Chemical Product Centric Sustainable Process Design

Tutorial Document

By

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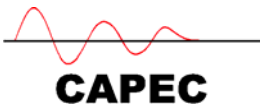

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Integrated Chemical Product Design – Tutorial document

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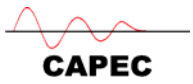
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1. Computer Aided Molecular Design

The objective of this section of the tutorial document is to present to the reader, a brief description of computer aided molecular design in terms of problem definition, methods of solution, and the issues and needs with respect to CAMD problem formulation and solution.

1. 1 CAMD PROBLEM DEFINITION

Computer aided molecular design (CAMD) problems are defined as

> *Given a set of building blocks and a specified set of target properties;*
> *Determine the molecule or molecular structure that matches these properties.*

In this respect, it is the reverse problem of property prediction where given the identity of the molecule and/or the molecular structure, a set of target properties is calculated. CAMD maybe performed at various levels of size and complexity of molecular structure representation. Most CAMD methods and tools used in PSE/CAPE applications, work at the macroscopic level where the molecular structure is represented by groups (Harper *et al*. 1999) and/or connectivity indices (Camarada and Maranas 1999). An evolutionary based CAMD method for design of fuel additives has been proposed by Sundaram *et al.* (2001). Figure 1 (from Harper *et al*. 1999) illustrates a typical group contribution based CAMD method, where the pre-design phase defines the *basic needs*, the design phase determines the feasible candidates (generates molecules and tests for desired properties) and the post-design phase performs higher level analysis of the molecular structure and the final selection of the product. The post-design phase may also address the question of manufacturing the designed product. CAMD methods based on macroscopic properties are suitable for design of relatively smaller molecules either as chemical products or as additives (or ingredients) for formulated products

For design of more complex and relatively larger molecules such as drugs, pesticides and specialty chemicals, molecular modelling based CAMD methods have been reported (Livingstone, 1995). Structure-based drug design has emerged as a valuable tool in medicinal chemistry where the integration of structure-based methods, virtual screening, and combinatorial chemistry is necessary. As the chemical product design involves molecules of larger size, distinction among isomers and or different molecular structures for the same chemical compound type become more important. Consequently, the molecular structural representation becomes more complex using smaller and smaller scales while the property prediction becomes more specialized.

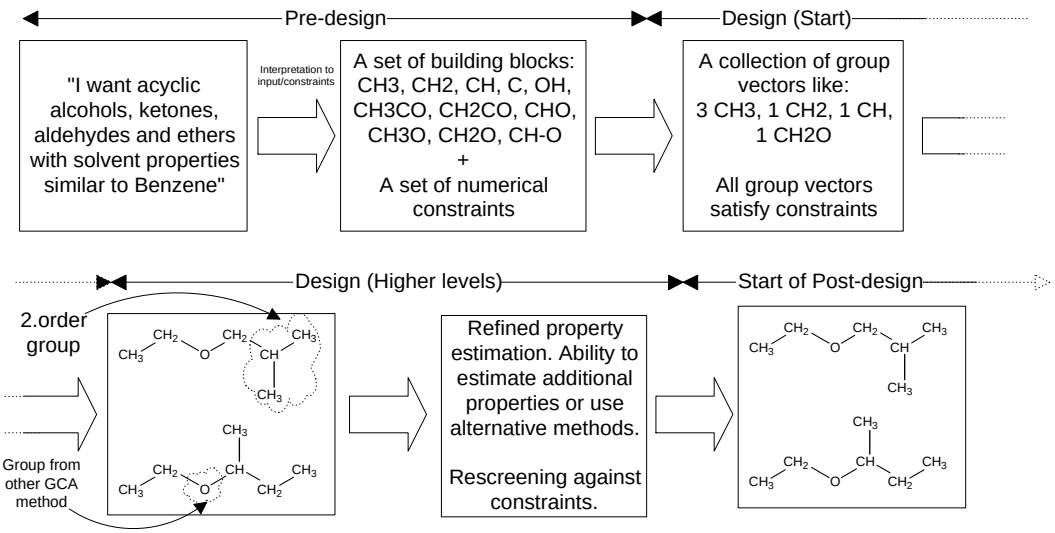


Figure 1: Basic steps of CAMD

1.2 METHODS OF SOLUTION

The main steps of any CAMD method are to generate chemically feasible molecular structures, to estimate the target properties for the generated structures and to screen/select those that satisfy the specified property constraints. Methods employing the generate & test approach (see Fig. 2) perform these steps sequentially, methods employing mathematical programming perform the steps simultaneously while hybrid methods decompose the problem into sub-problems and allow the use of different

solution approaches to the different sub-problems. In the text below, a few representative CAMD methods are discussed.

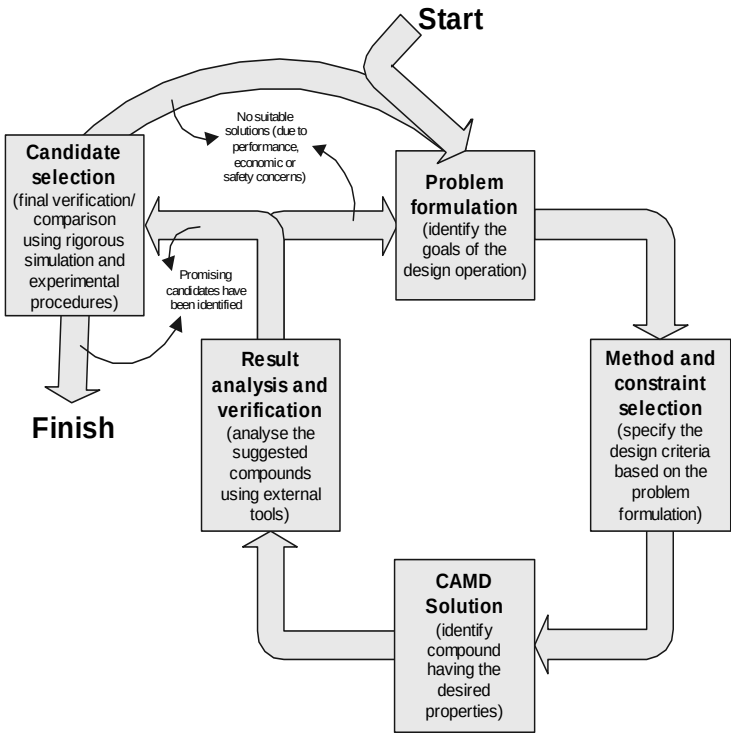


Figure 2: Multi-level hybrid CAMD method of solution

Cabezas *et al*. (2000) developed a database approach with interactive search for the appropriate solvent where the main tools needed are properties databases, target property estimation systems and a knowledge-based system for guiding the user through the solvent selection and screening steps. Note that because it is based on a search of the database, it therefore does not need to generate molecular structures. Harper and Gani (2000) proposed a multi-step, multi-level hybrid CAMD method that combines group contribution approach at a lower level and a molecular modelling approach at a higher level (see Fig. 3). At the lower levels, however, group contributions include first-order as well as second-order groups that are able to represent the molecular structural differences of some isomers.

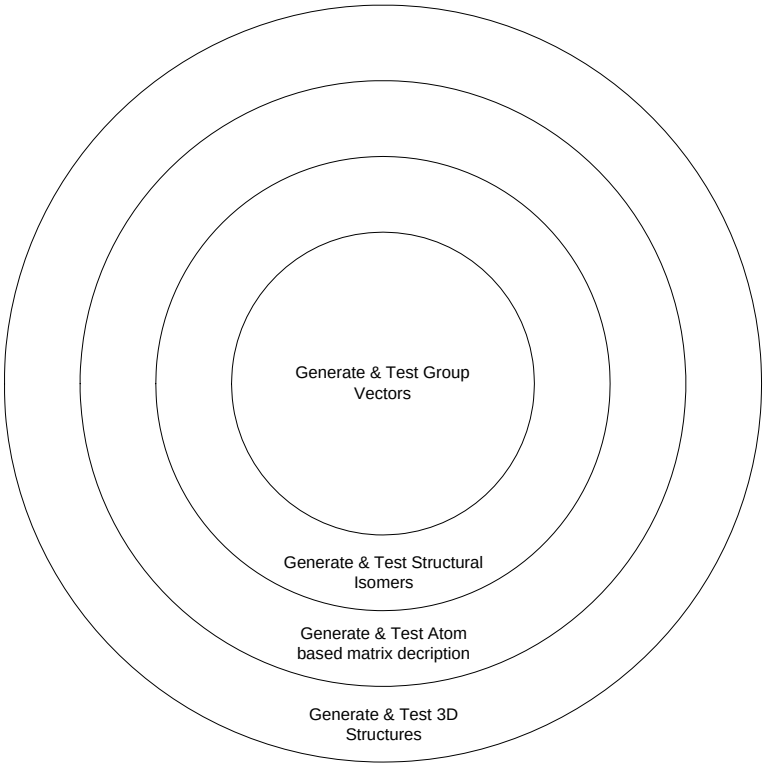


Figure 3: Multi-step and multi-level hybrid CAMD method

Venkatasubramanian *et al*. (1995) proposed the use of genetic algorithms with groups as the building blocks for polymer design. Camarada and Maranas (1999) and Duvedi and Achenie (1996) proposed the use of optimisation techniques to determine the optimal molecule with Camarada and Maranas employing connectivity indices while Duvedi and Achenie employing groups, respectively, for molecular structure representations. The problems solved with these methods all refer to small (solvent) molecules, although, repeat units of polymers, refrigerants and process fluids have also been designed through these methods.

QSAR based CAMD methods have been developed for design of large molecules. Sippl *et al*. (2001) recently described the construction, validation and application of a structure-based 3D QSAR model of novel acetylcholinesterase inhibitors. A generate and test approach was employed, where the target was a desired inhibitor activity (a macroscopic property) but the molecular structure that provides the desired target is obtained through study of binding conformation of protein-inhibitor complexes. Methods employing

optimization techniques related to complex molecule design have also been reported, for example, by Moore *et al*. (2000), who developed a predictive model for DNA recombination for the generation of novel enzymes. Klepeis and Floudas (2000) employed a combination of molecular dynamics and advanced mathematical techniques to protein structure prediction. Other examples of combination of higher-level modeling and molecular design can be found in the papers published in the Journal of Computer Aided Molecular Design.

1.2.1 Hybrid CAMD Method of Solution

The solution of all CAMD problems could be divided into the following four main steps.

Step 1: Problem Formulation – here, the CAMD problem is defined in terms of target properties (both the identity of the property as well as their target values).

Step 2: Initial Search - generate initial list of candidates through a search of a database (if available, for example, CAPEC database). This provides a good idea of which types of molecules one should be looking for. Note that the search should be made only with respect to the pure component target properties as a search with respect to mixture properties may not be possible.

Step 3: Generate and Test - use any CAMD technique (and software, for example, ProCAMD) to automatically generate and test candidates. The selected CAMD technique should be able to generate molecular structures and evaluate their properties with respect to the specified target properties.

Step 4: Verification – here, the selected candidates are further analyzed in terms of their performance when they are applied for their designed use. Models capable of simulating their performance in their process of application are needed. These models may be process simulation models (for example, ICASSIM or ICAS-utility) as well as product application models (such as delivery of an active ingredient).

1.3 ISSUES & NEEDS

Problem Definition: Identifying the needs of the chemical product through a set of target properties is a very important first step for all CAMD methods. Hostrup *et al.* (1999) include this as a pre-design step and propose the use of a knowledge-based system to guide the user in identifying the target properties as well as selecting the corresponding property values. Their examples, however, cover only solvent selection/design problems. Therefore, there is a need to develop knowledge based systems that may guide the chemical product designer to not only identify the target properties but also to specify their target (goal) values for a large range of chemical product design problems. The selection of target properties should also be closely linked with what can be estimated (and therefore, computed) and what must be measured? The knowledge-based system can help to reduce the number of experiments or to focus on a few specialized measurements from which a number of other target properties may be estimated. For example, if the solvent molecule type for a complex (large multifunctional molecule) solute can be identified, then experiments to measure solubility can be concentrated on some representatives of the identified molecular type to generate not only the unavailable property model parameters but also to identify the desired solvent. Note that because of the complex molecular structure of the solute, it is unlikely that the needed property model parameters would be available at the start of the problem solution.

1.3.1 CAMD Methods & Tools

Assuming that the target properties have been identified and their goal values have been specified, the main issues with all types of CAMD methods are the following:

- How to generate molecular structures?
- How to represent the molecular structure?
- What level of molecular structural information will be used?
- How the target properties will be obtained (calculated and/or measured)?

The complexity of the problem may be understood from the numbers of isomers that can be generated as a function of carbon number. As the carbon numbers for each molecular type increase, so does the number of possible isomers. So, to address the questions above, one needs to consider very carefully, the molecular structural parameters that would be used to represent the molecules. These same parameters will also need to be used for estimating the target properties. It can be noted that most group contribution based methods design small molecules and therefore, do not need to handle too many isomers. However, unless the groups are able to distinguish between isomeric structures, these methods would not be able to consider them. Also, since in this case, many different types of molecules are investigated, the number of candidates may still be quite large. The design of large complex molecules, on the other hand, mainly depends on differences in molecular structures of isomers or of molecular conformations of a particular molecular type. Therefore, in this case, molecular structures are represented at the mesoscopic and/or microscopic level and property estimation methods that use these variables are needed. In this case also, the number of candidates is very large because there may be too many isomers.

The corresponding needs for a CAMD method are the following:

- A tool for molecular structure representation at different scales.
- A tool for molecular structure generation (based on a set of rules that will ensure the generation of feasible chemical structures).
- Tools for analyzing molecular structural stability.
- Tools for target property estimation.
    - A tool for property estimation method selection (including identifying which properties can be estimated for which database and/or experimental techniques need to be used).
    - A library of property estimation models (methods and tools) that are particularly suitable for computer aided applications.

- A method of solution for the CAMD problem (the two inner steps of the design process).

Since it appears that multiple property models at different scales or levels of molecular structural variables will need to be considered if the isomers and/or multiple conformations are also going to be considered, a communication (link) between lower level modelling tools and higher levelling model tools also need to be established. Harper and Gani (2000) established such a link for their hybrid CAMD method. The idea is to first establish the molecular type in the search/design through macroscopic properties and then to link the promising candidates to higher-level mesoscopic or microscopic methods for more detailed analysis. One starts with a molecular description at the group level, which is then converted to a 2-dimensional atomic representation at the atomic level. This is then passed to molecular modelling software that converts the atomic representation to a 3-dimensional model, which is then optimized to obtain the final 3-dimensional structure. Once the optimized structure has been obtained, a whole range of *descriptors* and properties may be estimated.

1.3.2 Property Models

The application range of the property model is directly related to the application range of the CAMD method since every property model has its limits of application range. Selecting the property model, therefore, implicitly defines the search space and therefore, there is a need to develop property models that can be used reliably outside its boundary of application range (at least for some additional region).

Target properties usually include pure component as well as mixture properties and the selection of the property estimation model(s) raises other issues & needs, for example, uncertainties in property estimations, availability of model parameters and size of the search space. Maranas (1997) has incorporated the uncertainty of property estimation methods within the CAMD problem definition. Another difficulty is associated with unavailable model parameters. If model parameters are not available for a generated

molecule and a corresponding property, that generated molecule can no longer be considered as one of the candidates since its properties cannot be estimated. This may eliminate a potentially optimal molecule. The need therefore is to develop property estimation models with fewer parameters but having larger application ranges. In principle, property models suitable for CAMD methods need to be predictive. Therefore, further development of CAMD methods for applications in structured products and formulations is closely related to the availability and usability of the needed property models.

For design of complex molecules where a higher level of molecular structural information need to be considered in order to search among isomers, the CAMD methods usually employ problem specific models based on property-molecular structural relationships. Because the molecular structure plays an important role in the estimation of properties related to the design of these large molecules, QSAR based methods have become quite popular for these types of design problems. Properties estimated through parameters obtained from dynamic modelling and/or molecular modelling is necessary when microscopic and/or mesoscopic scales have been employed for molecular structural representations. The need is to develop special quantitative property models based on the data generated from dynamic and/or molecular modelling plus any available experimental data. The property estimation task could be arranged on a hierarchy based on the computational effort and cost related to obtaining a property value. Obviously, the experimental measurement of the property should be at one (high) end and simple, first-order group contribution methods could be at the other (low) end. The largest number of compounds of different types is handled at the lower end and as one proceeds upwards, the number of compounds of different types decrease but the number of isomers that can be handled increase. In this way, the computationally intensive calculations are saved only for those candidates that have satisfied all other constraints based on the lower level property models. An example of such a hierarchy is given through the listed properties in Table 1. Note that even in this approach, the uncertainties of prediction accuracy may eliminate some candidates. On the other hand, the method would systematically move towards the solution, provide useful insights and keep the computational load at a

manageable level. Note that if pure component and mixture properties were needed in a CAMD problem, the pure component properties would be estimated first. This would reduce the computational load significantly for the estimation of mixture properties. Also, this may make the mixture property model more acceptable since some molecules that could not otherwise be handled would be removed due to a specified property constraint and not because of unavailable model parameters.

Table 1: List of properties arranged in a hierarchical order.

Hierarchy	**Property type**	**Property**	**Calculation**
1	Primary	Critical temperature	Additive methods (group contribution, atomic contribution, connectivity index, *etc.*); QSAR; molecular modelling
		Critical pressure	
		Critical volume	
		Normal boiling point	
		Normal melting point	
		Heat of vaporization at 298 K	
		Heat of fusion at 298 K	
		Dipole moment	
		Gibbs energy of formation at 298 K	
		Solubility parameter	
		Log P	
		Log W_s	
2	Secondary	Surface tension	f (Sol Par)
		Refractive index	f (Sol Par)
		Acentric factor	f (T_c, P_c, T_b)
		H_v at T_b	f (T_c, P_c, T_b)
		Entropy of formation at 298 K	f (H_f, G_f)
3	Functional	Vapour pressure	f (T_c, P_c, ω, T)
		Density (liquid)	f (T_c, P_c, T_b, ω, T)
		Diffusion coefficient	f (V_m, T_b, T)
		Thermal conductivity	f (T_c, M_w, T_b, T)
		Solubility parameter	f (V_m, H_v, T)
4	Mixture	Activity coefficient	f (T, $\underline{x}$); f (T, P, $\underline{x}$)

		Fugacity coefficient	f (T, P, $\underline{x}$)
		Density (liquid)	f (T, P, $\underline{x}$)
		Saturation temperature	f (P, V, T)
		Saturation pressure	f (P, V, T)
		Solubility (liquid)	f ($\underline{\gamma}$, $\underline{x}$, T, P)
		Solubility (solid)	f ($\underline{\gamma}$, $\underline{x}$, T, P)

Typical pure component (macroscopic) properties are boiling points, melting points, heat of vaporization, partition coefficients, viscosity, surface tension, thermal conductivity, solubility parameter and many more. Typical properties from molecular modelling or quantum mechanics are bond energies, interaction energies, binding energies, *etc*. When working with large complex molecules, the structural changes in the molecular structure (for example, in isomers) need to be observed in a defined activity or property. Therefore, special QSAR based models are developed and used in design of special purpose molecules (as in Sippl *et al*. (2001)).

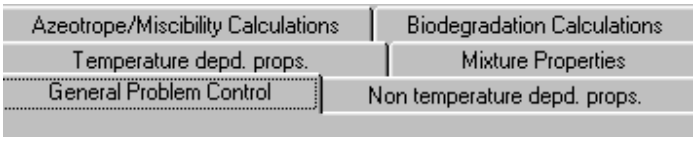
In the area of mixture properties, solubilities of solids, liquids and gases in solvents is a very common target property, mixture viscosities and diffusivity are also quite common for CAMD problems dealing with solvents. Properties related to different combinations of phase equilibrium involving vapour, liquid and solid are quite common. If the solute molecules are not large and complex, macroscopic properties from group-contribution methods are usually sufficient, provided the necessary group parameters are available. For large, complex molecules and or higher-level property modelling, special models based on quantitative structure relationships may need to be developed.

NOTE: See also the manuals for **ICAS**, **ProPred**, **ICAS-MoT** (available under "**CAPEC\ICAS\docs**" on the drive where ICAS has been installed)

2. Introduction to ProCamd

2.1 Overview of the ProCamd features

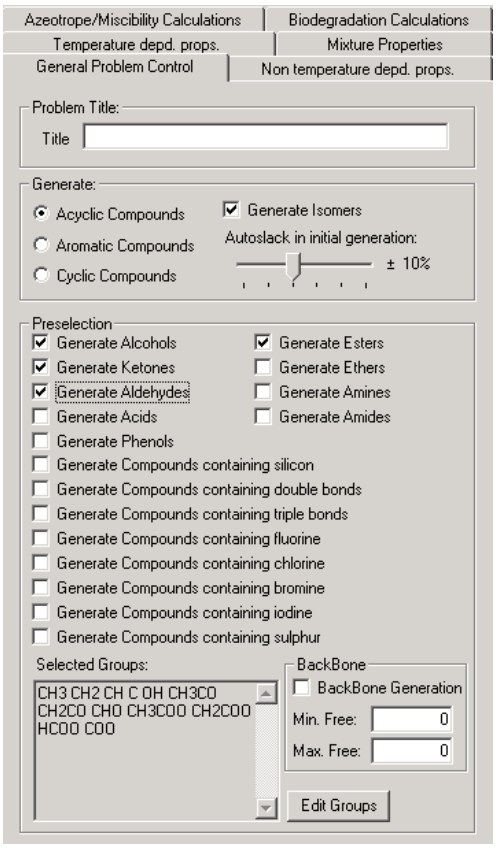
The user-interface of ProCamd consists of a specifications section and a results section. The user defines a CAMD problem by filling out only the necessary details of the following six problem specification pages.



In the text below, each of the six sections are explained.

