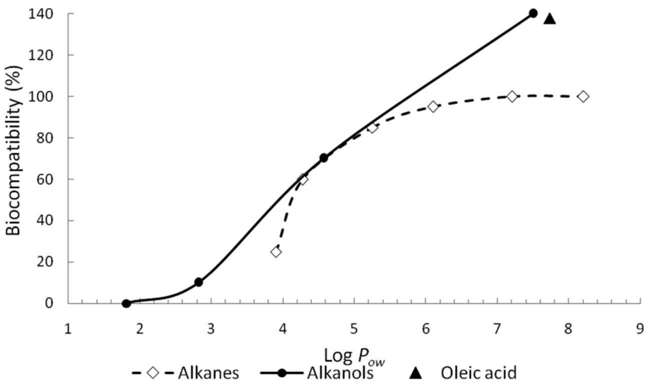

Figure 3. Biocompatibility of alkanes, alkanols, and oleic acid according to log P_{ow} values. (Adapted with permission from ref 42. Copyright 2009 John Wiley and Sons)

As mentioned above, the prediction of the log P_{ow} value is important because it provides information on partition coefficients of solutes between the raffinate and the extract phase and also gives information about biocompatibility of the solvent in bioprocesses as in the bioethanol production. The log P_{ow} values predicted by A-UNIFAC (Table 8) were closer to the experimental results than the UNIFAC values. This was to be expected due to the number of associative groups present in such mixtures. In Table 8 the log P_{ow} values for oleic alcohol and oleic acid are shown because these solvents display complete biocompatibility in the extraction process of ethanol.[43,44]

6. CONCLUSIONS

A new algorithm for molecular design of solvents, adapted also for application in biorefinery detoxification problems, has been presented in this work. The main modifications, compared to the previous MOLDES package, include the following: the implementation of the A-UNIFAC model for associating compounds, the option of evaluating solvents through an "inverse strategy" when there is a large number of solutes and just a few possible solvents, and the calculation of new properties of environmental interest.

The proposed inverted strategy was applied to a detoxification process where ethyl acetate and 1-pentanol are the possible solvents. The results show a better prediction of primary solvent properties with A-UNIFAC in comparison to UNIFAC, based on some experimental data available. From those predictions with A-UNIFAC it could be concluded that ethyl acetate would have a better performance than 1-pentanol in the extraction of toxic compounds. This is in agreement with recommendations found in the literature for the fermentation of lignocellulose hydrolysates. The values for the water−octanol partition coefficient also show higher accuracy when estimated from A-UNIFAC in comparison to UNIFAC.

■ APPENDIX

A-UNIFAC Model

The general expression for the association activity coefficient contribution is a function of the nonbonded fraction of the group k through the site l, in the solution $X^{(l,k)}$ and in pure component i $X_i^{(l,k)}$:

$$\ln \gamma^{\text{asoc}} = \sum_{k=1}^{\text{NGA}} \left\{ \nu_k^i \sum_{l=1}^{M_k} \left[\ln\left(\frac{X^{(l,k)}}{X_i^{(l,k)}}\right) + \frac{X_i^{(l,k)} - X^{(l,k)}}{2} \right] + \sum_{l=1}^{M_k} \left(\frac{1}{X^{(l,k)}} - \frac{1}{2}\right) n_k^* \left(\frac{\partial X^{(l,k)}}{\partial n_i}\right)_{T,P,n_j} \right\} \quad (1)$$

where n_k^* is the mole number of the associative group k, ν_k^i the number of groups of the group k in the component i. $X^{(l,k)}$ is a function of the associating group density function of the associating group n in the solution (ρ_n^*) and the association strength between site l of the group k and the site m of the group n ($\Delta^{(l,k,m,n)}$), and it has the following expression:

$$X^{(l,k)} = \left[1 + \sum_{n=1}^{\text{NGA}} \sum_{m=1}^{M_n} \rho_n^* X_i^{(m,n)} \Delta^{(l,k,m,n)}\right]^{-1} \quad (2)$$

In similar way, the nonbonded fraction of the group k through the site l in the pure component is

$$X_i^{l,k} = \left[1 + \sum_{n=1}^{\text{NGA}} \sum_{m=1}^{M_n} (\rho_n^*)_i X_i^{(m,n)} \Delta^{(l,k,m,n)}\right]^{-1} \quad (3)$$

The density of the associating group n in the mixture ρ_n^* and in the pure component $(\rho_n^*)_i$ are dimensionless and are calculated through the following expression:

$$\rho_n = \frac{\sum_{i=1}^{\text{NC}} \nu_n^i x_i}{\sum_{i=1}^{\text{NC}} r_i x_i} \quad (4)$$

and

$$(\rho_n)_i = \frac{\nu_n^i}{r_i} \quad (5)$$

Where x_i is the molar fraction of component i in the mixture, ν_n^i is the number of times associating group n is contained in molecule i, NC is the number of components in the mixture, and r_i the van der Waals volume of component i.