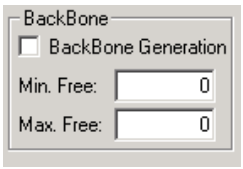
2.1.1 General Problem Control

1. Preselect molecule types



- Select the molecule type (acyclic, cyclic or aromatic).
- Select "isomer" generation option, if necessary
- Select the specific molecule type (preselection of molecule types automatically selects the groups to be used as building blocks)

2. Backbone generation



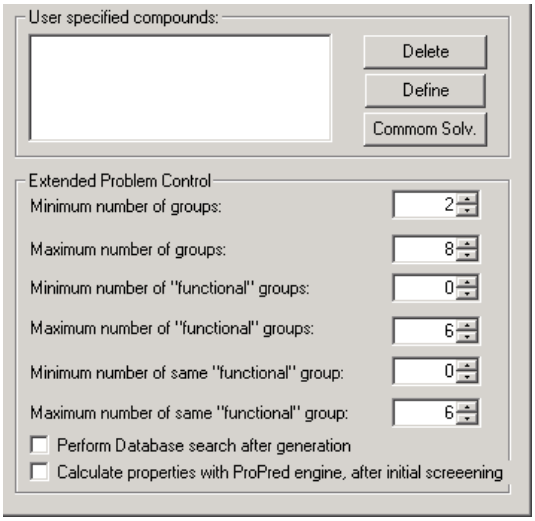
- Select "backbone generation" option if incomplete structures are to be generated.
- Give the maximum and minimum number of free connections

3a. Select user-specified compounds

3b. Select the size of molecules

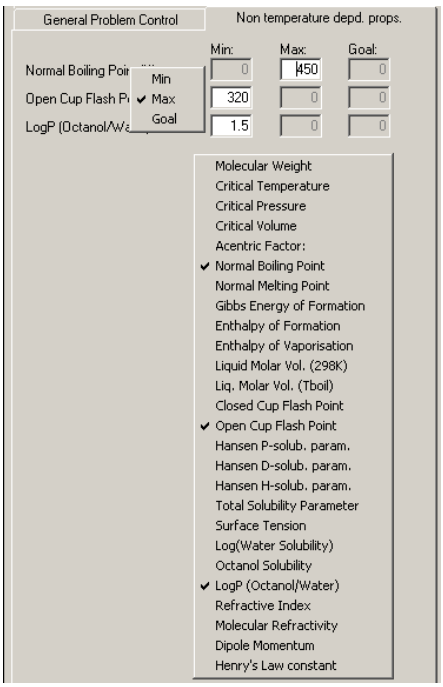
3c. Database search option

3d. Screening of properties from ProPred



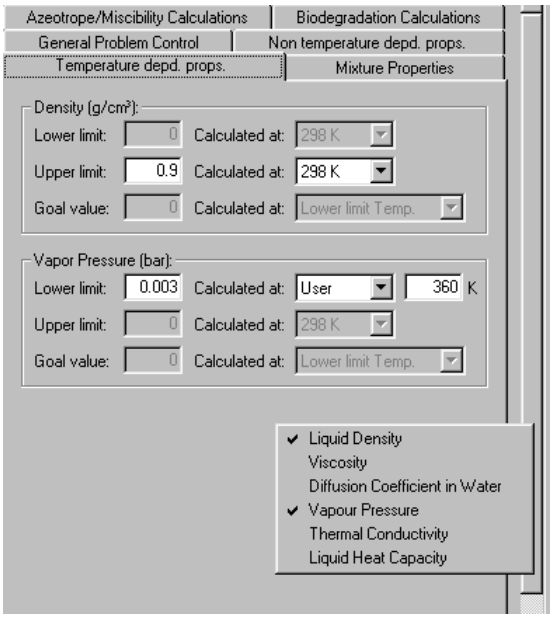
- User-specified compounds can be given by defining the molecules in terms of groups or from a table of preselected solvents (click on "common solv")
- Select the minimum and maximum compound sizes through the number of groups allowed
- ProCamd will search the DIPPR database if "perform database search…" option is selected
- ProCamd will estimate properties with ProPred for the generated molecules if "calculate properties …" option is chosen

2.1.2 Non-Temperature Dependent Properties



Right click on the left-hand side to obtain the list of properties. Left click on the property to select it and then fill out the data. In order to establish the limits the property can take, click on the property and uncheck the corresponding bounds.

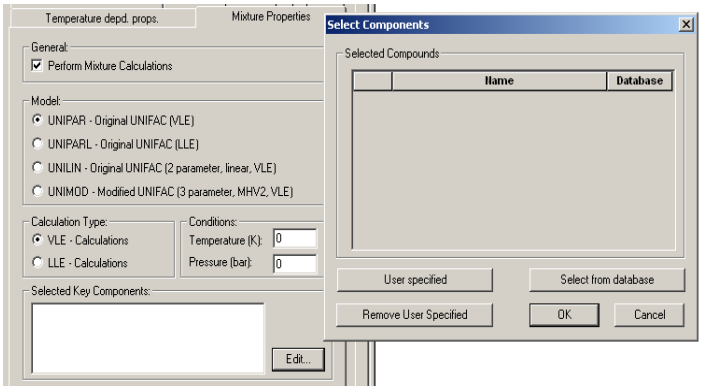
2.1.3 Temperature Dependent Properties



Right click on the left-hand side to obtain the list of properties. Left click on the property to select it and then fill out the data.

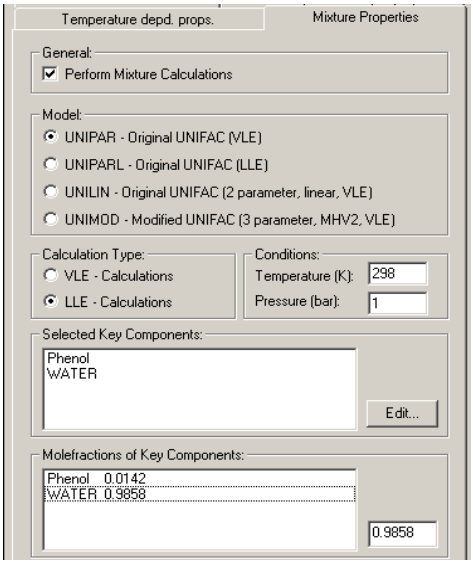
2.1.4 Mixture Properties.

1. Select UNIFAC model



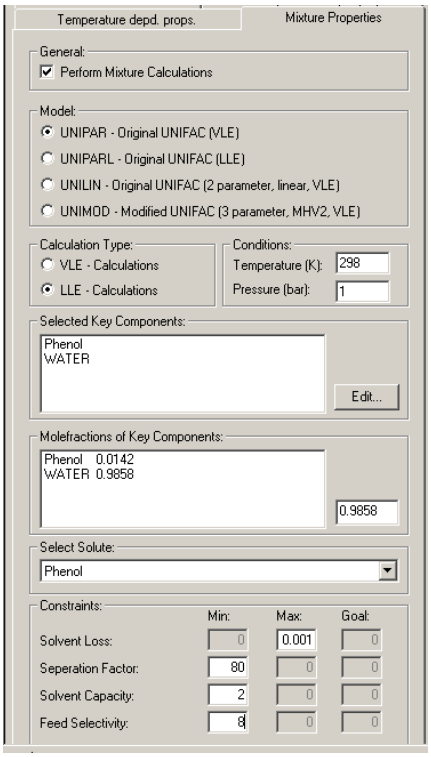
In the "Mixture Properties" tab check the "Perform Mixture Calculations" box. Click on "Edit..." in the "Selected Key Components" cage; in the displayed window click on "Select from database", the "Component Selector" window will appear: select your compounds. Click "Ok".

2. Select compounds and specify the mixture compositions



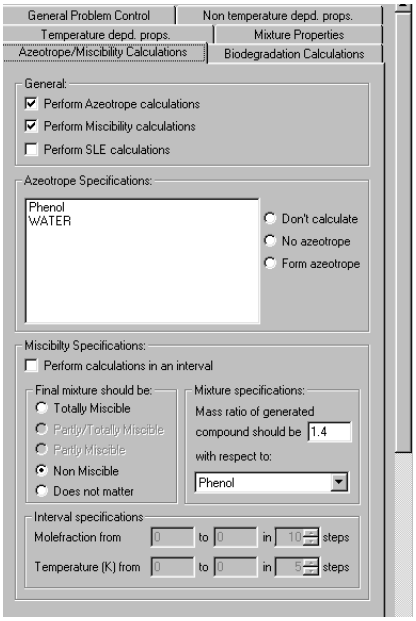
Enter the mole fractions. Click on the component (in the "Molefractions" cage) then type in the box the desired value and press "Enter".

3. Specify the mixture property constraints



Right click on the left-hand side to obtain the list of constraints (solvent properties). Left click on "Constraints" to select it and then fill out the data.

2.1.5 Azeotrope/Miscibility Calculations.



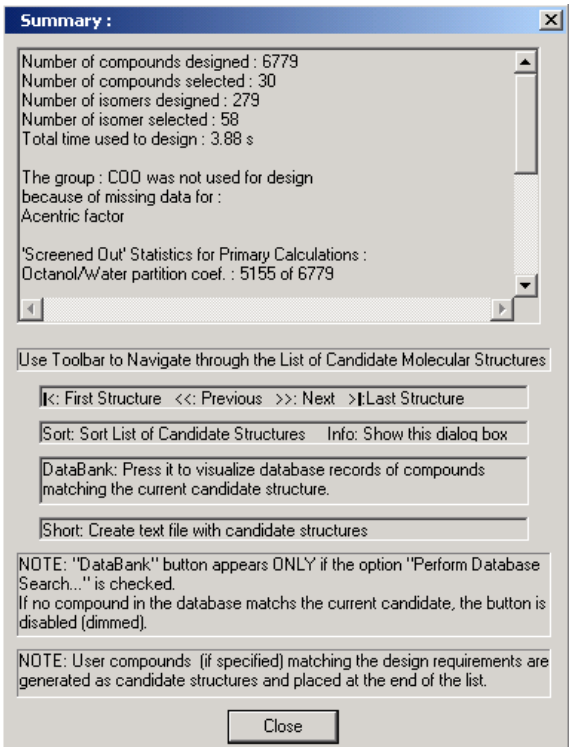
- Select "perform azeotrope …" if ProCamd should also look for binary azeotrope formation (or not formation). Highlight the compound and then select one of the 3 available options.
- If liquid miscibility is to be checked, select this option and then choose from the 2 available options – check miscibility for a fixed solvent amount (1.4 times the solute mass) or at different intervals of temperature and composition. At least 2 intervals must be chosen. Note that totally miscible or immiscible solutions may be difficult to find.

2.1.6 Biodegradation Calculations

The options on this page are currently not recommended. A new version with more reliable models will be implemented in the near future. The current version has methods of small application range.

2.1.7 Starting a Calculation & Viewing of Results

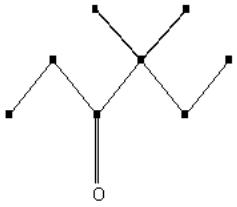
Click on  to start the calculations. On completion, the following screen is shown.



This summary of results provides information on how many compounds were generated and why some of them were rejected. Analysis of these results helps to reformulate the CAMD problem.

The generated (feasible) compounds will be listed first by ProCamd

Compound 1 :

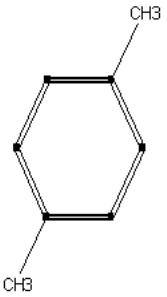


Description :	
No	Groupname
4	CH3
1	CH2
1	C
1	CH2CO

Properties :			
Property	Value	2. Value	Unit
Octanol/Water partition coef.	2.12	2.12	
Flash Temperature (open cup)	321.65	321.65	K
Normal Boiling point	441.26	441.26	K
Vapour Pressure at 360.00 K	0.101	0.101	bar
Liquid density at 298.15 K	0.814	0.814	g/cm³
Select. based on feed Comp.	9.48	9.48	
Capacity	24.49	24.49	
Separation factor	86.60	86.60	
Solvent loss	2.50E-004	2.50E-004	
NO AZEOTROP w. keycomp. no 1			
IS NOT miscible with feed.			

The user-specified (feasible) compounds will be listed at the end

Compound 62 (User spec.):



Description :	
No	Groupname
4	ACH
2	ACCH3

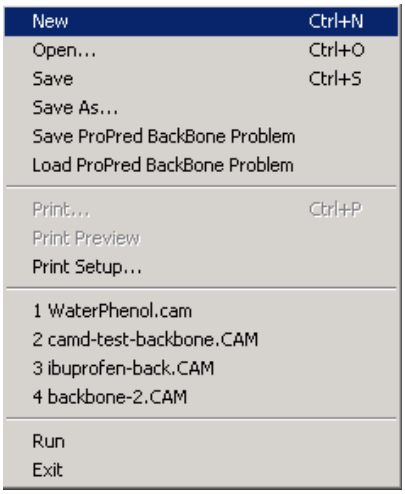
Properties :			
Property	Value	2. Value	Unit
Octanol/Water partition coef.	3.19	3.19	
Flash Temperature (open cup)	322.68	322.68	K
Normal Boiling point	415.88	415.88	K
Vapour Pressure at 360.00 K	0.170	0.170	bar
Liquid density at 298.15 K	0.866	0.866	g/cm³
Select. based on feed Comp.	46.39	46.39	
Capacity	2.72	2.72	
Separation factor	389.00	389.00	
Solvent loss	1.77E-005	1.77E-005	
NO AZEOTROP w. keycomp. no 1			
IS NOT miscible with feed.			

Explanation of the lower menu-bar items

- Click OK and then use the “>>” or “<<” buttons to move up or down to see the various feasible candidate solvents.
- “sort” option orders the feasible compounds in the user-specified order.
- “info” option shows the “summary” page again
- “ProPred” option indicates that the current compound can be represented by ProPred and that it can be launched directly from ProCamd
- “Databank” option indicates that the current compound has been found in the DIPPR database and its stored data can be retrieved and viewed.
- “Short” option puts all the results on the screen into a text file.

2.1.8 Other Options

Under “file” in the top menu-bar, the following options are now available.



Files from ProCamd can be saved and re-used. Note that “backbone” problems need to be saved and loaded differently from complete molecular structure problems.

Backbone files generated by ProPred need to be loaded before they can be terminated.

3 Tutorials with ProCamd

3.1 Solvent search for vapour-liquid separation

3.1.1 Acetone-chloroform example

Problem Description

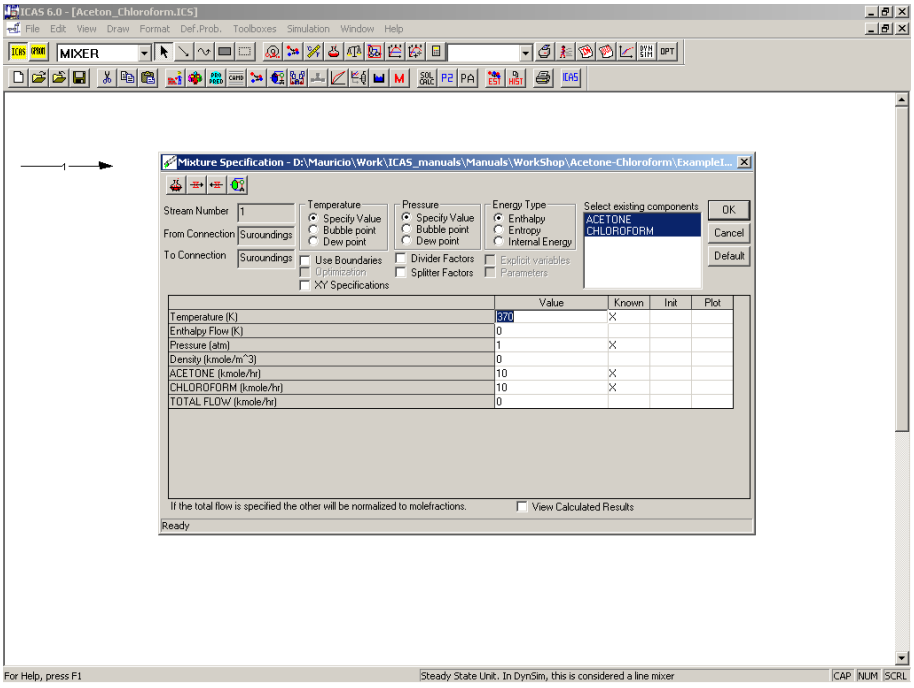
A mixture of acetone and chloroform is to be separated into pure products. To solve this problem with ICAS, follow the steps given below.

- First the mixture is to be analysed, in order to identify the azeotrope formed by acetone and chloroform.
- It is decided to use extractive distillation for the separation. Use CAMD (Computer Aided Molecular Design) to identify a good solvent. We know from beforehand that benzene is a solvent for this separation. Therefore compare the performance of the designed solvent with that of benzene. Use ProCamd to identify new solvents.
- Use of ICAS- PDS (Process Design Studio) to design distillation columns.
- Make a simulation in ICAS of the extractive-distillation flowsheet.

Mixture Analysis

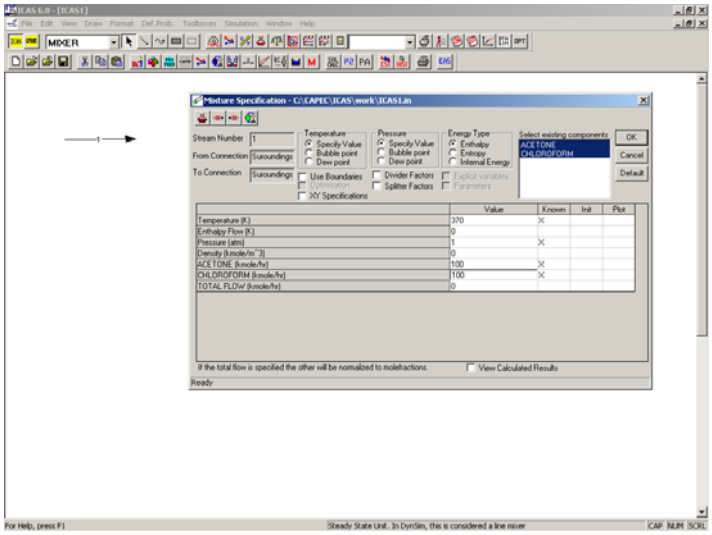
Compound Selection

Draw a stream and then select compounds by clicking on the "compounds"  button.

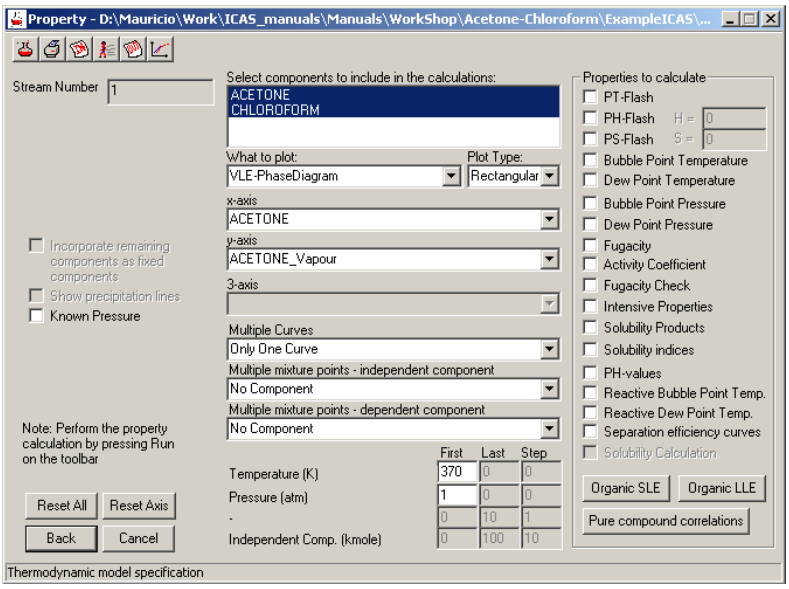


Stream Specification

1. Double click on the stream to enter the "mixture specification" window
    - Specify the equimolar mixture
    - Temp. = 370 K
    - Pressure = 1atm.

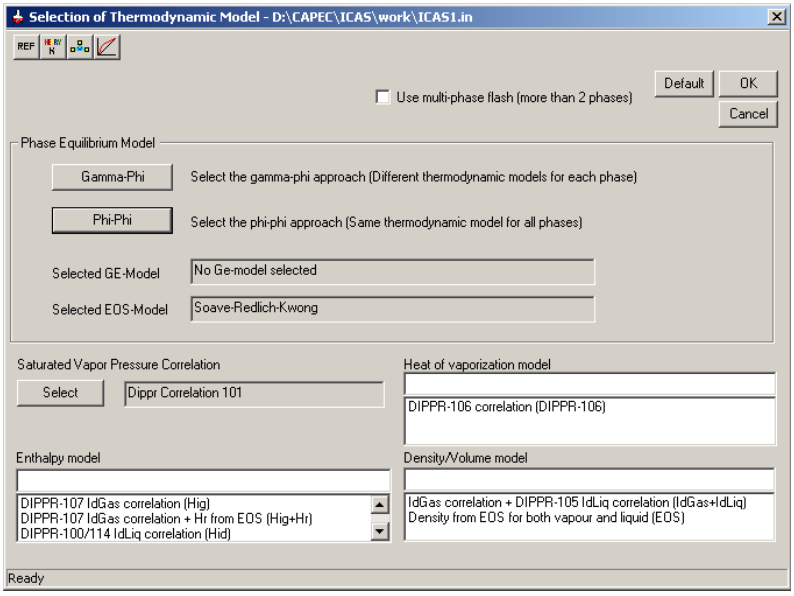


2. After specifying the temperature, pressure and component flows (as shown above) click on the top-left button  to enter the "property" window. Click on the top-left button  to go to the "property model" selection window.

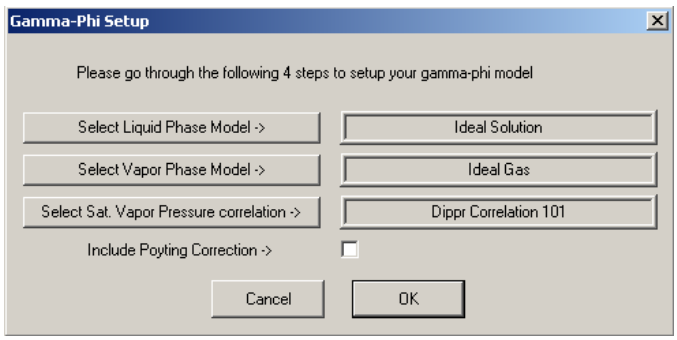


Thermodynamic Model Selection

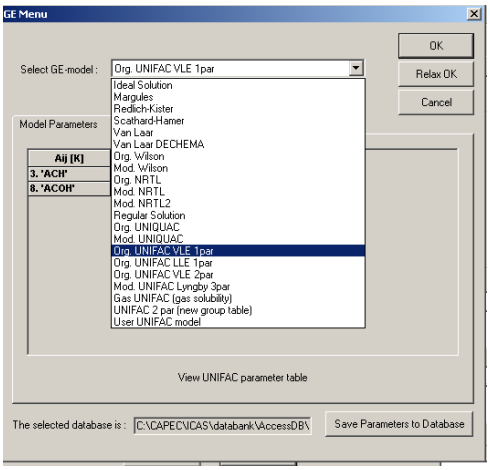
1. Click on the "gamma-phi" option for this example

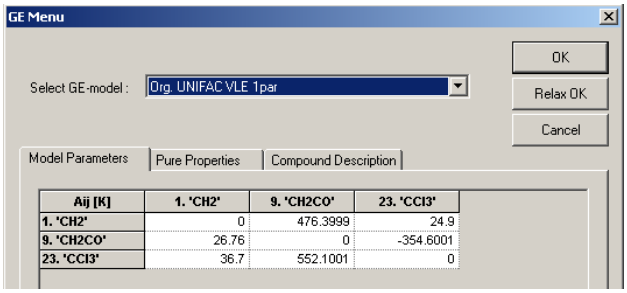


2. Click on the “select liquid phase model”

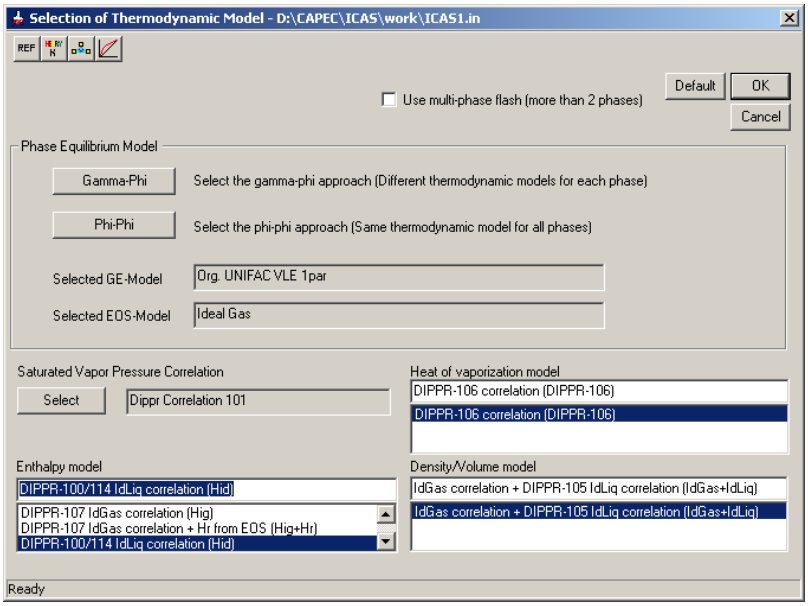


3. Select the UNIFAC model as shown below. The UNIFAC model parameters are shown and if all parameters are available (as in this example), click OK (“Ideal Gas” is fine for this problem), click OK

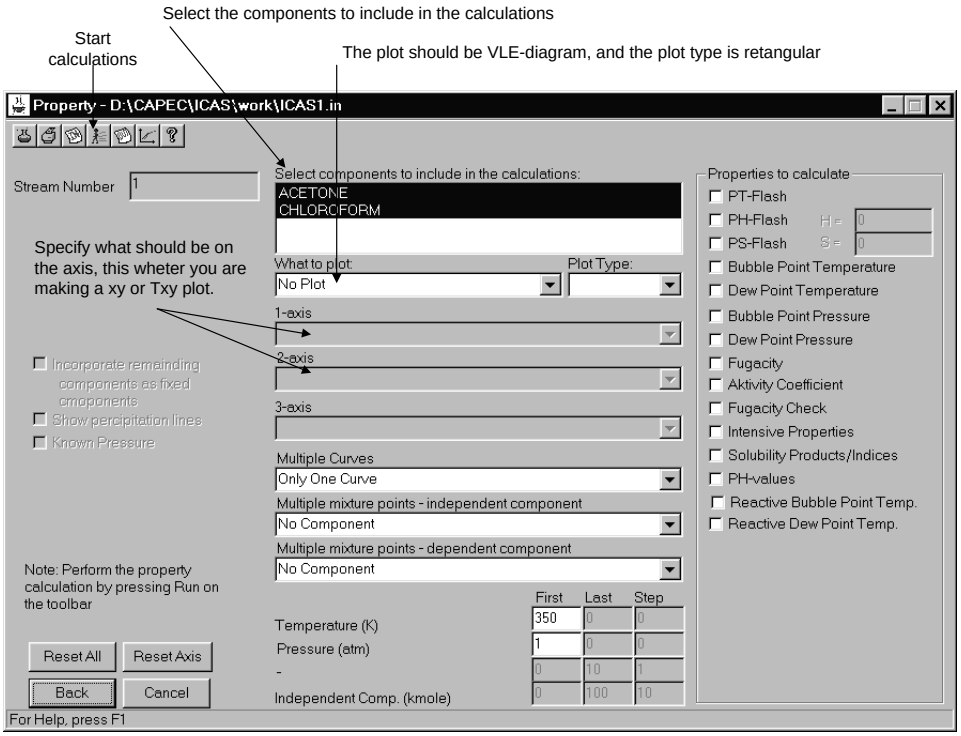




4. On return to the main property model selection window click on default to select all the other model options (as shown below) and click OK.

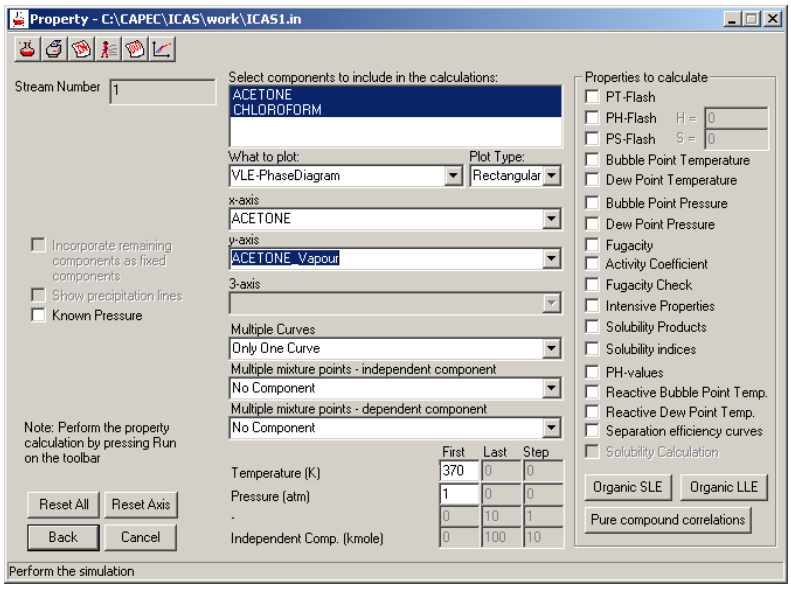


5. In order to come to the mixture analysis click  in the stream specification window. This brings up the following dialog:

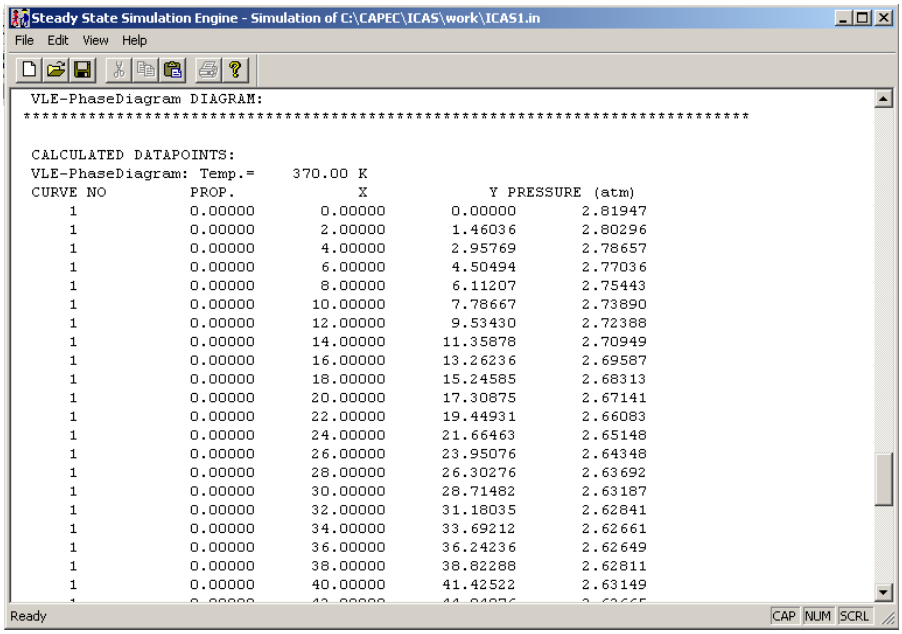


Liquid-Vapour equilibrium calculation

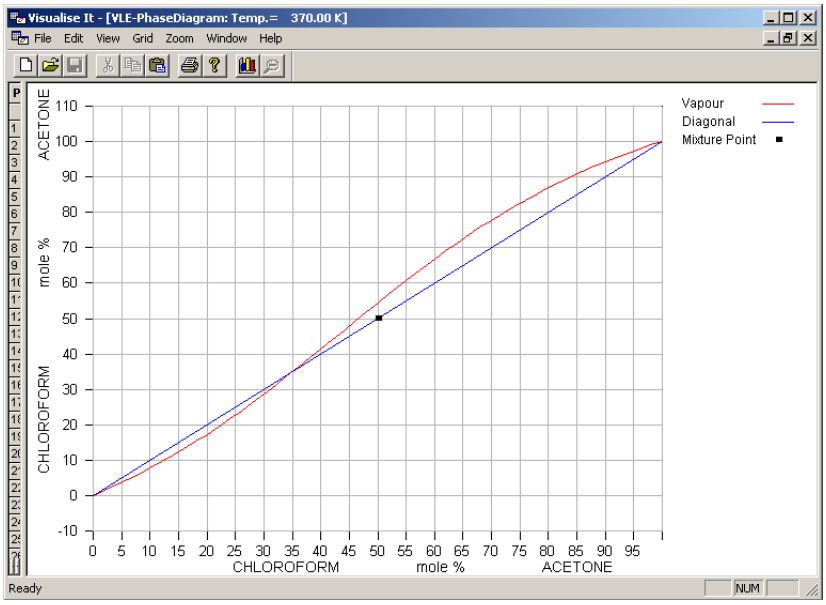
1. Highlight acetone and chloroform, select "VLE-phase diagram", select "rectangular" for plot type, select "acetone" for x-axis, and select "acetone vapour" for y-axis.



2. Click on "run"  to start the computations.



3. After the calculations are done and for continue with the mixture analysis, first start the plotting facility by clicking  on the toolbar. Here you will the rectangular diagram under the tools menu.

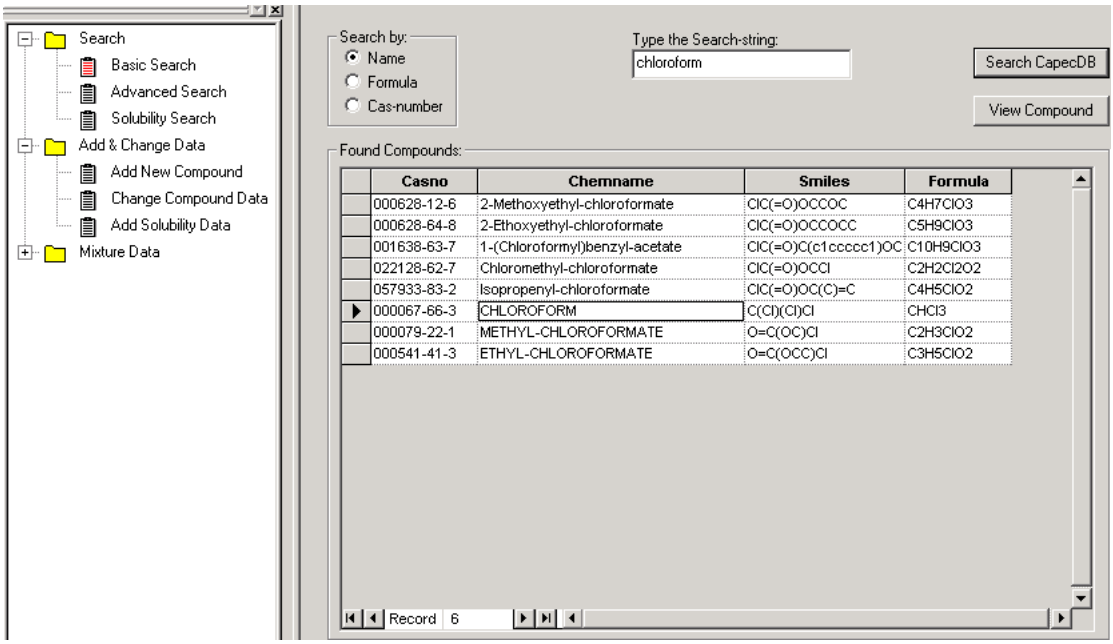


Solvent identification with ProCamd

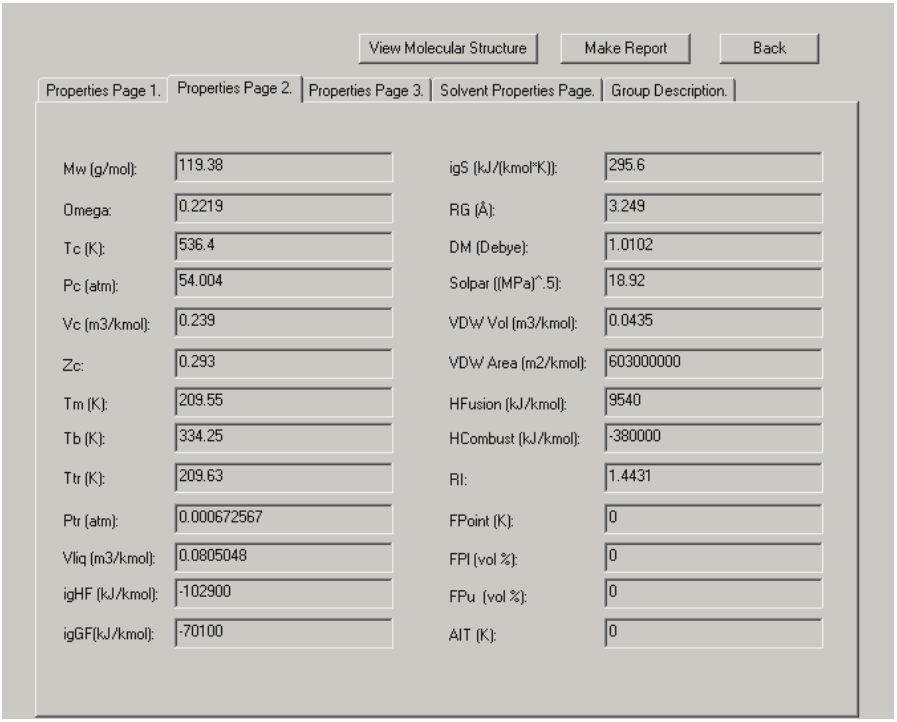
The above problem description and mixture analysis helps us to define the CAMD problem (step 1).

Step 1: We would like to find a solvent that breaks the azeotrope between acetone-chloroform (or moves the azeotrope point sufficiently to one side to allow separation by distillation) so that high purity acetone and chloroform can be recovered by extractive distillation. The solvent should be more selective to chloroform than acetone. The solvent, acetone and chloroform must form a totally miscible liquid. The solvent must not form azeotrope with either acetone or chloroform. The solvent should be easy to recover and recycle. The solvent should have favourable EH&S properties.

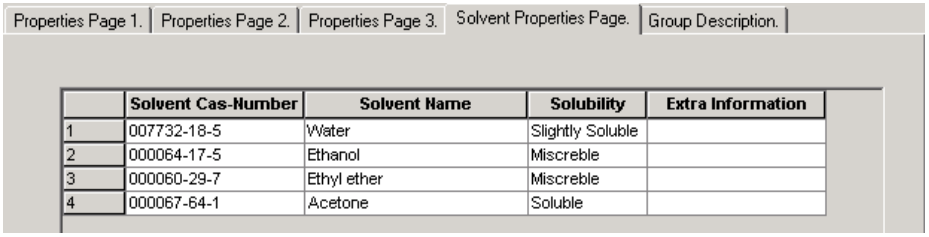
Step 2: Since the solvent is selective to chloroform, search in the database to find known solvents for chloroform that are also miscible with acetone. Use the CAPEC database  to identify the solvents. Use the "basic options" and search for chloroform.



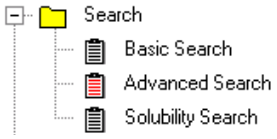
View the chloroform data - highlight chloroform and click "view compound"



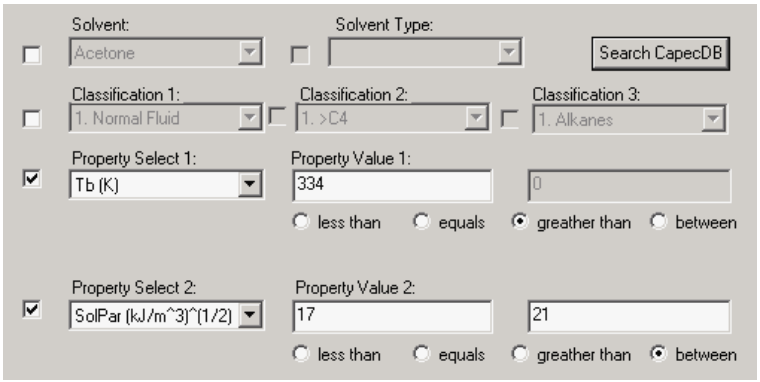
Note the values of Tb (normal boiling point) and SolPar (Hildebrand Solubility parameter). Note also the solvent properties page – chloroform is soluble in acetone.



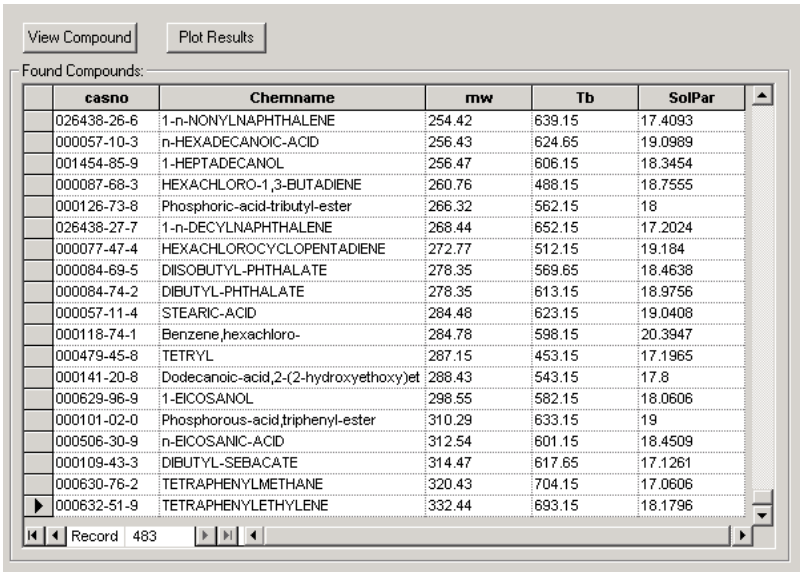
	Solvent Cas-Number	Solvent Name	Solubility	Extra Information
1	007732-18-5	Water	Slightly Soluble	
2	000064-17-5	Ethanol	Miscreble	
3	000060-29-7	Ethyl ether	Miscreble	
4	000067-64-1	Acetone	Soluble	



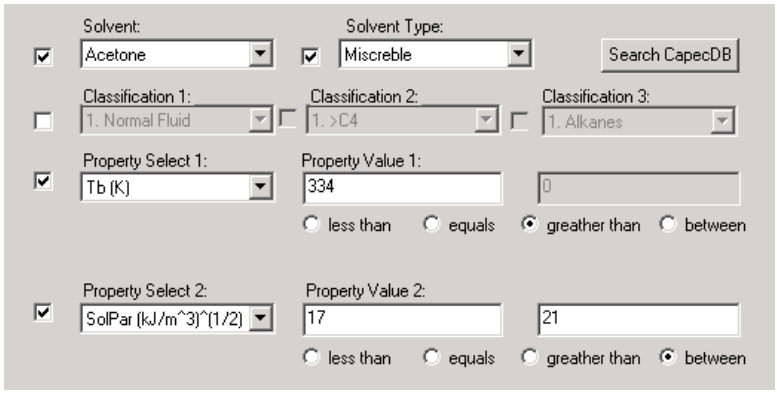
Now use the "advanced search" option to find solvents based on search of data. Use the Tb and SolPar as constraints as shown below

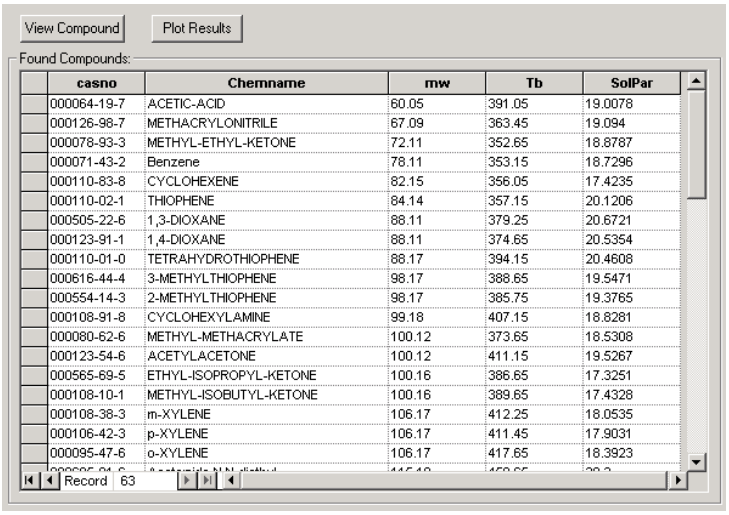


Click on "search CapecDB" to obtain the following result



Now refine the search by adding that the solvent must also be totally miscible with acetone





	casno	Chemname	mw	Tb	SolPar
	000064-19-7	ACETIC-ACID	60.05	391.05	19.0078
	000126-98-7	METHACRYLONITRILE	67.09	363.45	19.094
	000078-93-3	METHYL-ETHYL-KETONE	72.11	352.65	18.8787
	000071-43-2	Benzene	78.11	353.15	18.7296
	000110-83-8	CYCLOHEXENE	82.15	356.05	17.4235
	000110-02-1	THIOPHENE	84.14	357.15	20.1206
	000505-22-6	1,3-DIOXANE	88.11	379.25	20.6721
	000123-91-1	1,4-DIOXANE	88.11	374.65	20.5354
	000110-01-0	TETRAHYDROTHIOPHENE	88.17	394.15	20.4608
	000616-44-4	3-METHYLTHIOPHENE	98.17	388.65	19.5471
	000554-14-3	2-METHYLTHIOPHENE	98.17	385.75	19.3765
	000108-91-8	CYCLOHEXYLAMINE	99.18	407.15	18.8281
	000080-62-6	METHYL-METHACRYLATE	100.12	373.65	18.5308
	000123-54-6	ACETYLACETONE	100.12	411.15	19.5267
	000565-69-5	ETHYL-ISOPROPYL-KETONE	100.16	386.65	17.3251
	000108-10-1	METHYL-ISOBUTYL-KETONE	100.16	389.65	17.4328
	000108-38-3	m-XYLENE	106.17	412.25	18.0535
	000106-42-3	p-XYLENE	106.17	411.45	17.9031
	000095-47-6	o-XYLENE	106.17	417.65	18.3923

Revise now the CAMD problem definition based on the above information – The solvent can be acyclic hydrocarbons and ketones (aromatic compounds, chlorides, dioxanes are not considered for EH&S concerns). The normal boiling point should be higher than that of chloroform (334 K), the molecular weight could be between 70-120, must not form azeotrope with either acetone or chloroform, and, must be totally miscible with the binary mixture of acetone and chloroform.

Step 3: Start the ProCamd toolbox from the ICAS toolbar by clicking 

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General problem control

First the type of compounds and size has to be selected. This is done on the "general problem control" page.

Guidelines:

- ☑ Design acyclic compounds containing groups of C, H and O atoms (select all molecule types with C, H & O atoms)
- ☑ The size should be from 4 to 8 groups and with maximum 1 functional group
- ☑ Select the "perform database search after generation"

"Non-temperature dependent" & "temperature dependent property" specifications

1. Specify non-temperature dependent properties.

   Guidelines:

- ☑ Use molecular weight from 70 to 120 g / mole. (uncheck "goal")
- ☑ Normal boiling point from 340 to 420 K. (uncheck "goal")

2. No "temperature dependent properties" needs to be specified.

Mixture properties

- ☑ Specify the azeotropic mixture as the feed mixture (0.344 acetone and 0.656 chloroform) at 345 K and 1atm.
- ☑ Specify a minimum selectivity of 1.7 for chloroform
- ☑ Select Chloroform as Solute.

Azeotrope/Miscibility calculations.

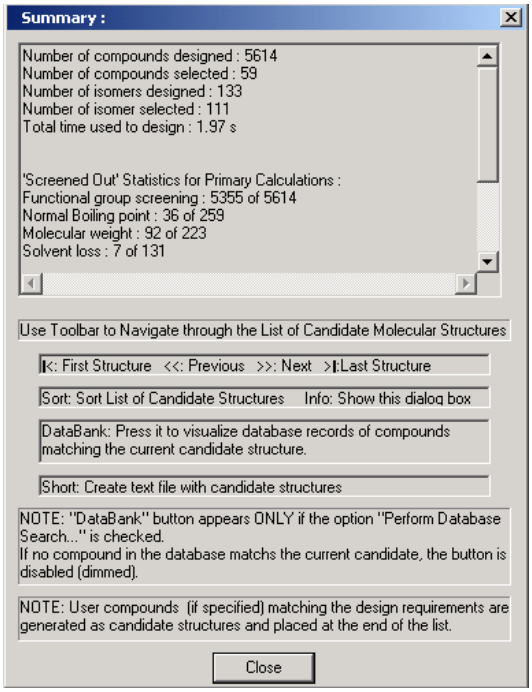
- ☑ For azeotrope calculation specify that the designed compound should not form azeotropes with any of the compounds in the mixture.
- ☑ Miscibility calculation may be made at fixed amount of solvent, calculations at intervals are not necessary, and the final mixture of acetone-chloroform and solvent must be totally miscible.
- ☑ Mass ratio of generated compound should be 3 times (by weight) with respect to chloroform.