The association strength $\Delta^{(l,k,m,n)}$ is a function of the association energy $\varepsilon^{(l,k,m,n)}$ and the association volume ($\kappa^{(l,k,m,n)}$)

$$\Delta^{(l,k,m,n)} = \kappa^{(l,k,m,n)}\left[\exp\left(\frac{\varepsilon^{(l,k,m,n)}}{kT}\right) - 1\right] \tag{6}$$

The values of $\kappa^{(l,k,m,n)}$ and $\varepsilon^{(l,k,m,n)}$ are taken from the work of Ferreira et al.[26]

The computation of γ^{assoc} requires the calculation of the nonbonded fraction of associating groups and their partial derivates. With the minimization procedure reported by Michelsen and Hendriks,[45] this partial derivative is simplified and eq 1 is reduced to

$$\ln \gamma^{\text{asoc}} = \sum_{k=1}^{\text{NGA}} \left\{ \nu_k^i \sum_{l=1}^{M_k} \left[\ln\left(\frac{X^{(l,k)}}{X_i^{(l,k)}}\right) + \frac{X_i^{(l,k)} - 1}{2} \right] + r_i \rho_k \sum_{l=1}^{M_k} \left(\frac{1 - X_i^{(l,k)}}{2}\right) \right\} \tag{7}$$

This expression for the associating contribution of activity coefficient in the A-UNIFAC model will depend on the amount and type of associating sites and compounds present in the mixture.

Notation

J_i = number of J groups with i attachments
J = number of J groups, $J = \sum_i J_i$
K_i = number of K groups with i attachments
K = number of K groups, $K = \sum_i K_i$
$X^{(l,k)}$ = fraction of nonbonded sites in solution
$X_i^{(l,k)}$ = fraction of nonbonded sites in pure component i
γ = activity coefficient
Δ = association strength
ε = energy of association
κ = dimensionless volume of association
ν = number of groups in a molecule
ρ = dimensionless molar density
NGA = number of associating groups
NJF = number of J free attachments

■ ASSOCIATED CONTENT

Supporting Information

Table of UNIFAC groups with similar combination properties. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ebrignole@plapiqui.edu.ar.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank the Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina (CONICET) for financial support.

■ REFERENCES

(1) Huang, H.-J.; Ramaswamy, S.; Tschirner, U. W.; Ramarao, B. V. A Review of Separation Technologies in Current and Future Biorefineries. *Sep. Purif. Technol.* **2008**, *62*, 1.

(2) Sivers, M. Von; Zacchi, G.; Olsson, L.; Hahn-Hügerdal, B. Cost Analysis of Ethanol Production from Willow Using Recombinant Escherichia Coli. *Biotechnol. Prog.* **1994**, *10*, 555.

(3) Gani, R.; Brignole, E. A. Molecular Design of Solvents for Liquid Extraction Based on UNIFAC. *Fluid Phase Equilib.* **1983**, *13*, 331.

(4) Achenie, L.; Venkatasubramanian, V.; Gani, R. *Computer Aided Molecular Design: Theory and Practice*; Elsevier, 2002; Vol. *12*.

(5) Sherman, J.; Chin, B.; Huibers, P. D.; Garcia-Valls, R.; Hatton, T. A. Solvent Replacement for Green Processing. *Environ. Health Perspect.* **1998**, *106*, 253.

(6) Fredenslund, A.; Jones, R. L.; Prausnitz, J. M. Group-Contribution Estimation of Activity Coefficients in Nonideal Liquid Mixtures. *AIChE J.* **1975**, *21*, 1086.

(7) Fredenslund, A. *Vapor-Liquid Equilibria Using UNIFAC: A Group-Contribution Method*; Elsevier, 1977.

(8) Pretel, E. J.; Lopez, P. A.; Mengarelli, A.; Brignole, E. A. Prediction of physical properties for molecular design of solvents. *Latin American Applied Research* **1992**, *22*, 187−194.