Start calculations

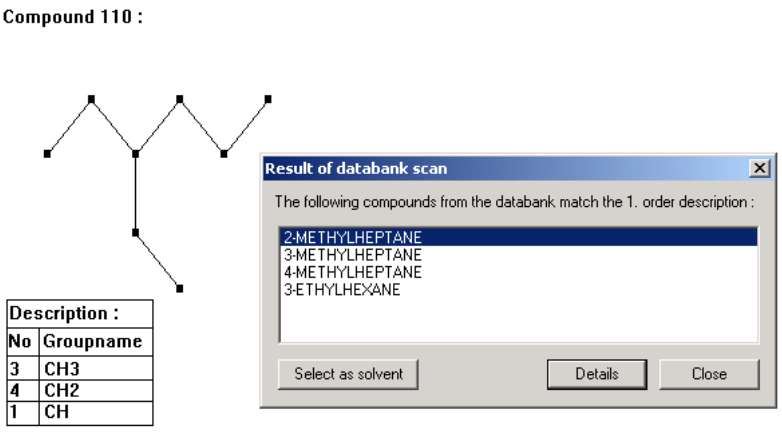
Click on "GO" to start the calculations (generate and test with ProCamd)

Results

After the execution has been completed, the results will be shown on the right hand side of the user-interface and a "summary" page of results will be shown. Check the information given and then click on OK to close it. This page can be opened at any time by clicking on "info".



Scroll up or down to analyze the different feasible compounds. Reorder the compounds according to specified sorting criteria.



Description :	
No	Groupname
3	CH3
4	CH2
1	CH

Properties :			
Property	Value	2. Value	Unit
Normal Boiling point	396.54	396.54	K
Molecular weight	114.22	114.22	g/mol
Solvent loss	0.161	0.161	
Selectivity	3.35	3.35	
NO AZEOTROP w. keycomp. no 2			
NO AZEOTROP w. keycomp. no 1			
IS miscible with feed.			

Use the ">>" or "<<" buttons to move up or down to see the various feasible candidate solvents. If the solvent candidate is available in the database, "databank"

will be highlighted on the lower menu-bar. If the solvent candidate can be represented by ProPred, "propred" will be highlighted. Identify and chose the "**2-methylheptane**" as a solvent, by clicking on "Databank" button.

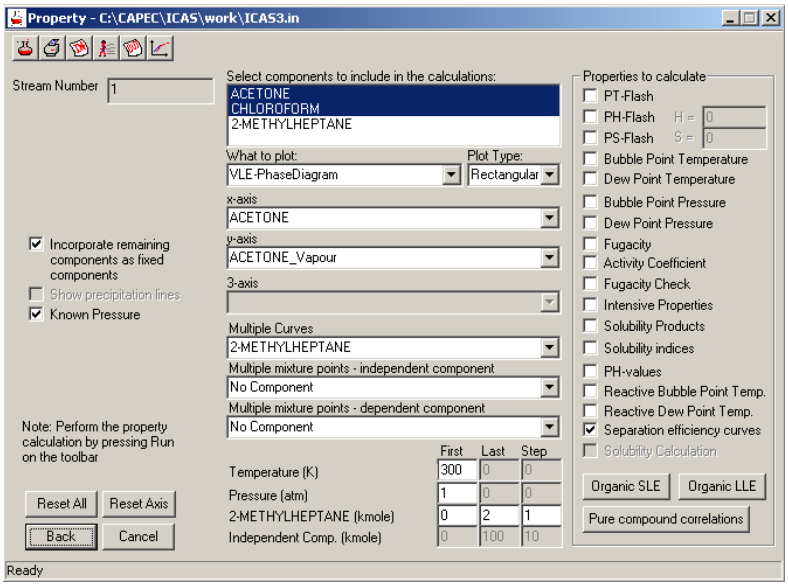
To transfer the solvent information to ICAS, click on "Select as solvent" in the "Results and Database scan" window.

Separation efficiency computation

Problem Setup

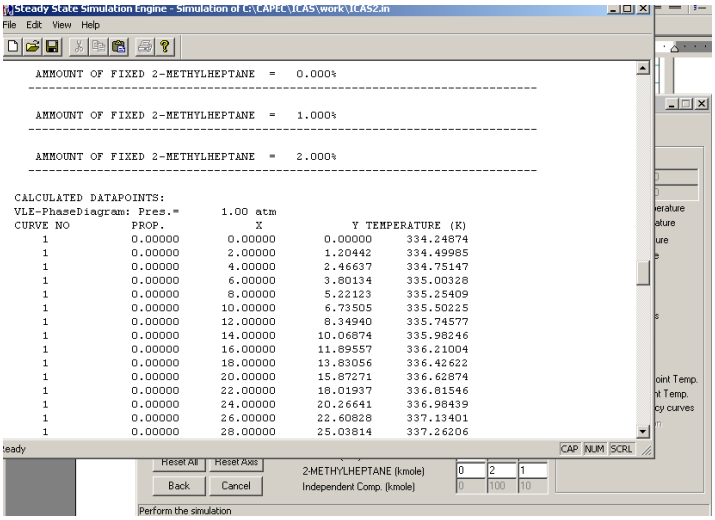
In the ICAS main window add the solvent by "selecting the compounds".

Then return to the property "utility" window, highlight acetone and chloroform, select "VLE-phase diagram", select "rectangular" for plot type, select "acetone" for x-axis, select "acetone vapour" for y-axis, select "2-methylheptane" under multiple curves. Check also the items shown in the window below. Click on "run"  to start the computations.



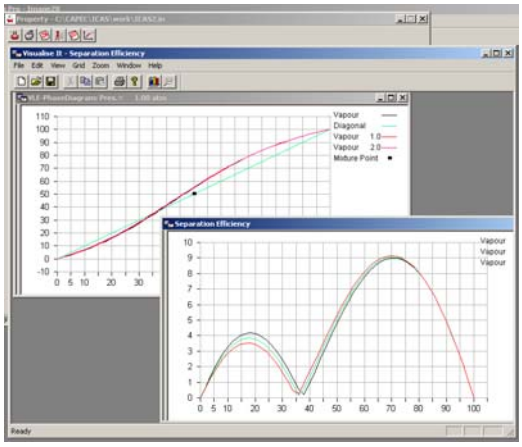
Calculation steps

The calculated values are shown on the output window (as shown below).



Plot view

Close this window and then click on the “plot-view” button the main property “utility” window to see the plots.

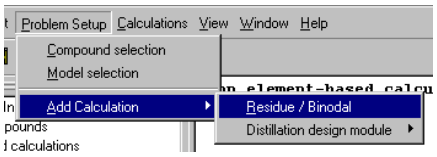


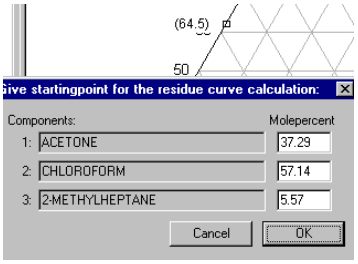
Distillation Design and Simulation

This part shows the use of ICAS, PDS, and the simulation engine for the synthesis, design and analysis of an extractive distillation operation.

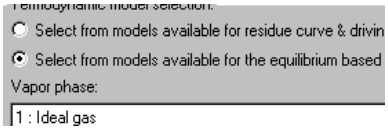
Design

1. Select the stream in ICAS.
2. Start Process Design Studio (PDS)  from ICAS
3. Go to “Standard calculation” in the project tree, and then go to “Problem Setup” and “Add Task”. Include all compounds and accept the default thermo.
4. Add a residue curve diagram task. Plot residue curves to find the separation boundaries. Identify the obtainable products.

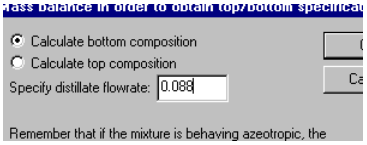




5. Now add an equilibrium based distillation design task and remember to set the thermo model to equilibrium based thermo model.

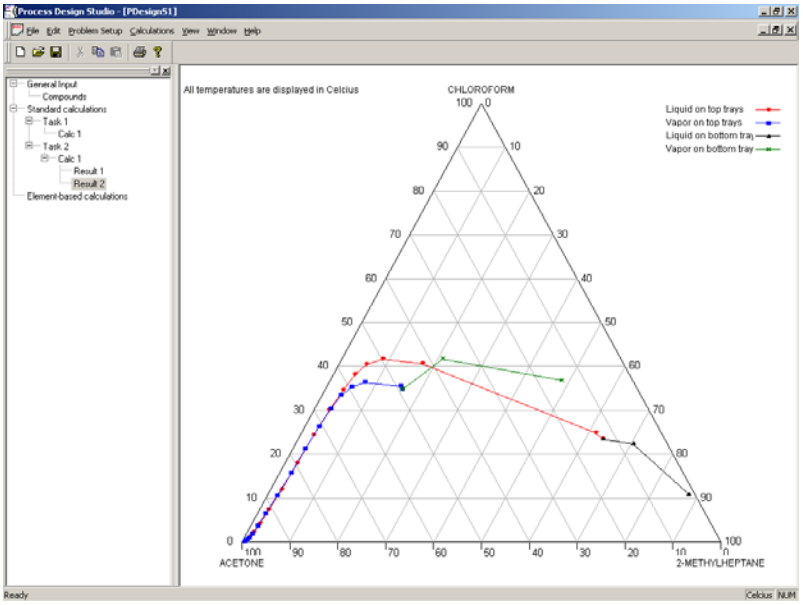


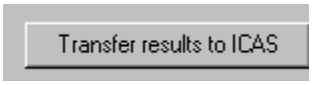
6. Set the feed conditions to the column (350K, 1atm, 1 mole, 0.1 molefrac Acetone, 0.1 molefrac Chloroform, 0.8 molefrac 2-MethylHeptane). Set reflux ratio to 15. Set the lightkey to Acetone. Set distillate to 0.98 Acetone, 0.01 Chloroform, 0.01 2-MethylHeptane. Click the "Get top/bottom spec" button and specify the distillate flowrate to 0.088. Click "Calculate".



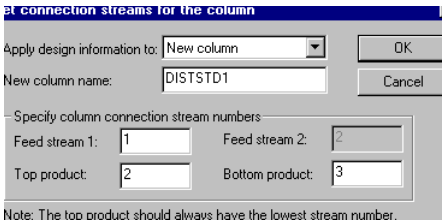
Change the reflux ratio until a feasible and acceptable/desirable design is obtained. (The tray-by-tray calculated values are shown if and only if the specified reflux ratio is greater than the minimum. Otherwise, an error message is given.)

7. Click on "results" to get a visual picture.



8. Click "Transfer results to ICAS" 

to transfer the data to the ICAS for steady state simulation. Following the steps all the design data will be transfer (number of trays, product specifications, reflux ratio, feed tray, product rates, as well as temperature and composition profiles).

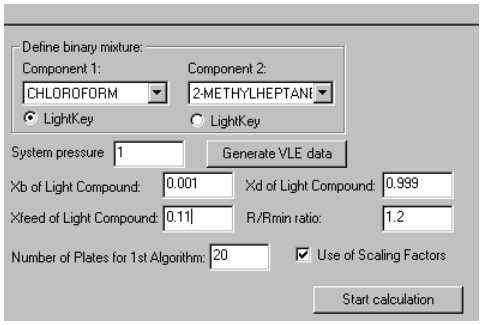


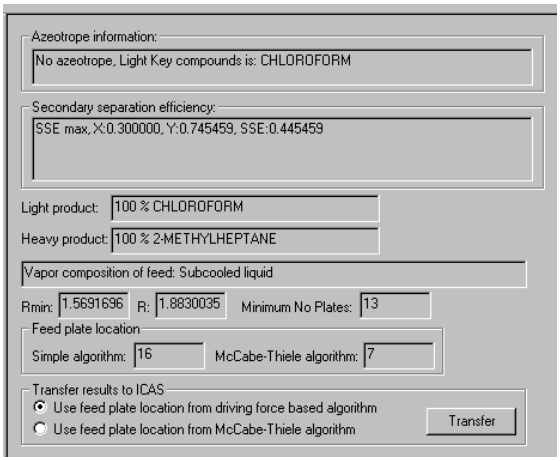
Simulation

1. Start ICASSim  to perform a steady state simulation of the extractive distillation column using the results from PDS as initial estimates for the rigorous model.

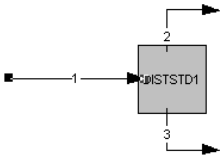
LIQUID FRACTION	1.00000	0.00000	1.00000
--------(Kmole/hr)----------			
ACETONE	10.00000	8.88275	1.11725
2-METHYLHEPTANE	80.00000	0.04789	79.95211
CHLOROFORM	10.00000	0.06936	9.93064
TOTAL	100.00000	9.00000	91.00000

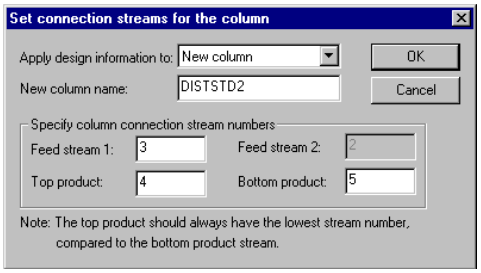
2. Design and add the solvent recovery column: Use the driving forced based distillation design algorithm. Go back to PDS and choose the driving force algorithm to design the second (solvent recovery) column). The specifications and results are highlighted below:



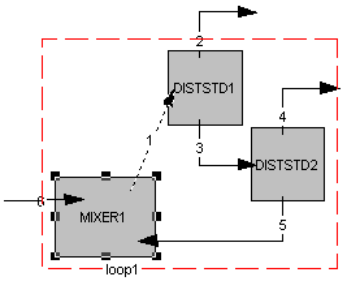


3. Transfer the results to ICAS as in steps as in steps 8-9 section 5.1. ICAS will open up the following dialogue to place the second column.





4. Add the recycle-loop in ICAS and perform simulation on the total flowsheet: The recycle loop is closed manually by placing a mixer. In stream 6 the flows should be 10 kmole/h acetone, 10 kmole/h chloroform, 1 kmole/h 2-methylheptane. In stream 1 the values should be marked as initial estimates. Finally the outlet temperature from the mixer should be 350 K.



STREAM NUMBER	1	2	3	4
TEMPERATURE (K)	350.00000	332.04270	373.15131	342.63881
PRESSURE (atm)	1.00000	1.00000	1.00000	1.00000
ENTHALPY(K/Kmole)	-27615.86917	-24505.51626	-26910.01571	-14287.60495
ENTROPY(1/Kmole)	41.50294	35.62145	44.69363	37.41181
U-ENERGY(K/Kmole)	-27616.02699	-24532.76285	-26910.18654	-14315.72103
DENS. (Kmole/m^3)	6.33628	0.03670	5.85403	0.03557
VAPOUR FRACTION	0.00000	1.00000	0.00000	1.00000
LIQUID FRACTION	1.00000	0.00000	1.00000	0.00000
--------(Kmole/hr)----------				
ACETONE	10.00039	9.05476	0.94563	0.94524
CHLOROFORM	10.98840	0.85620	10.13220	9.14408
2-METHYLHEPTANE	89.89447	0.06853	89.82593	0.93118
TOTAL	110.88325	9.97949	100.90376	11.02051

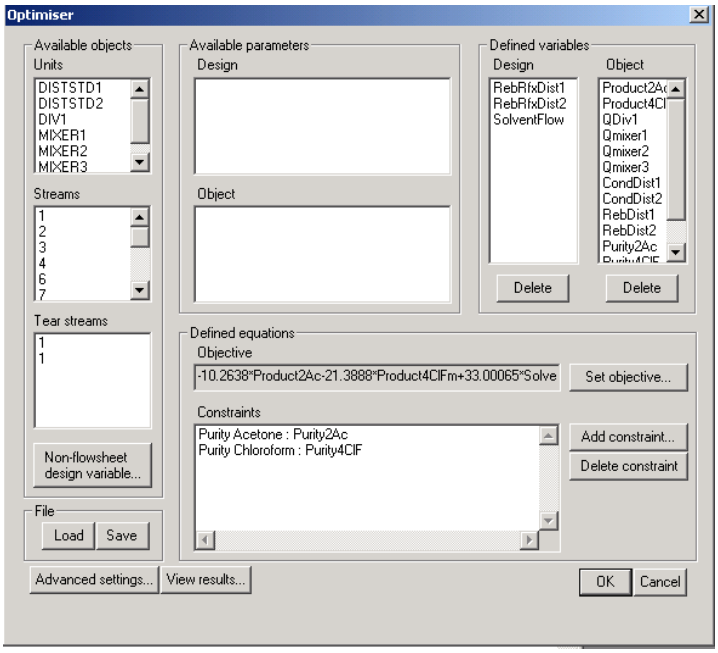
STREAM NUMBER	5	6
TEMPERATURE (K)	389.00747	350.00000
PRESSURE (atm)	1.00000	1.00000
ENTHALPY(K/Kmole)	-27545.64659	-19114.10880
ENTROPY(1/Kmole)	47.80138	36.69383
U-ENERGY(K/Kmole)	-27545.83081	-19142.82893
DENS. (Kmole/m^3)	5.42829	0.03482
VAPOUR FRACTION	0.00000	1.00000
LIQUID FRACTION	1.00000	0.00000
--------(Kmole/hr)----------		
ACETONE	0.00039	10.00000
CHLOROFORM	0.98811	10.00000
2-METHYLHEPTANE	88.89475	1.00000
TOTAL	89.88325	21.00000

Optimisation

Save your problem

Go the following directory C:\CAPEC\ICAS\work\Ex\Opt\AcetoneChloro

Open the file AC_CH_MPE.ICS and then click on OPT to enter the optimisation toolbox.



- Click on “set objective” to see the objective function
- Double click on the “constraints” names to see the constraint functions
- Double click on the “design” variables to see their details
- Click on “advanced settings” to see the NLP solver specification
- Click on “OK” to return to ICAS and then click on  to start the optimisation run. On convergence, click on  to return to the optimisation window and then click on “view results” to see the detailed optimisation results.

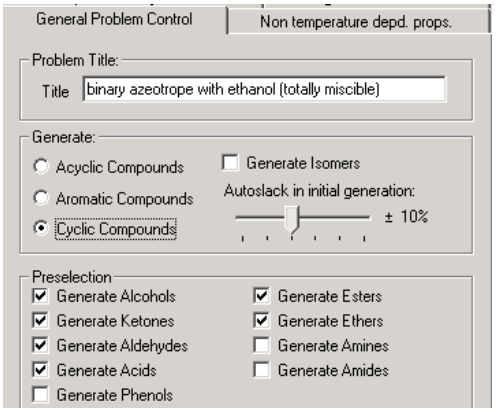
Related problems

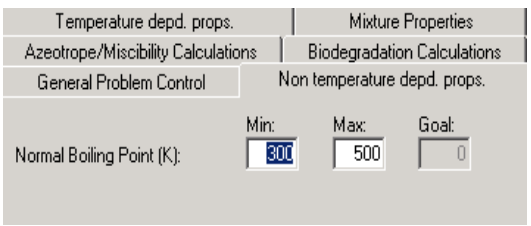
Find solvents to separate acetone from methanol separation (VLE separation)
Find solvents for methyl acetate from methanol separation (VLE separation)

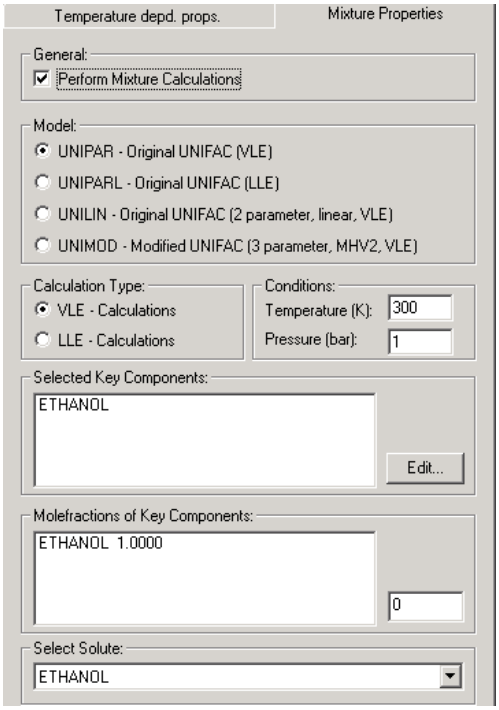
3.1.2 Azeotrope Search

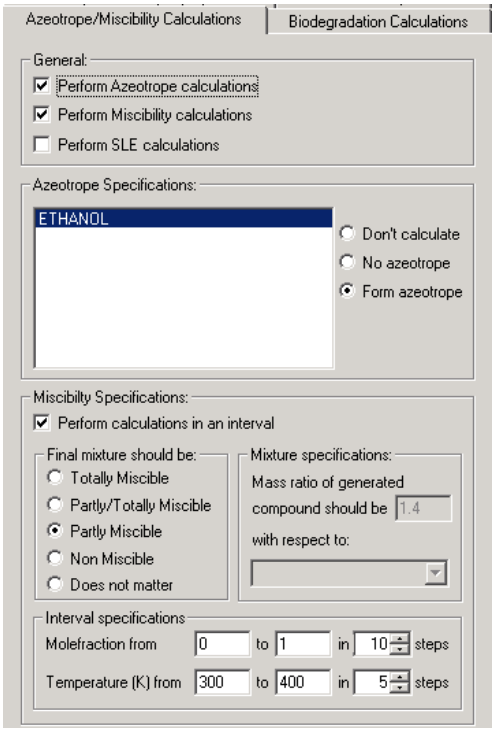
Find all binary mixtures that form an azeotrope with ethanol at 1 atm pressure and where the second compound is a cyclic compound, with 300 K < T_b < 500 K.

To solve this problem, we need to use ProCamd (“General problem control”, “non-temperature dependent. properties”, “mixture properties” and “azeotrope/miscibility” pages). A sample of the data specified is shown below.









One of the feasible mixtures is shown below (note that what ProCamd provides is the information that the two compounds will form a single-phase solution. The exact compositions will need to be calculated separately, depending on the desired mixture property, for example, the bubble point temperature.

Compound 37 :

Description :	
No	Groupname
4	CH2
1	CH2COO

Properties :		
Property	Value	Unit
Normal Boiling point	400.14	K
AZEOTROP w. keycomp. 1 at Xgen/Taz:	0.60 / 341.53 K	

Miscibility :										
T \ x	0.00	0.11	0.22	0.33	0.45	0.56	0.67	0.78	0.89	1.00
300.00	M	M	M	M	M	M	M	M	M	M
325.00	M	M	M	M	M	M	M	M	M	M
350.00	M	IM	M	M	M	M	M	M	M	M
375.00	M	M	M	M	M	M	M	M	M	M
400.00	M	M	M	M	M	M	M	M	M	M

- Repeat the above problem to find acyclic compounds that form azeotropes with ethanol

- Repeat the above problem where the cyclic compounds do not form azeotrope with ethanol

3.2 Solvent Search for Liquid-Liquid Separation & Mixture Design

3.2.1 Solvent search for liquid-liquid extraction

We have a water stream that is contaminated with phenol (0.0142 mole fraction of phenol in water). We need to remove the phenol through solvent-based liquid-liquid extraction. The solvent must be totally immiscible with water and dissolve the phenol. The extraction operation will take place at 298 K and 1 atm. Find an environmentally friendly solvent.

For this example, we skip steps 1 and 2 and go directly to step 3 for the following CAMD problem specification.

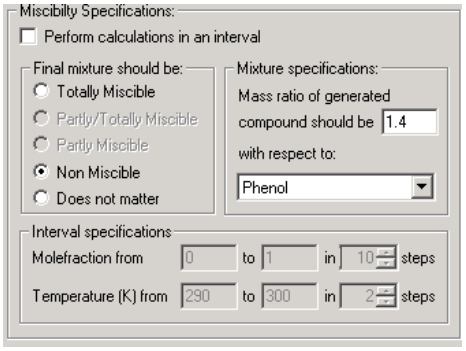
- **General problem control**: Find acyclic compounds (and isomers) from hydrocarbons plus alcohols, ketones, aldehydes, acids, ethers and esters; minimum number of groups is 2, maximum number of groups is 9, maximum number of "functional" groups is 6, maximum number of same "functional" groups is 6; search the database.
- **Non-temperature dependent properties**: Maximum normal boiling point is 450 K; Minimum open cup flash temperature is 320 K; Minimum LogP (octanol/water) is 1.5
- Temperature dependent properties: Upper limit of density at 298 K is 0.9; lower limit of vapour pressure at user specified temperature of 360 K is 0.003 bar
- **Mixture properties**: Select "perform mixture calculations"; select UNIPARL – Original UNIFAC-LLE; LLE calculation type; phenol and water as the selected key components (note that if a stream with phenol and water was defined before entering ProCamd, this information would be automatically transferred together with the mole fractions of the mixture); select phenol as the solute; and the

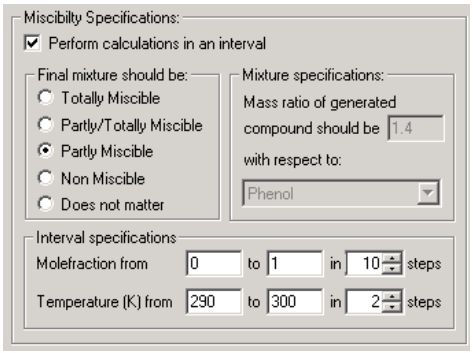
following constraints – maximum solvent loss = 0.001, minimum separation factor = 80, minimum solvent capacity = 2, minimum feed selectivity = 8

- **Azeotrope/miscibility calculations**: Select azeotrope calculation and miscibility calculation; solvent must not form azeotrope with phenol;

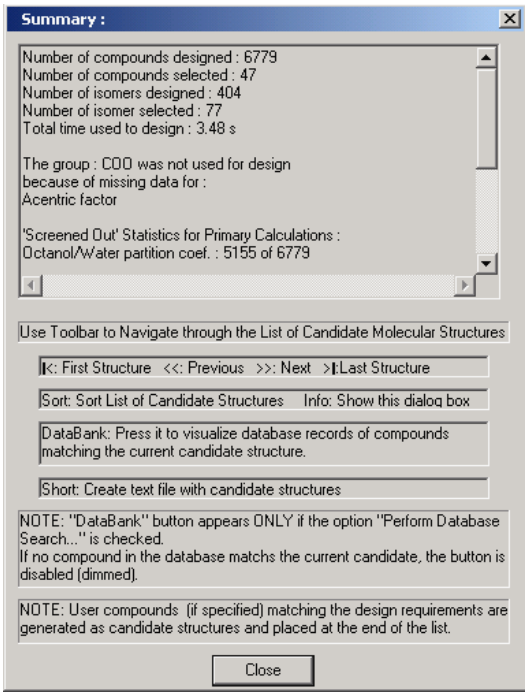
perform miscibility calculation with fixed amount of solvent (1.4 times that of phenol)

repeat the calculations with miscibility calculations at intervals of 0-1 mole fraction in 10 intervals and 290-300 K in 2 intervals and "partly miscible"

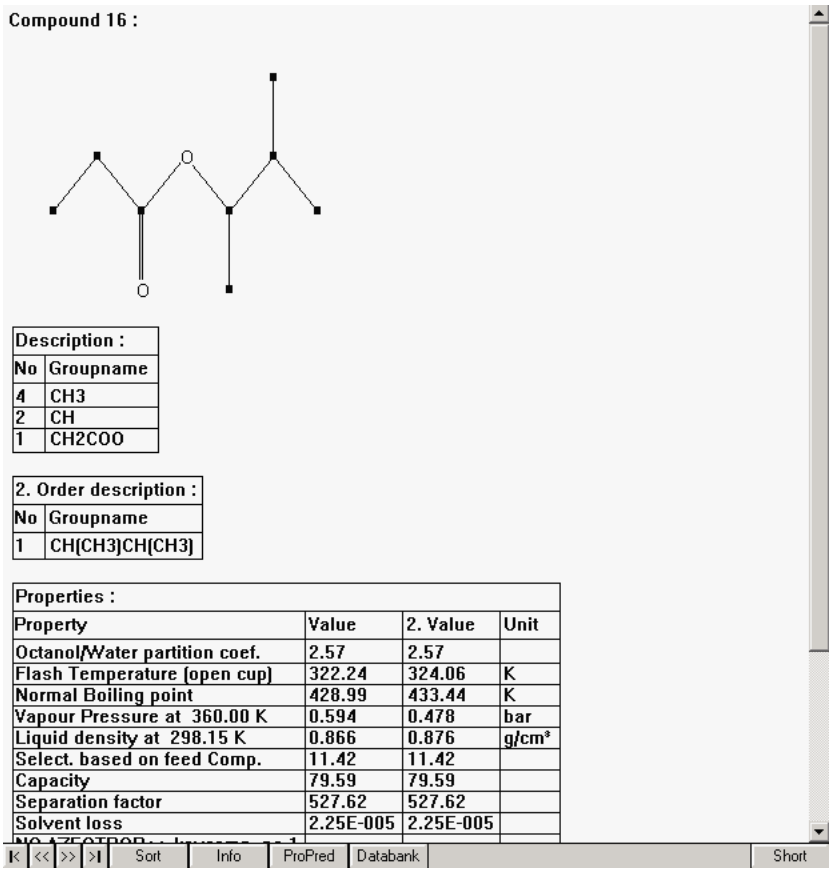




Start calculations by clicking on "GO" – when calculations are completed, the following "summary" of results is given by ProCamd (as shown below).



The structural description of the generated (feasible) molecule together with the calculated property (constraints) values is shown on the left-hand side of the user-interface for each feasible molecule.



Compound 16 :

Description :

No	Groupname
4	CH3
2	CH
1	CH2COO

2. Order description :

No	Groupname
1	CH(CH3)CH(CH3)

Properties :

Property	Value	2. Value	Unit
Octanol/Water partition coef.	2.57	2.57	
Flash Temperature (open cup)	322.24	324.06	K
Normal Boiling point	428.99	433.44	K
Vapour Pressure at 360.00 K	0.594	0.478	bar
Liquid density at 298.15 K	0.866	0.876	g/cm³
Select. based on feed Comp.	11.42	11.42	
Capacity	79.59	79.59	
Separation factor	527.62	527.62	
Solvent loss	2.25E-005	2.25E-005	

|K | << | >> | >| Sort | Info | ProPred | Databank | Short

Repeating the calculations with miscibility calculations at intervals of composition and temperatures, gives the same results with the following additional information

Miscibility :

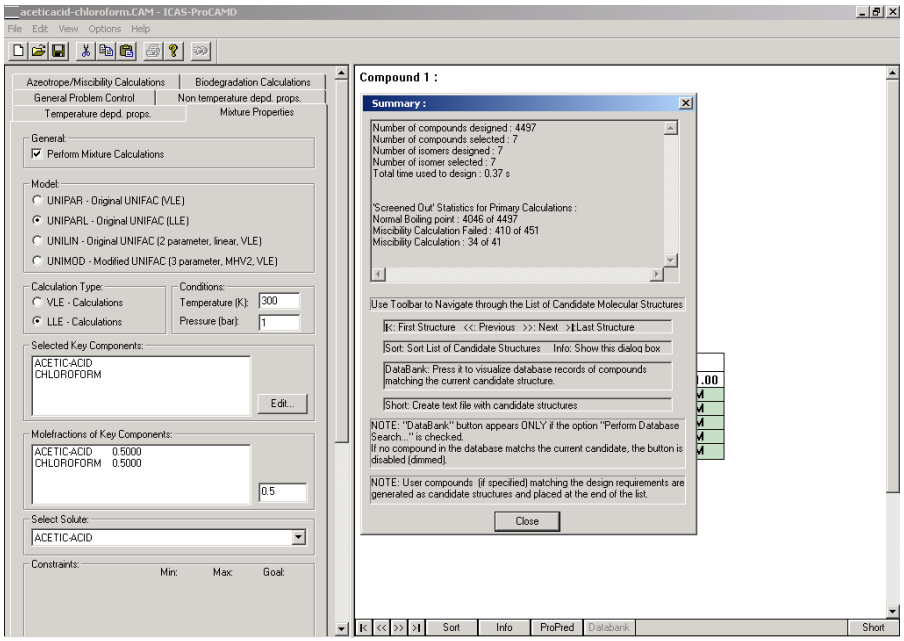
T \ x	0.00	0.11	0.22	0.33	0.45	0.56	0.67	0.78	0.89	1.00
290.00	IM	IM	IM	IM	IM	IM	IM	IM	IM	M
300.00	IM	IM	IM	IM	IM	IM	IM	IM	IM	M

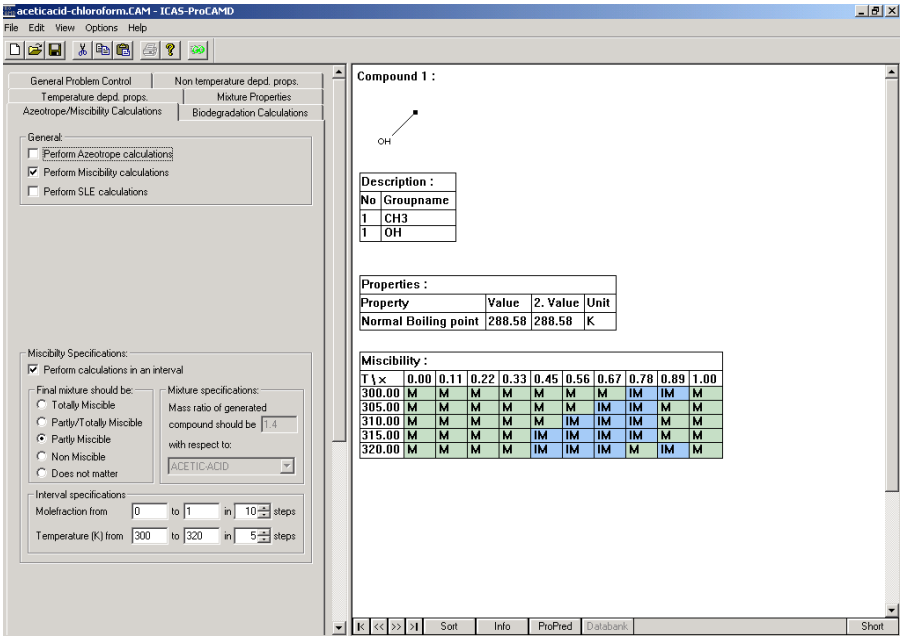
Step 4: Verification – Add the selected solvent to the phenol-water system and use ICAS-Utility option to draw the ternary LLE phase diagram to verify the creation of two phases and separation of phenol from water.

Related problems

** Find non-aromatic organic molecules (with T_b less than 400 K) that when added to a mixture of acetic acid – chloroform in the liquid phase, causes a phase split. Assume T=300 K and P=1 atm*

ProCamd problem definition requires General Problem Control; Non-temperature Dependent properties; Mixture Properties; and, Miscibility Calculations. The Screen shots below show the problem definition pages and the results from ProCamd.





* *Find solvents for hexane-benzene separation (LLE separation)*

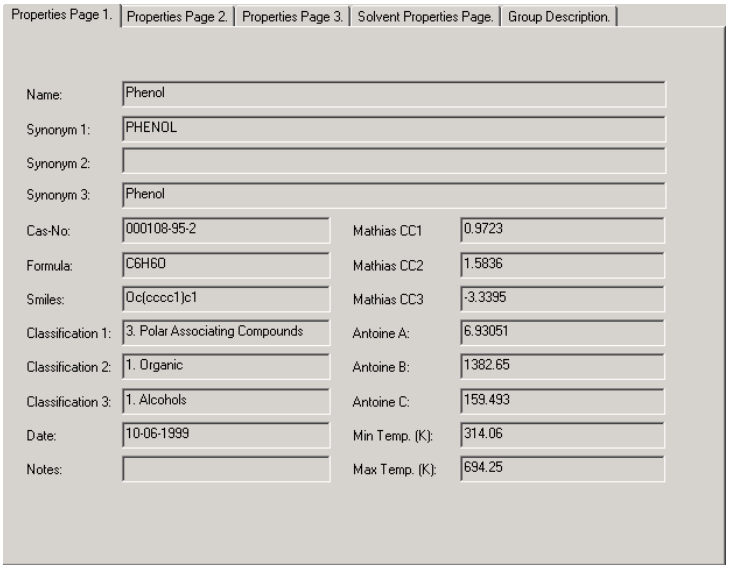
3.3 Solvent-based Solid Separation

3.3.1 Solvent Substitution

We have phenol deposits as a solid and we need to clean the equipment before our product can be produced. We already know that we can use benzene or toluene to dissolve the phenol. We would like to investigate if it is possible to use a more environmentally friendly anti-solvent to extract the phenol.

Step 1: Problem Formulation

We need to establish the needed properties for the replacement solvent. We can use the CAPEC database to search for the properties of phenol, benzene and toluene. In the screen shot below, the properties of phenol are highlighted (see appendix 1 on how to perform search in the CAPEC database M.



Other properties:

T_m = 314.06 K

T_b = 454.99 K

δ_{SP} = 24.63 $(MPa)^{1/2}$

H_{fus} = 11510 kJ/kmole

T_c = 694.25 K

P_c = 60.498 atm

V_c = 0.229 m^3/kmole

v = 0.889 m^3/kmole

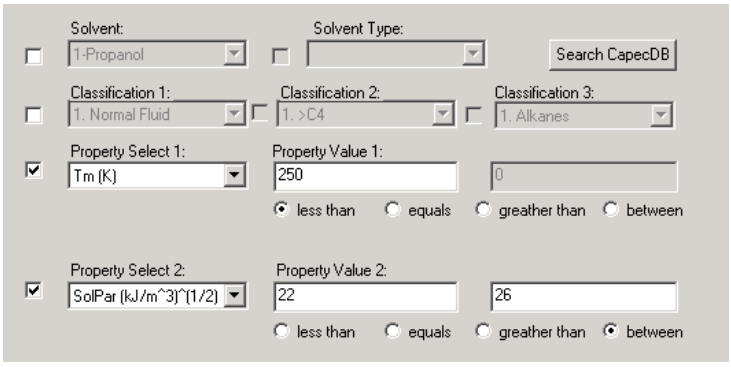
Mw = 94.113

Pure component data for Phenol obtained by "basic search" in the CAPEC database

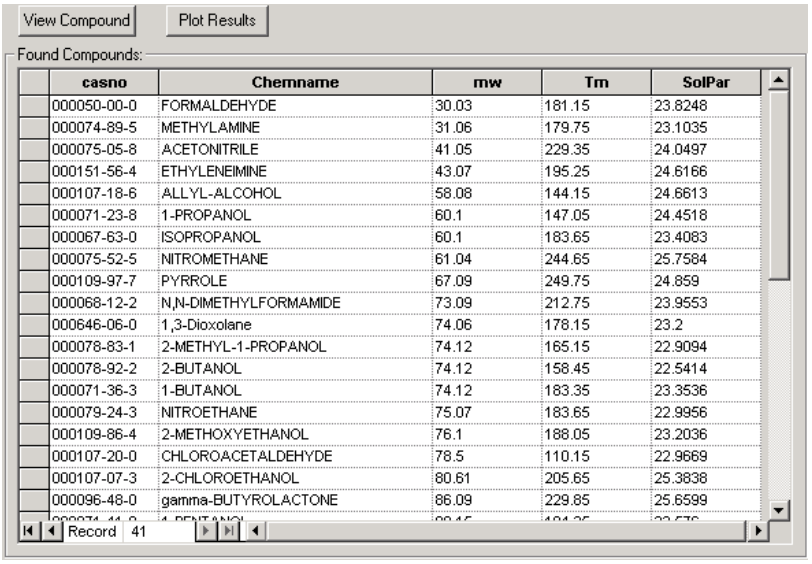
Based on the phenol data, we can formulate the solvent search problem as follows – The temperature of the operation is below 314 K (assume 300 K), at this condition, solvent plus phenol must form a liquid solution and the composition of the phenol must be reasonably high. As a measure of solubility, initially, we can search for solvents having melting points below 250 K and having the Hildebrand solubility parameters $22 < \delta_{SP} < 26$ $(MPa)^{1/2}$. This problem can also solved through the CAPEC database (using the "advanced search" option) or ProCamd.

Step 2: Generation of candidates through CAPEC database search

To use the advanced search option in the CAPEC database, click on  and then click on "advanced search" in the CAPEC database. Then select the options for the search engine as shown below.



Now click on Search CapecDB to start the search engine. The search result is shown in the figure below. It can be noted that 41 candidates have been found.

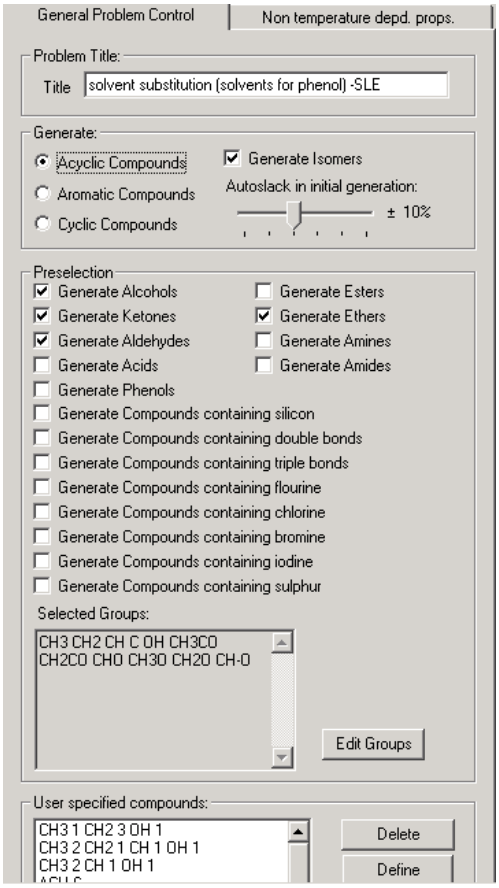


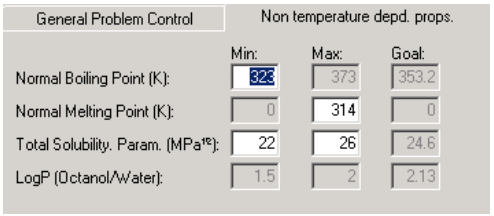
casno	Chemname	mw	Tm	SolPar
000050-00-0	FORMALDEHYDE	30.03	181.15	23.8248
000074-89-5	METHYLAMINE	31.06	179.75	23.1035
000075-05-8	ACETONITRILE	41.05	229.35	24.0497
000151-56-4	ETHYLENEIMINE	43.07	195.25	24.6166
000107-18-6	ALLYL-ALCOHOL	58.08	144.15	24.6613
000071-23-8	1-PROPANOL	60.1	147.05	24.4518
000067-63-0	ISOPROPANOL	60.1	183.65	23.4083
000075-52-5	NITROMETHANE	61.04	244.65	25.7584
000109-97-7	PYRROLE	67.09	249.75	24.859
000068-12-2	N,N-DIMETHYLFORMAMIDE	73.09	212.75	23.9553
000646-06-0	1,3-Dioxolane	74.06	178.15	23.2
000078-83-1	2-METHYL-1-PROPANOL	74.12	165.15	22.9094
000078-92-2	2-BUTANOL	74.12	158.45	22.5414
000071-36-3	1-BUTANOL	74.12	183.35	23.3536
000079-24-3	NITROETHANE	75.07	183.65	22.9956
000109-86-4	2-METHOXYETHANOL	76.1	188.05	23.2036
000107-20-0	CHLOROACETALDEHYDE	78.5	110.15	22.9669
000107-07-3	2-CHLOROETHANOL	80.61	205.65	25.3838
000096-48-0	gamma-BUTYROLACTONE	86.09	229.85	25.6599

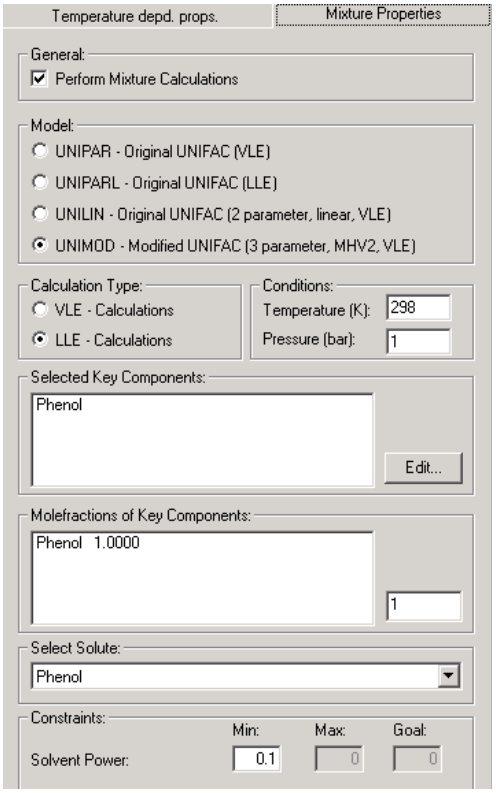
Using the results from above, the next step would be to perform a search through ProCamd, which will generate new molecules as well as check known compounds.

Step 3: Generation of candidates through ProCamd

We start by entering ProCamd from ICAS and then we need to fill-out the pages according to the instruction manual from section 1. The screens corresponding to the different pages of ProCamd are shown below.