(9) Brignole, E. A.; Bottini, S.; Gani, R. A Strategy for the Design and Selection of Solvents for Separation Processes. *Fluid Phase Equilib.* **1986**, *29*, 125.

(10) Venkatasubramanian, V.; Chan, K.; Caruthers, J. M. Computer-Aided Molecular Design Using Genetic Algorithms. *Comput. Chem. Eng.* **1994**, *18*, 833.

(11) Joback, K. G. Designing Molecules Possessing Desired Physical Property Values. Ph. D. Thesis, Massachusetts Institute of Technology, 1989.

(12) Churi, N.; Achenie, L. E. K. Novel Mathematical Programming Model for Computer Aided Molecular Design. *Ind. Eng. Chem. Res.* **1996**, *35*, 3788.

(13) Pretel, E. J.; López, P. A.; Bottini, S. B.; Brignole, E. A. Computer-Aided Molecular Design of Solvents for Separation Processes. *AIChE J.* **1994**, *40*, 1349.

(14) Gani, R.; Nielsen, B.; Fredenslund, A. A Group Contribution Approach to Computer-Aided Molecular Design. *AIChE J.* **1991**, *37*, 1318.

(15) Marcoulaki, E. C.; Kokossis, a. C. On the Development of Novel Chemicals Using a Systematic Optimisation Approach. Part II. Solvent Design. *Chem. Eng. Sci.* **2000**, *55*, 2547.

(16) Folić, M.; Adjiman, C. S.; Pistikopoulos, E. N. The Design of Solvents for Optimal Reaction Rates. *AIChE J.* **2004**, *53*, 1240−1256.

(17) Cismondi, M.; Brignole, E. A. Molecular Design of Solvents: An Efficient Search Algorithm for Branched Molecules. *Ind. Eng. Chem. Res.* **2004**, *43*, 784.

(18) Mengarelli, A. C.; Brignole, E. A.; Bottini, S. B. Activity Coefficients of Associating Mixtures by Group Contribution. *Fluid Phase Equilib.* **1999**, *163*, 195.

(19) Wertheim, M. Fluids with highly directional attractive forces. I. Statistical thermodynamics. *J. Statist. Phys.* **1984**, *35*, 19.

(20) Wertheim, M. Fluids with highly directional attractive forces. II. Thermodynamics perturbation theory and integral equations. *J. Statist. Phys.* **1984**, *35*, 35.

(21) Wertheim, M. Fluids with highly directional attractive forces. IV. Equilibrium polymerization. *J. Statist. Phys.* **1986**, *42*, 459.

(22) Wertheim, M. Fluids with highly directional attractive forces. III. Multiple attraction sites. *J. Statist. Phys.* **1986**, *42*, 477.

(23) Zabaloy, M. S.; Mabe, G. D. B.; Bottini, S. B.; Brignole, E. A. Vapor Liquid Equilibria in Ternary Mixtures of Water-Aloohol-Non Polar Gases. *Fluid Phase Equilib.* **1993**, *83*, 159.

(24) Gros, H. P.; Bottini, S.; Brignole, E. A. A Group Contribution Equation of State for Associating Mixtures. *Fluid Phase Equilib.* **1996**, *116*, 537.

(25) Scilipoti, J.; Cismondi, M.; Brignole, E. A. Prediction of Physical Properties for Molecular Design of Solvents. *Fluid Phase Equilib.* **2013**, *362*, 74.

(26) Ferreira, O.; Macedo, E. A.; Bottini, S. B. Extension of the A-UNIFAC Model to Mixtures of Cross-and Self-Associating Compounds. *Fluid Phase Equilib.* **2005**, *227*, 165.

(27) Luo, C.; Brink, D. L.; Blanch, H. W. Identification of Potential Fermentation Inhibitors in Conversion of Hybrid Poplar Hydrolyzate to Ethanol. *Biomass Bioenergy* **2002**, *22*, 125−138.

(28) Gmehling, J.; Rasmussen, P.; Fredenslund, A. Vapor-Liquid Equilibriums by UNIFAC Group Contribution. Revision and Extension. 2. *Ind. Eng. Chem. Process Des. Dev.* **1982**, *21*, 118.

(29) Macedo, E. A.; Weidlich, U.; Gmehling, J.; Rasmussen, P. Vapor-Liquid Equilibriums by UNIFAC Group Contribution. Revision and Extension. 3. *Ind. Eng. Chem. Process Des. Dev.* **1983**, *22*, 676.