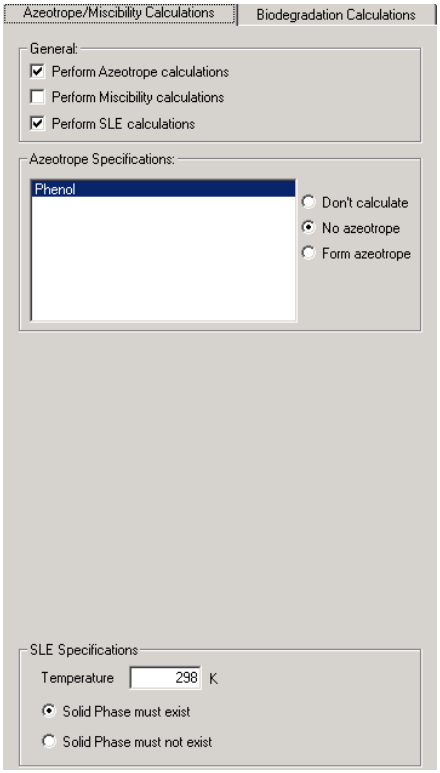




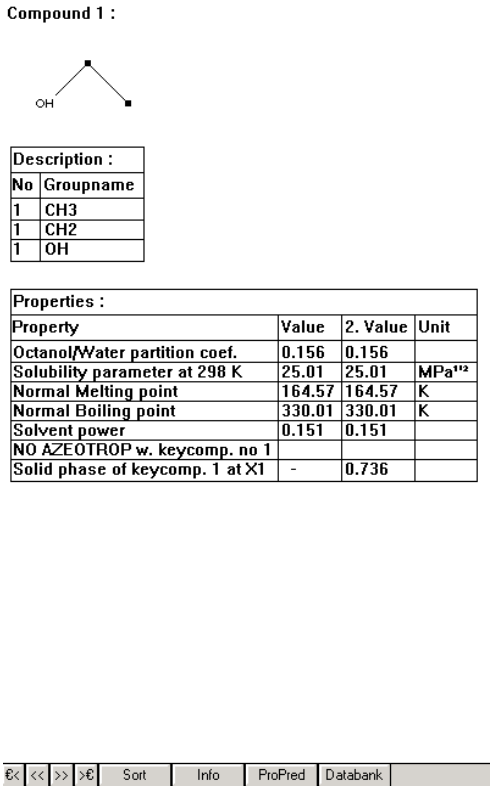


Define as user-specified compounds, some of the solvents that appear in "common solv"

Problem specification pages from ProCamd for the solvent substitution exercise

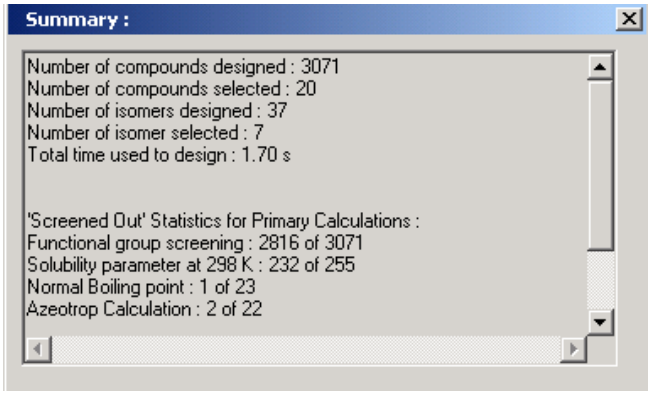


Problem specification page from ProCamd.



Results section from ProCamd. Note that "ProPred" and "Databank" are highlighted. This means that we can use these tools for this compound.

The solution statistics are shown in the figure below. This screen can also be obtained by clicking on "Info".

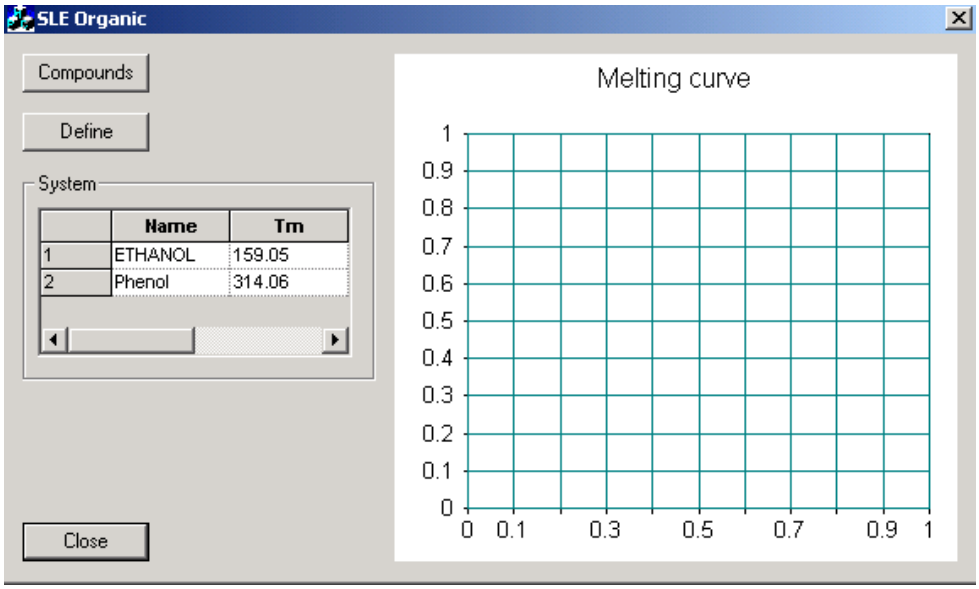


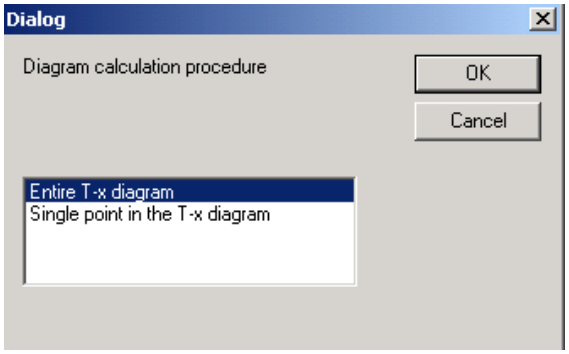
From the figures above, it can be noted that ethanol is also a feasible candidate as a solvent. We will verify the feasibility of ethanol in the next step.

Step 4: Verification of solvent through a solid-liquid equilibrium phase diagram

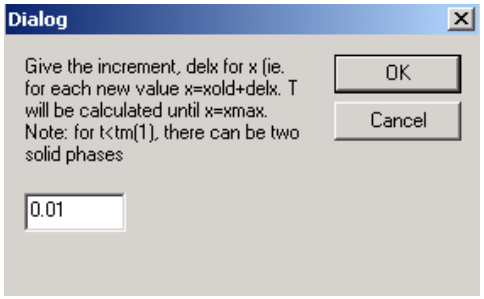
In order to obtain a solid-liquid equilibrium phase diagram, follow the steps given in appendix A3. The following steps are necessary:

1. Draw a stream in the ICAS-main window
2. Select the compounds phenol and ethanol
3. Select the property models (select UNIFAC-VLE model for liquid phase activity coefficients
4. Double click on the stream, specify the pressure (1 atm) and any values for temperature (for example, 300 K) and composition (for example, 1 and 1). Click on located on the top left hand corner.
5. Click on "Organic SLE" and then specify the data as shown below.

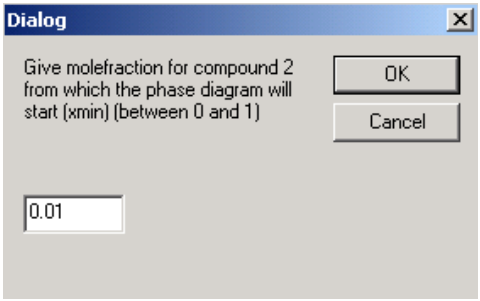




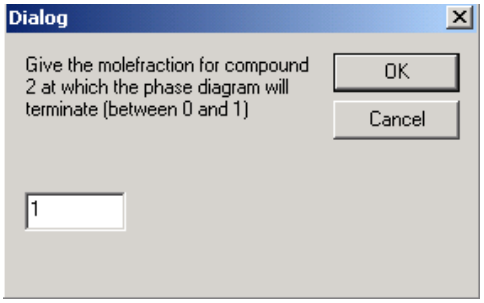
a



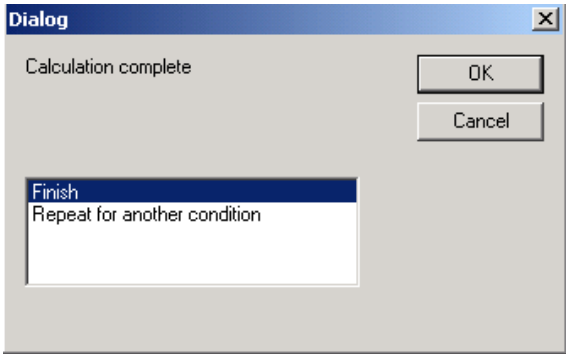
b



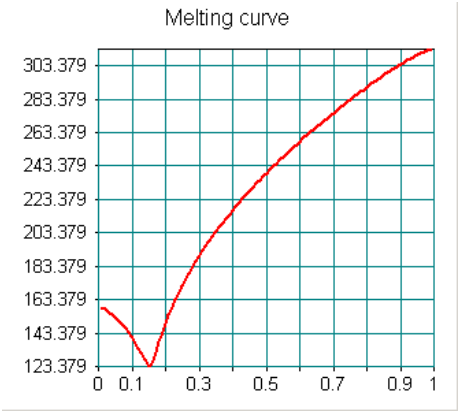
c



d



e



f

The specifications to generate the “entire T-X” diagram with the organic SLE toolbox of ICAS. Figure f shows the generated diagram. Clearly, at 300 K, a large amount of phenol can be dissolved.

Exercises related to solvent substitution

A. Solve the problem in step 2 with ProCamd (note that only the "general problem control" and the "non-temperature dependent properties" need to be specified.
B. Verify another solvent through step 4
C. If you change the solubility parameter bounds to less than 22 or more than 26, will the solvents be valid for phenol? Find solute products that will be valid for solvents with solubility parameter < 22 and > 26 (use both database search and ProCamd).
D. Find solvents for Naphthalene.

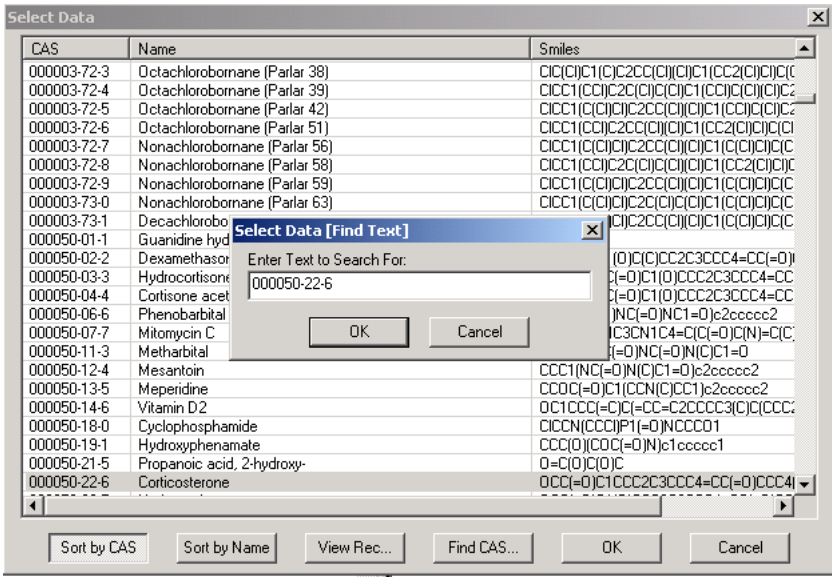
3.4 Design of Backbones and Termination of Backbones

3.4.1 Generate backbone in ProPred, terminate in ProCamd & verify in ProPred

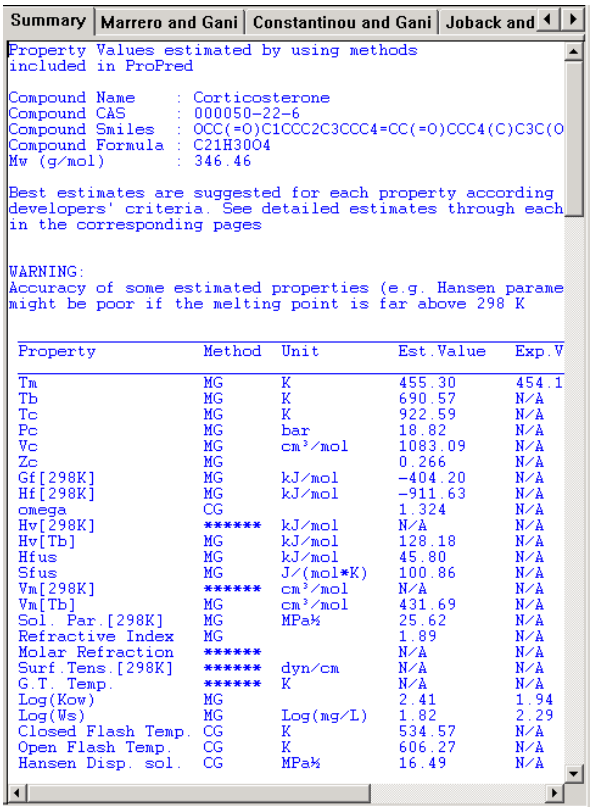
In this problem, we will start with ProPred, take a known molecule (for example, Corticosterone), use the new features in ProPred to create free attachments in the molecule (that is, create a backbone). The Backbone is then transferred to ProCamd, where terminated structures are generated.

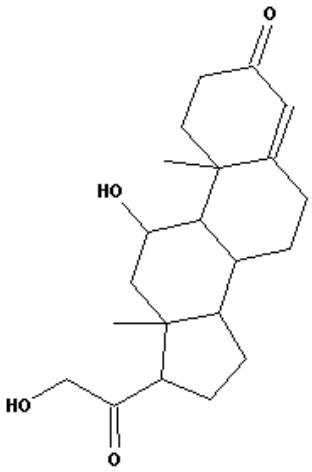
Step 1: Start ProPred from ICAS

Step 2: Click on  (database) , click on "Find CAS", type the CAS Number for Corticosterone (00005-22-6), select the compound by clicking on OK.

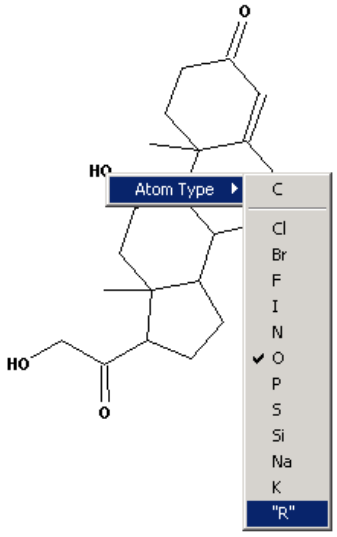


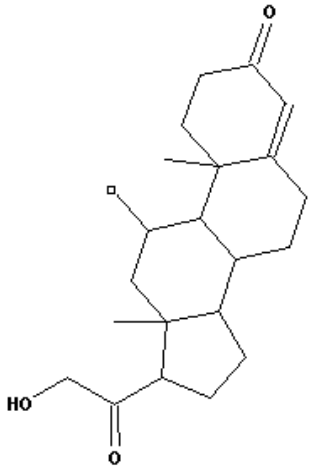
Step 3: ProPred draws the molecule and predicts the properties (as shown below)



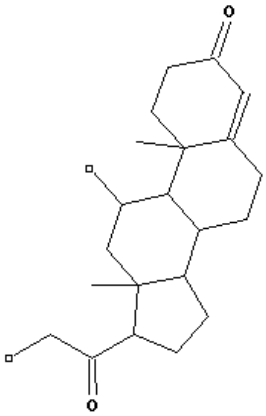


Step 4: Remove the OH group connection from the molecular structure at the two locations (as shown below)





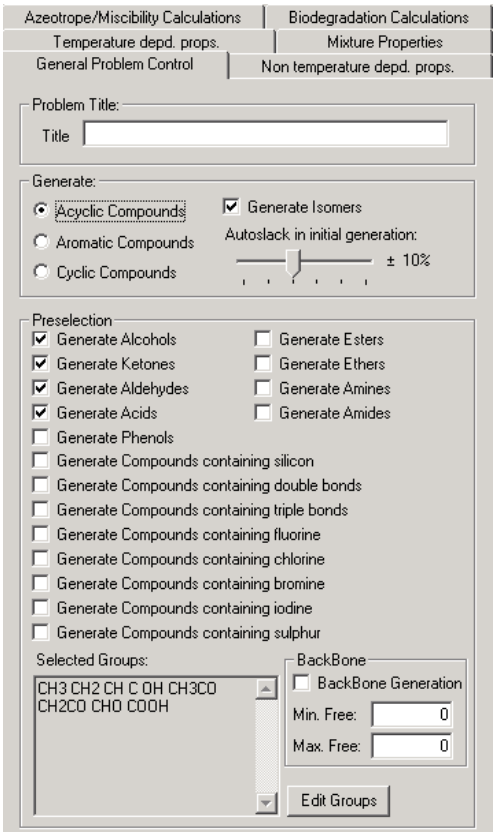
Backbone with one-free attachment

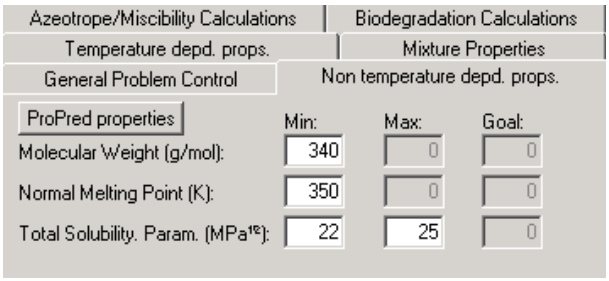


Backbone with two-free attachments. Note that as ProCamd generates molecular structures only with the Constantinou & Gani groups, it must be possible for the Constantinou & Gani method to represent the backbone. Otherwise, ProPred will not launch ProCamd.

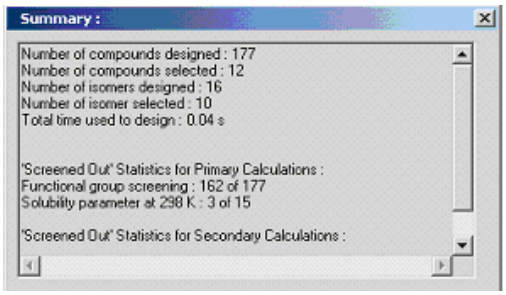
Step 5: Launch ProCamd from ProPred from the tools menu in ProPred.

Step 6: Fill-out the necessary problem definition pages in ProCamd (general problem control, non-temperature dependent properties) as shown below.





Step 7: Terminate the backbone by clicking on "GO". The following results "summary" is obtained.



The generated (feasible) compound number 2 is Corticosterone.

Compound 2 :

Description :	
No	Groupname
2	CH3
6	CH2
5	CH
2	C
1	CH=C
2	OH
2	CH2CO

Properties :			
Property	Value	2. Value	Unit
Solubility parameter at 298 K	23.71	23.71	$MPa^{1/2}$
Normal Melting point	355.21	355.21	K
Molecular weight	346.45	346.45	g/mol

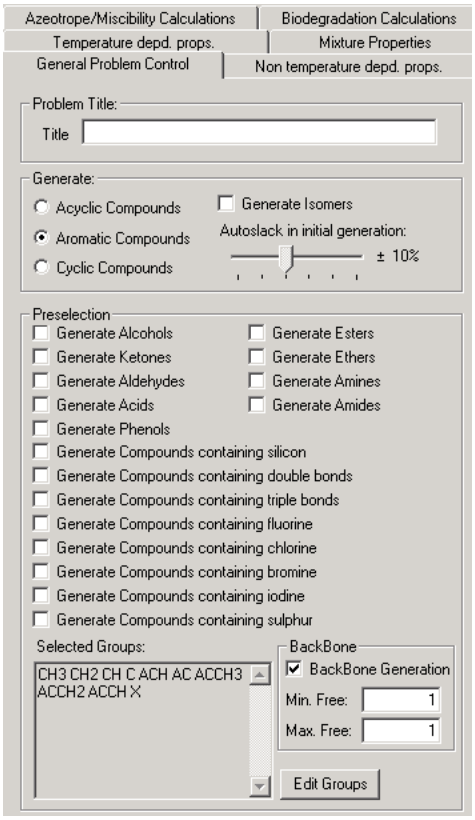
Step 8: Save the backbone-termination problem as "save ProPred backbone problem" under the file menu. To use this file later, the saved backbone file must be loaded from the file menu.

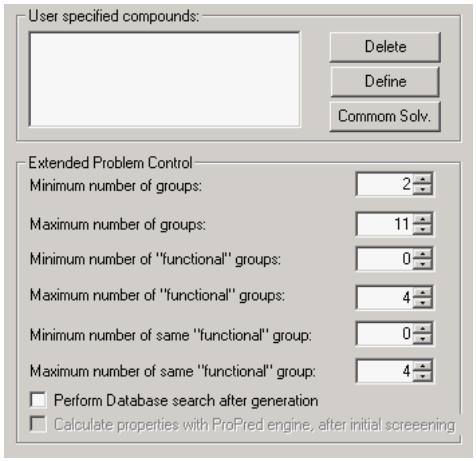
Note that for backbone termination step, the options for ProPred properties and database search cannot be used.

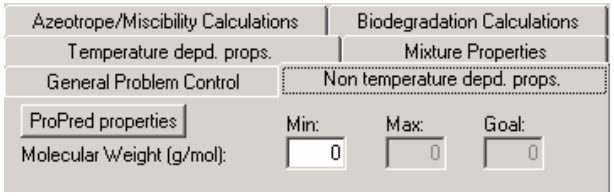
3.4.2 Generate backbone in ProCamd and terminate (manually) in ProPred

In this problem, we will first generate a backbone with ProCamd using only the C & H atoms and with 1 free-attachment in the backbone. We will then go to ProPred to draw the molecular structure and work on the structure without terminating the structure. We will then launch ProCamd from ProPred to find the final terminated structure through ProCamd.

Step 1: Start ProCamd and specify the following backbone generation problem.

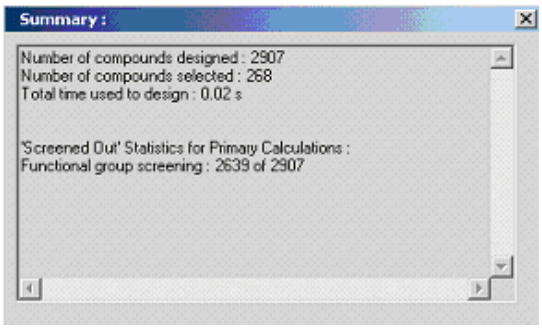






Note: at this stage specification of any other property is not necessary

Step 2: Run ProCamd to generate the backbone alternatives. Note that for the backbone generation, "isomer" generation is not allowed. For the problem formulated in step 1, the following result is obtained.



Compound 221 :

Description :	
No	**Groupname**
3	CH3
1	CH
4	ACH
1	ACCH2
1	ACCH
1	X

Properties :		
Property	**Value**	**Unit**
Molecular weight	161.26	g/mol

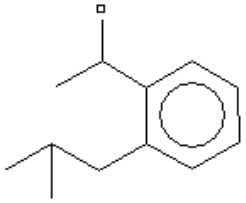
X indicates a free attachment

Step 3: Click on ProPred to transfer the backbone structure. Propred draws the structure and calculates all properties, as shown below.

Compound Name : unknown
Compound CAS : unknown
Compound Smiles : CC(C)Cc1ccccc1C(C)[*]
Compound Formula : C12H17
Mw (g/mol) : 161.26

Best estimates are suggested for each property according developers' criteria. See detailed estimates through each in the corresponding pages

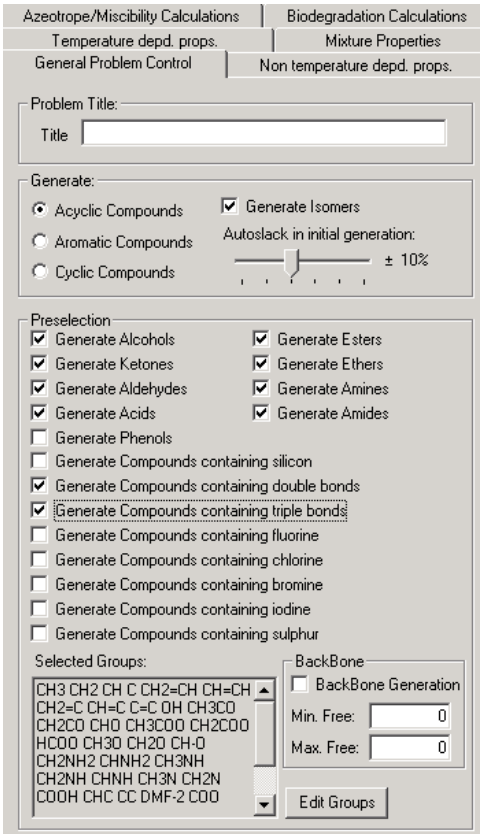
Property	Method	Unit	Est.Value	Exp.V
Tm	MG	K	167.89	N/A
Tb	MG	K	473.15	N/A
Tc	MG	K	674.34	N/A
Pc	MG	bar	24.56	N/A
Vc	MG	cm³/mol	585.33	N/A
Zc	MG		0.256	N/A
Gf[298K]	MG	kJ/mol	152.06	N/A
Hf[298K]	MG	kJ/mol	-53.68	N/A
omega	CG		0.388	N/A
Hv[298K]	MG	kJ/mol	60.97	N/A
Hv[Tb]	MG	kJ/mol	42.82	N/A
Hfus	MG	kJ/mol	8.94	N/A
Sfus	MG	J/(mol*K)	53.23	N/A
Vm[298K]	MG	cm³/mol	184.18	N/A
Vm[Tb]	MG	cm³/mol	226.51	N/A
Sol. Par.[298K]	MG	MPa½	17.82	N/A
Refractive Index	MG		1.49	N/A
Molar Refraction	MG		53.54	N/A
Surf.Tens.[298K]	MG	dyn/cm	30.84	N/A
G.T. Temp.	CG	K	290.24	N/A
Log(Kow)	MG		4.00	N/A
Log(Ws)	MG	Log(mg/L)	1.86	N/A
Closed Flash Temp.	CG	K	333.31	N/A
Open Flash Temp.	CG	K	368.44	N/A
Hansen Disp. sol.	CG	MPa½	16.88	N/A
Hansen Polar sol.	CG	MPa½	0.86	N/A
Hansen Hydr. sol.	CG	MPa½	1.41	N/A
Dipolar moment	CG	debye	0.31	N/A
Dielectric const.	CG		4.72	N/A
Henry[298K]	CG	bar*m³/mol	0.041	N/A

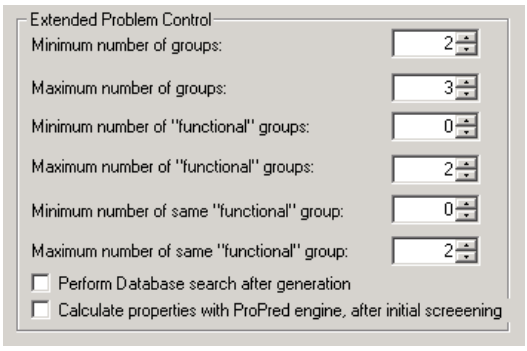


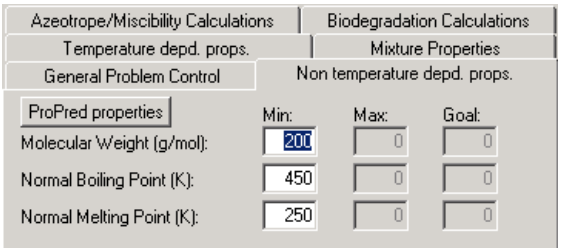
Step 4: Launch ProCamd from ProPred from the “tools” menu

A new ProCamd application is opened. ProPred sends back the same backbone structure that ProCamd generated.

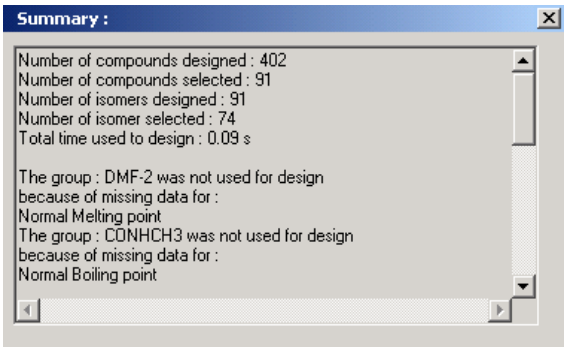
Step 5: Complete the backbone termination problem with ProCamd.



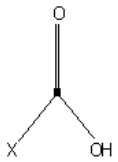




ProCamd generates 74 terminated structures out of which compound 1 is Ibuprofen



Compound 1 :



Description :	
No	Groupname
3	CH3
1	CH
4	ACH
1	ACCH2
1	ACCH
1	COOH

Properties :			
Property	Value	2. Value	Unit
Normal Melting point	295.13	295.13	K
Normal Boiling point	573.09	573.09	K
Molecular weight	206.27	206.27	g/mol

3.5 Design of Large Molecules

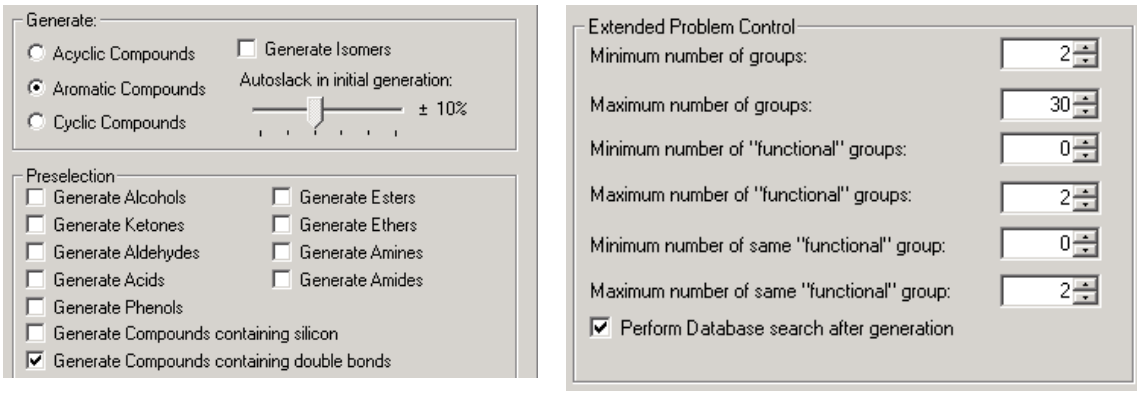
Design a large molecule having the following properties,

$M_w > 300$

$T_b > 400$ K

$T_m > 300$ K

Solve the problem with ProCamd and then switch to ProPred and further investigate the properties of the large molecule, including further increase of the size of the molecule. Only the "general problem control" and the "non-temperature depd props" need to be specified. In the "general problem control", select the following,



Repeat the problem for acyclic compounds and cyclic compounds

3.6 Refrigerant Design

A refrigerant needs to have the following properties: Vapor pressure as a function of temperature (> 0.15 atm at 272 K & < 15 atm 315 K), Heat of vaporization (< 24 kJ/mole) at 298 K, Heat capacity (< 134 kJ/mole K).

In addition, use ProCamd to generate the candidates and then use ProPred to verify the selection. Generate the P-H thermodynamic diagram through ProPred to validate the refrigeration cycle.

Related problem: Design of heat pump fluid.

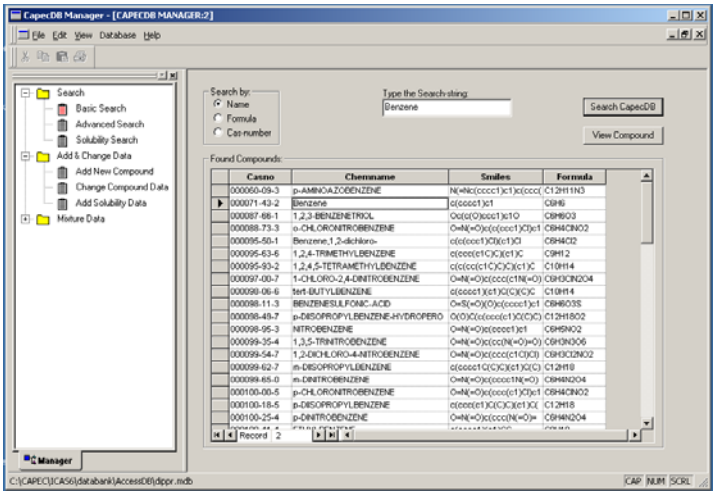
Appendix A: CAPEC Database Manager

In this section the use of the Database Manager is briefly discussed.

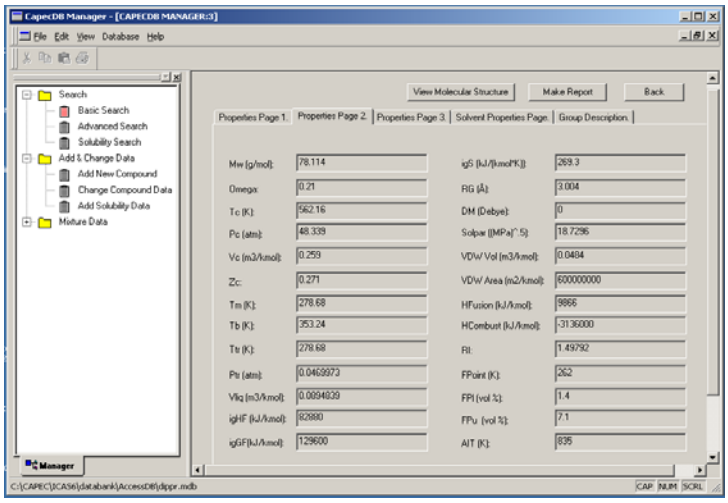
Click on the ”Database Manager” icon in the task bar of ICAS main window.

A1. Basic Search

Under the “Search” directory in the left panel you will find different options to perform the search of a compound. Select “Basic Search” → Type the name of your component → Click on “Search CapecDB” → Select your component from the displayed list → Click on “View Compound”.

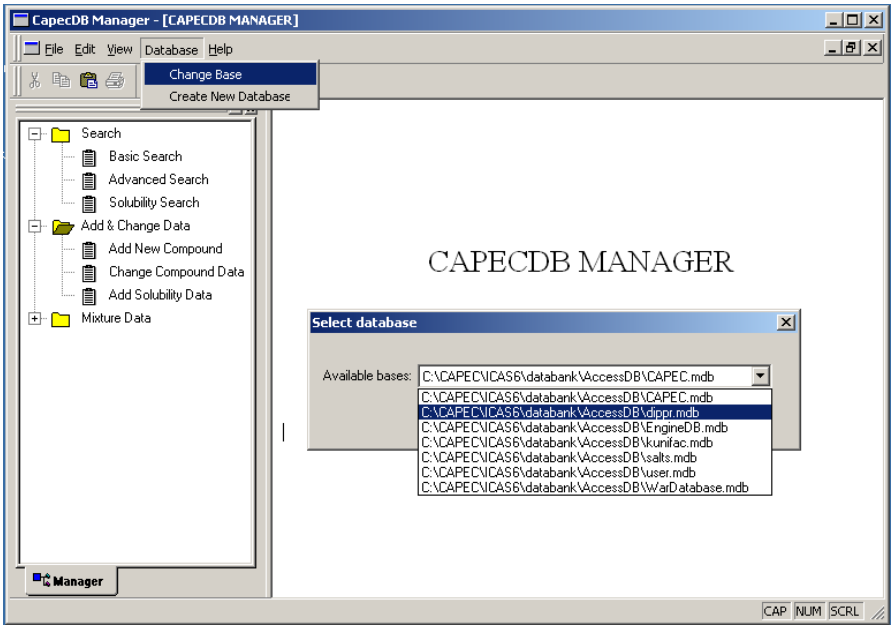


The Property pages will be displayed. Here you can find from Antoine Constants, Critical properties, property temperature dependent correlations, solvent properties and Group description. Click on ”Back” button to return to the initial page.


CapecDB Manager - [CAPECDB MANAGER:3]
File Edit View Database Help
Search
Basic Search
Advanced Search
Solubility Search
Add & Change Data
Add New Compound
Change Compound Data
Add Solubility Data
Mixture Data
Manager
View Molecular Structure
Make Report
Back
Properties Page 1
Properties Page 2
Properties Page 3
Solvent Properties Page
Group Description
Mw (g/mol): 78.114
Omega: 0.21
Tc (K): 562.16
Pc (atm): 48.339
Vc (m3/kmol): 0.259
Zc: 0.271
Tm (K): 278.68
Tb (K): 353.24
Tlt (K): 278.68
Plt (atm): 0.0469973
Vliq (m3/kmol): 0.0894839
igHF (kJ/kmol): 82680
igGF(kJ/kmol): 129600
igS (kJ/(kmolºK)): 269.3
RG (Å): 3.004
DM (Debye): 0
Solpar ((MPa)^.5): 18.7296
VDW Vol (m3/kmol): 0.0484
VDW Area (m2/kmol): 600000000
HFusion (kJ/kmol): 9866
HCombust (kJ/kmol): -3136000
Rl: 1.49792
FPoint (K): 262
FPl (vol %): 1.4
FPu (vol %): 7.1
AIT (K): 835
C:\CAPEC\ICAS6\databank\AccessDB\dippr.mdb
CAP NUM SCRL

A2. Add and Change of Data

1. Data can be changed only on the user-database. Go to the user-database where your compound exists (Database → Change to any of the user-databases)

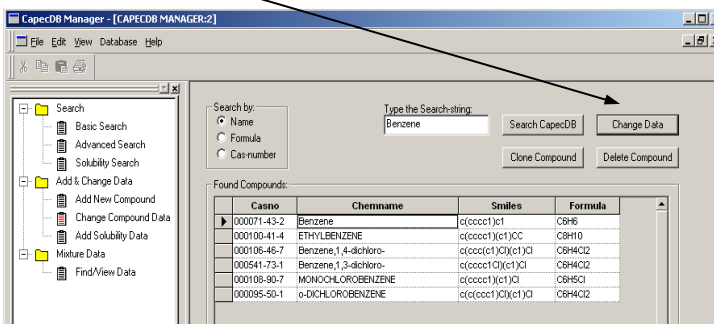


2. Change of Data:

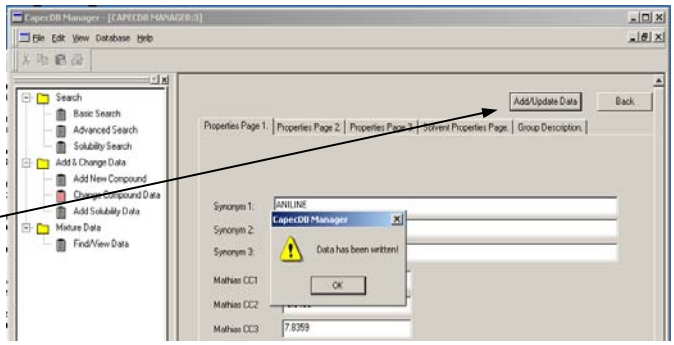
✓ Go to "Change compound data" on the left panel.

✓ Type your component in the box → click on "Search CapecDB" → Select it.

✓ Click on the "Change Data" button



✓ Change the desired information in the corresponding fields. Once you finished click on "Add/Update Data" button. An updating message will appear.

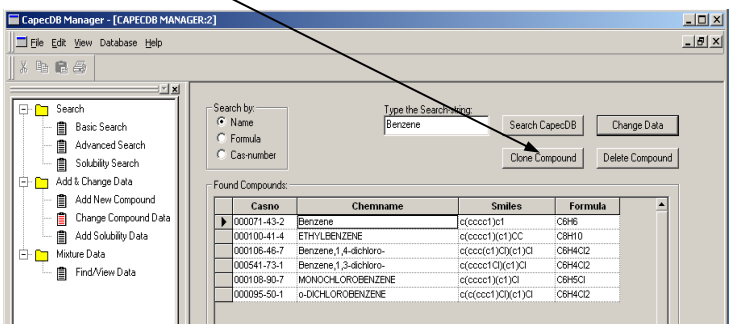


3. Clone of a Compound

✓ Go to "Change compound data" on the left panel.

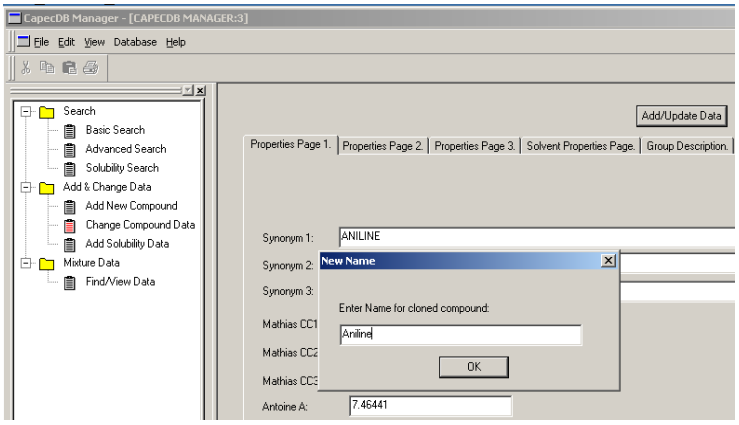
✓ Type your component in the box → click on "Search CapecDB" → Select it.

✓ Click on "Clone Compound".

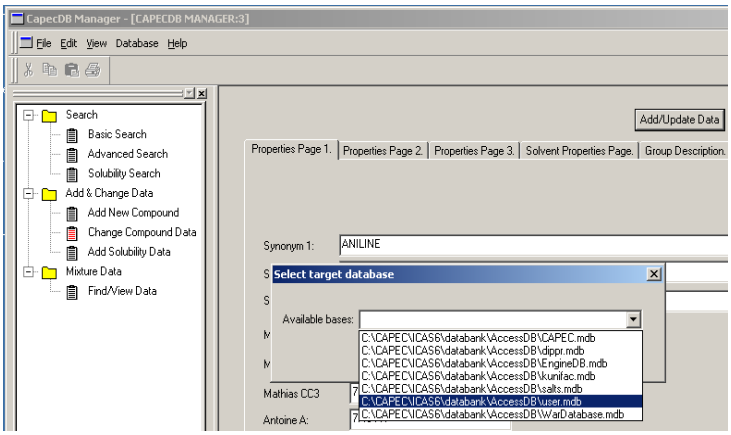


✓ If you change some information do it in the corresponding fields. Once you finished click on "Add/Update Data" button.

✓ Give a name in the "New Name" window → Click on "Ok",



✓ Allocate the cloned component in a database (only to the "user" database"),



✓ Now there is a new compound in the selected database!

A3. How to Estimate Properties of a Chemical Product Not Found in the Database?

- Launch the CAPEC database and then select the user-database.
- Click on “add/change” data
- Click on ProPred
- In ProPred, either draw the molecule or import the SMILES or import the mol.file corresponding to the chemical product. The database in ProPred can also be searched, if necessary.
- Check if all the necessary properties have been estimated by ProPred, if yes, exit from ProPred.
- Click on “update” data

Try the following exercise:

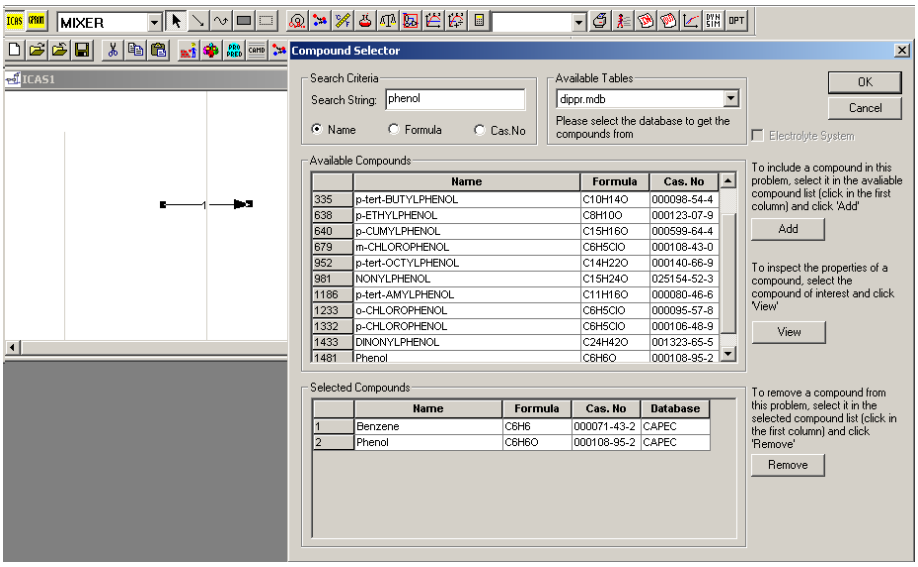
Try to put Morphine (Oc1ccc2CC3N(C)CCC45C3C=CC(O)C4Oc1c25) into the user-database. CAS number of morphine is 000057-27-2 (the database in ProPred has this compound).