(30) Tiegs, D.; Rasmussen, P.; Gmehling, J.; Fredenslund, A. Vapor-Liquid Equilibria by UNIFAC Group Contribution. 4. Revision and Extension. *Ind. Eng. Chem. Res.* **1987**, *26*, 159.

(31) Hansen, H. K.; Rasmussen, P.; Fredenslund, A.; Schiller, M.; Gmehling, J. Vapor-Liquid Equilibria by UNIFAC Group Contribution. 5. Revision and Extension. *Ind. Eng. Chem. Res.* **1991**, *30*, 2352.

(32) Wittig, R.; Lohmann, J.; Gmehling, J. Vapor-Liquid Equilibria by UNIFAC Group Contribution. 6. Revision and Extension. *Ind. Eng. Chem. Res.* **2003**, *42*, 183.

(33) Ferreira, O.; Brignole, E. A.; Macedo, E. A. Phase Equilibria in Sugar Solutions using the A-UNIFAC Model. *Ind. Eng. Chem. Res.* **2003**, *42*, 6212.

(34) Wilson, J. J.; Deschatelets, L.; Nishikawa, N. K. Comparative Fermentability of Enzymatic and Acid Hydrolysates of Steam-Pretreated Aspenwood Hemicellulose by Pichia Stipitis CBS 5776. *Appl. Microbiol. Biotechnol.* **1989**, *31*, 592.

(35) Palmqvist, E.; Hahn-Hägerdal, B. Fermentation of Lignocellulosic Hydrolysates. I: Inhibition and Detoxification. *Bioresour. Technol.* **2000**, *74*, 17.

(36) Colombo, A.; Battilana, P.; Ragaini, V.; Bianchi, C. L.; Carvoli, G. Liquid-Liquid Equilibria of the Ternary Systems Water + Acetic Acid + Ethyl Acetate and Water + Acetic Acid+ Isophorone (3, 5, 5-Trimethyl-2-Cyclohexen-1-One). *J. Chem. Eng. Data* **1999**, *44*, 35.

(37) Fahim, M. A.; Al-Muhtaseb, S. A.; Al-Nashef, I. M. Phase Equilibria of the Ternary System Water+ Acetic Acid+ 1-Pentanol. *J. Chem. Eng. Data* **1996**, *41*, 562.

(38) Alvarez Gonzalez, J. R.; Macedo, E. A.; Soares, M. E.; Medina, A. G. Liquid-Liquid Equilibria for Ternary Systems of Water-Phenol and Solvents: Data and Representation with Models. *Fluid Phase Equilib.* **1986**, *26*, 289.

(39) Clark, T. A.; Mackie, K. L. Fermentation Inhibitors in Wood Hydrolysates Derived from the Softwood Pinus Radiata. *J. Chem. Technol. Biotechnol. Biotechnol.* **1984**, *34*, 101.

(40) Cruz, J. M.; Domínguez, J. M.; Domínguez, H.; Parajó, J. C. Solvent Extraction of Hemicellulosic Wood Hydrolysates: A Procedure Useful for Obtaining Both Detoxified Fermentation Media and Polyphenols with Antioxidant Activity. *Food Chem.* **1999**, *67*, 147.

(41) Laane, C.; Boeren, S.; Vos, K.; Veeger, C. Rules for Optimization of Biocatalysis in Organic Solvents. *Biotechnol. Bioeng.* **1987**, *30*, 81.

(42) Zautsen, R. R. M.; Maugeri-Filho, F.; Vaz-Rossell, C. E.; Straathof, A. J. J.; Van Wielen, L.A. M.; de Bont, J. A. M. Liquid−liquid Extraction of Fermentation Inhibiting Compounds in Lignocellulose Hydrolysate. *Biotechnol. Bioeng.* **2009**, *102*, 1354.

(43) Daugulis, A. J.; Axford, D. B.; Ciszek, B.; Malinowski, J. J. Continuous Fermentation of High-Strength Glucose Feeds to Ethanol. *Biotechnol. Lett.* **1994**, *16*, 637.

(44) Jassal, D. S.; Zhang, Z.; Hill, G. A. In-situ Extraction and Purification of Ethanol Using Commercial Oleic Acid. *Can. J. Chem. Eng.* **1994**, *72*, 822.

(45) Michelsen, M. L.; Hendriks, E. M. Physical Properties from Association Models. *Fluid Phase Equilib.* **2001**, *180*, 165.