APPENDIX B. Manual for SLE

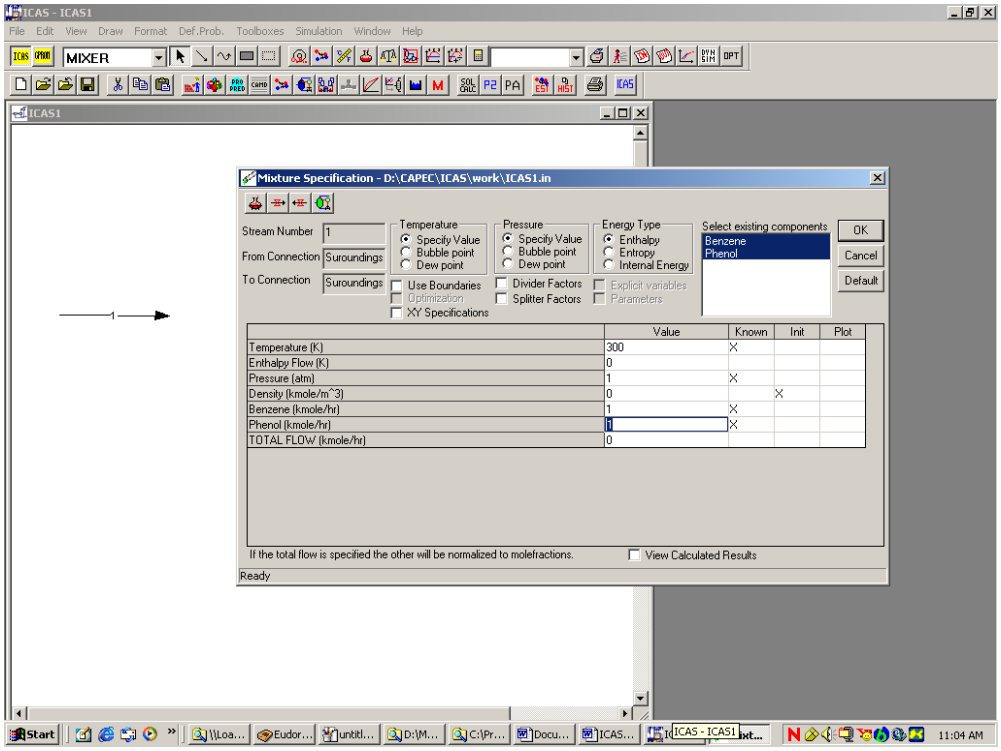
B1. Use of Utility Toolbox

B1.1. Compound selection & property model selection

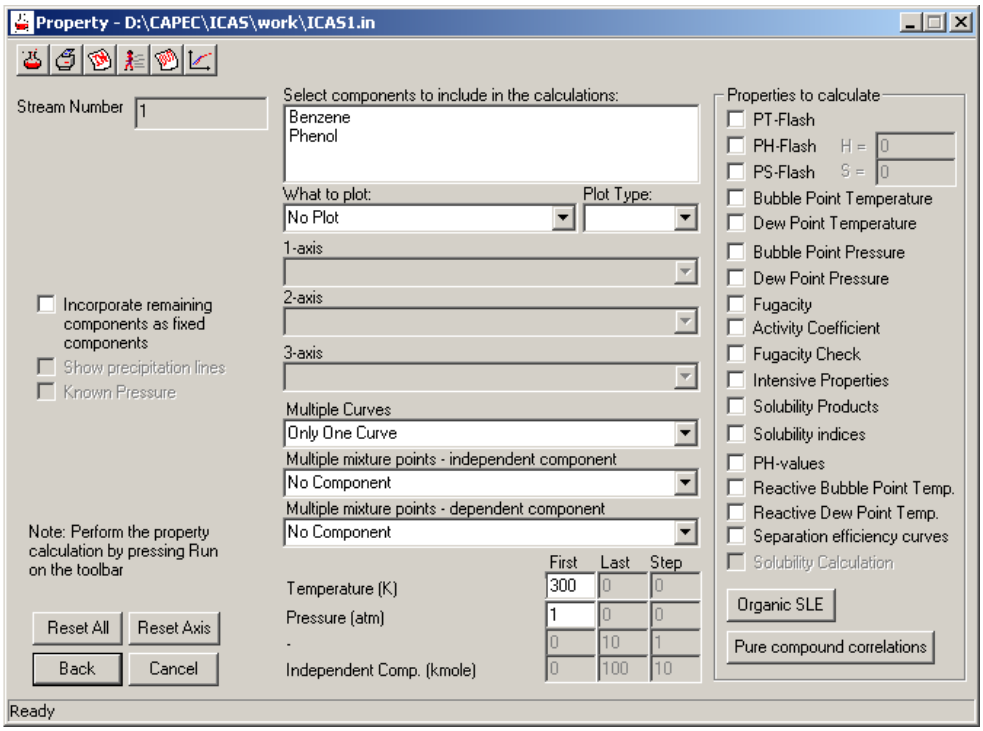
I. Draw a stream and then select compounds by clicking on the "compounds"  button.



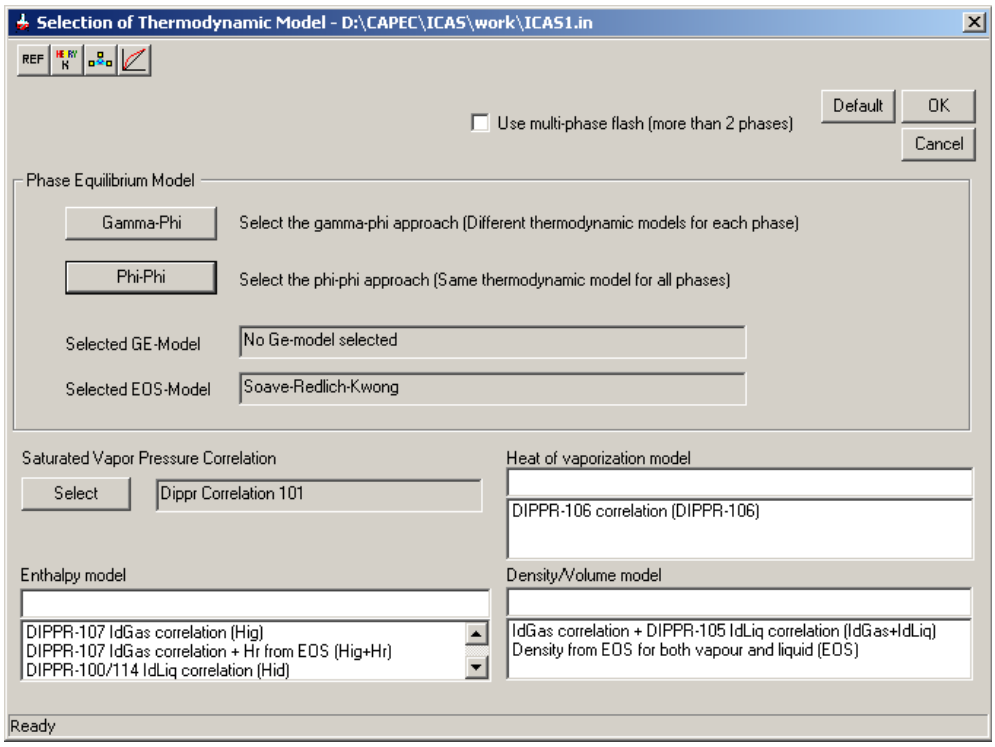
II. Double click on the stream to enter the "mixture specification" window



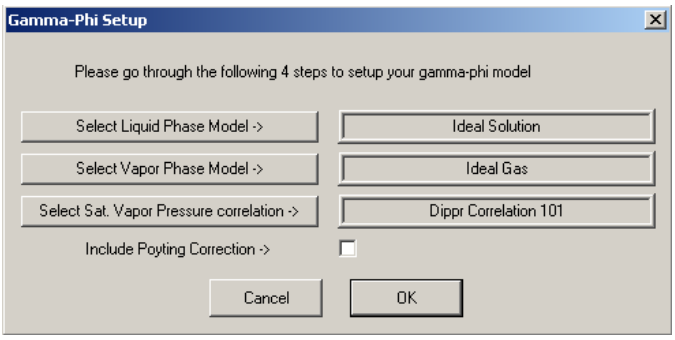
III. After specifying the temperature, pressure and component flows (as shown above) click on the top-left button to enter the "property" window. Click on the top-left button to go to the "property model" selection window.



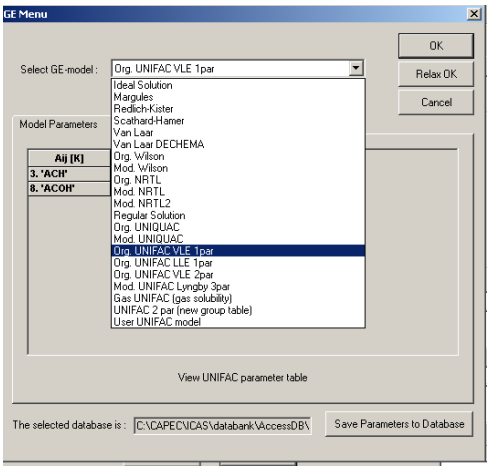
IV. Click on the “gamma-phi” option for this example

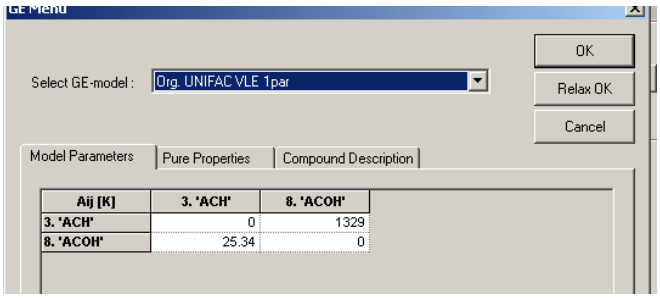


V. Click on the “select liquid phase model”

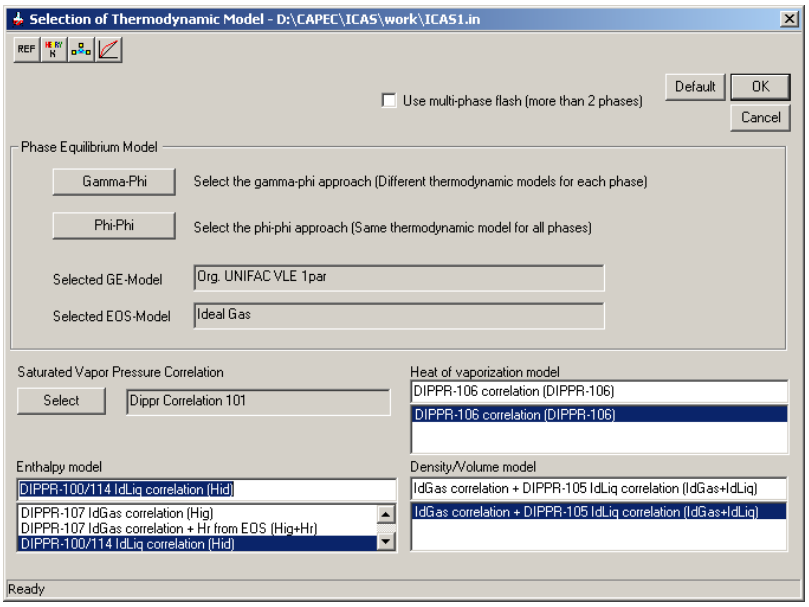


VI. Select the UNIFAC model as shown below. The UNIFAC model parameters are shown and if all parameters are available (as in this example), click OK



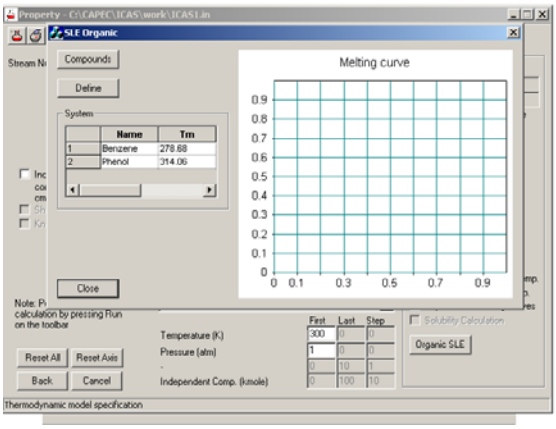


VII. On return to the main property model selection window click on default to select all the other model options (as shown below) and click OK.

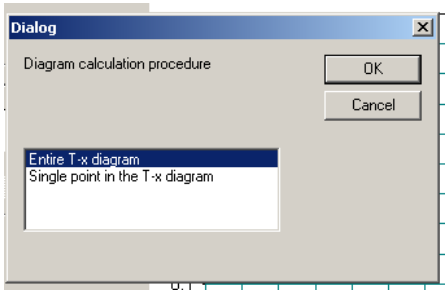


B1.2 Utility calculation option (SLE)

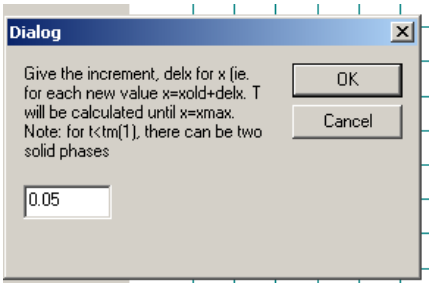
I. On return to the Property "Utility" window, select the option(s) of choice for calculations. For this example, select the "SLE" option and follow the screens SLE-a to SLE-f.



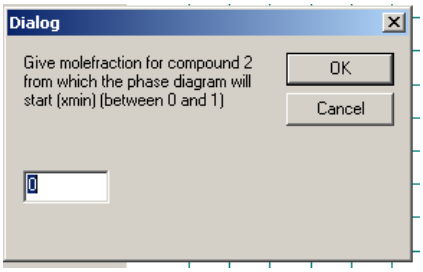
SLE-a



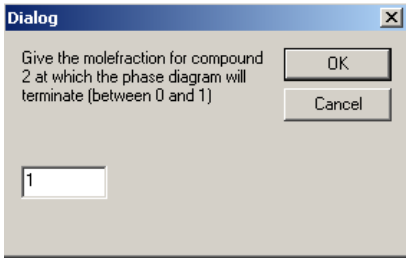
SLE-b



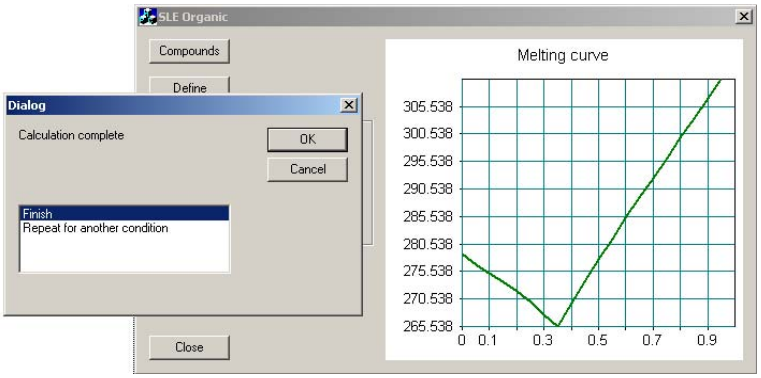
SLE-c



SLE-d



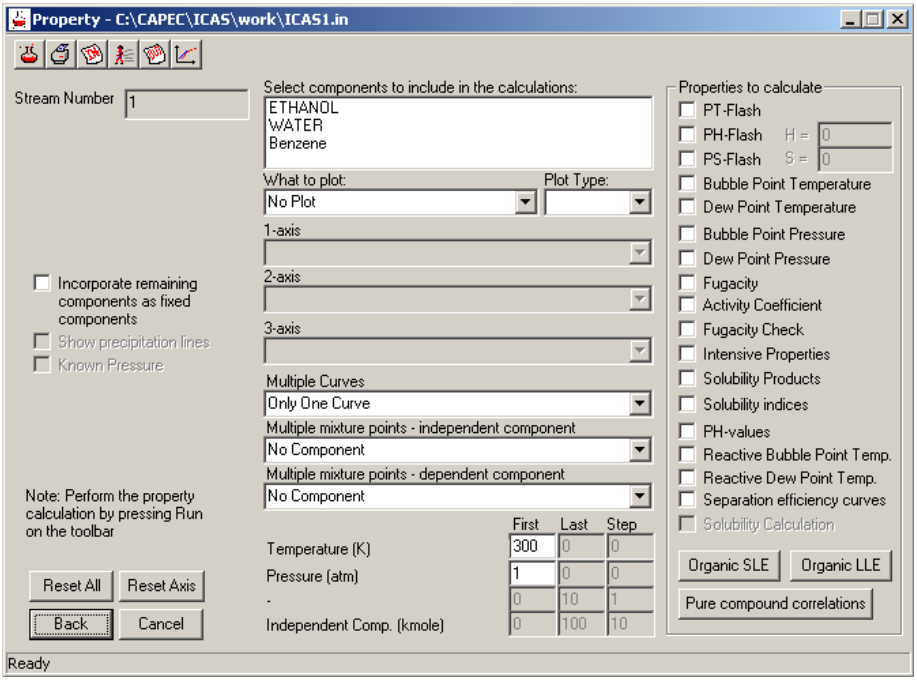
SLE-e



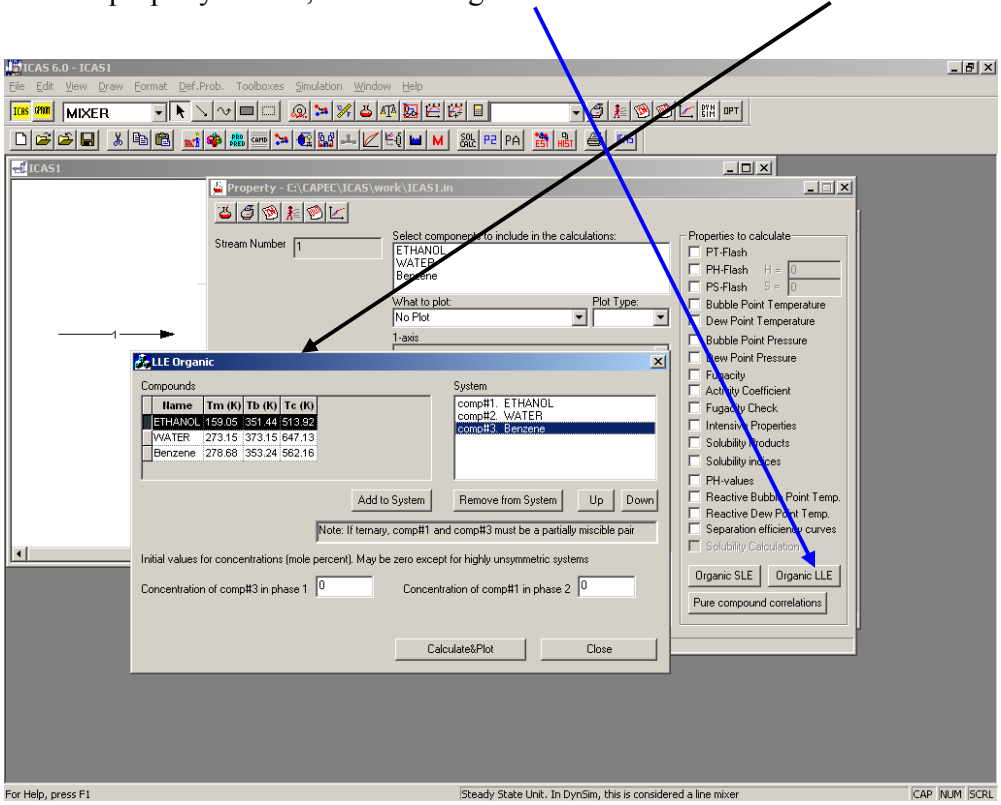
SLE-f

B2. LLE Phase Diagram

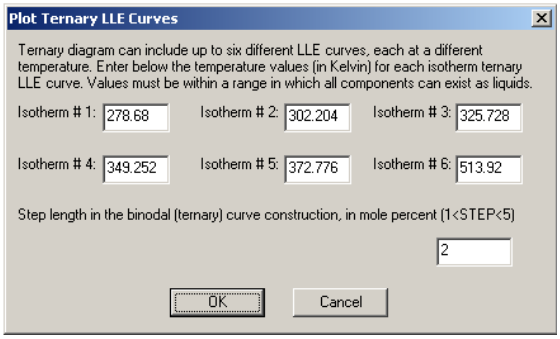
The mixture is changed to water-ethanol-benzene. The UNIFAC-LLE model is chosen and the LLE-phase diagram option is called from the ICAS-utility toolbox, as shown below.



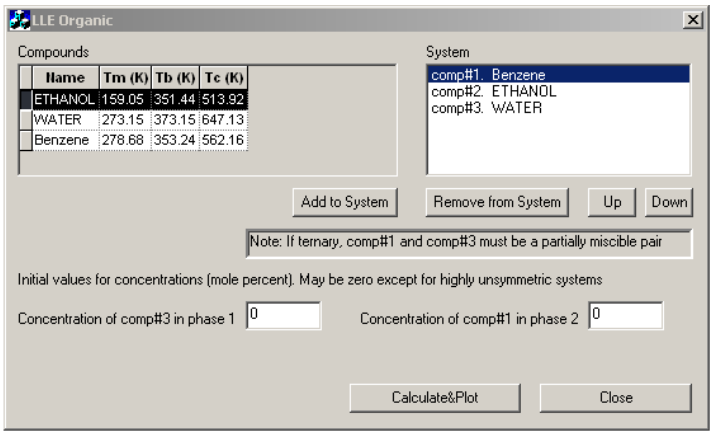
- From the “property” menu, click on “organic LLE” to enter the LLE tool-box:



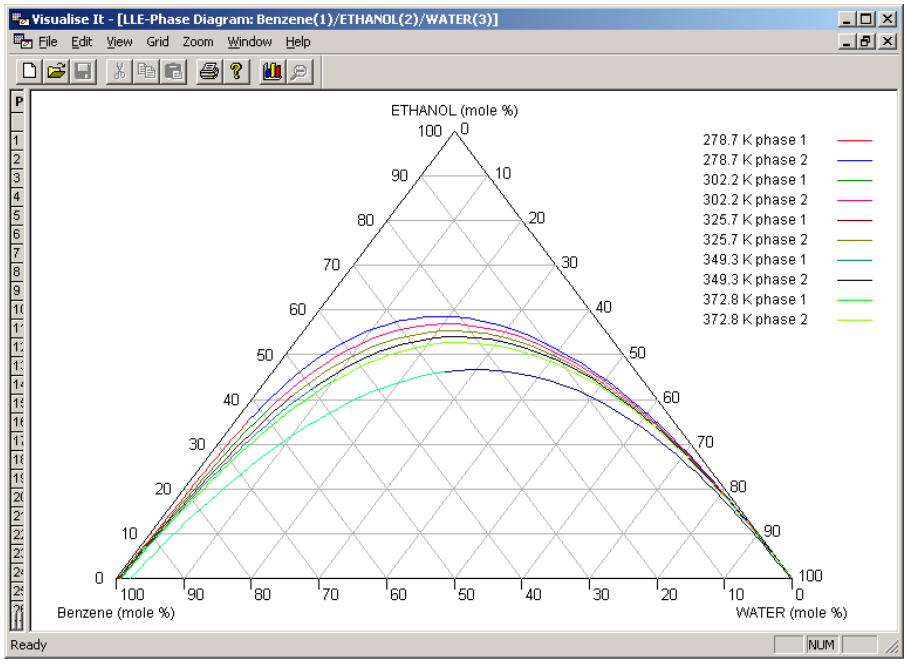
- From the “LLE organic” window, click on “Calculate & Plot” to enter the “Plot Ternary LLE Curves”



- Click in OK in order to calculate a ternary LLE phase diagram:



- The calculated LLE phase diagram is shown:



Appendix C: Additional exercises

Conceptual problem (for solving without any software)

For the groups listed in the table below and using the corresponding rules for joining them, determine,

- ✓ How many 4 group structures are there if no other rules are considered? That is, find in how many ways, the 7 groups in the Table can be joined in structures containing only 4 groups?
- ✓ How many structures can you generate when in addition to having 4 groups, the following rule is also satisfied –
  The number of free attachments is zero
- ✓ How many structures can you find when groups of category 2-5 can appear only once? How many of these structures are chemically feasible or can be found in the database?
- ✓ How many of the structures satisfy the criteria of 345 K < T_b < 355 K

Groups Table

Class	Category				
	1	2	3	4	5
1	CH3	CH2NO2	CH3CO	OH	CH2=CH
2	CH2				
3	CH				

Class Number: Defines the number of free attachments

-CH3; -CH2-; -CH-; -C-

Category Number: Defines degree of restriction to joining with other groups. Examples -

1: no restrictions; 2-4: cannot join with each other; 5: only one per molecule of specified size

Group Contributions for normal boiling point (T_b)

CH3	0.8894
CH2	0.9225
CH	0.6033
CH2NO2	5.7619
CH3CO	3.5668
OH	3.2152
CH2=CH	1.7827

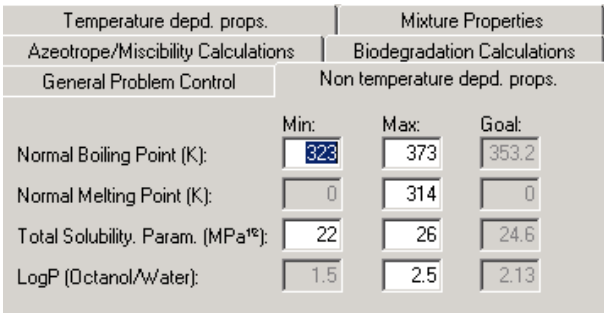
$\text{Exp}\,(T_b/T_{b0}) = \Sigma_i N_i C_i$

Where T_{b0} = 204.359 K, N_i is the number of times group i is present in the molecule, C_i is the contribution of the group property.

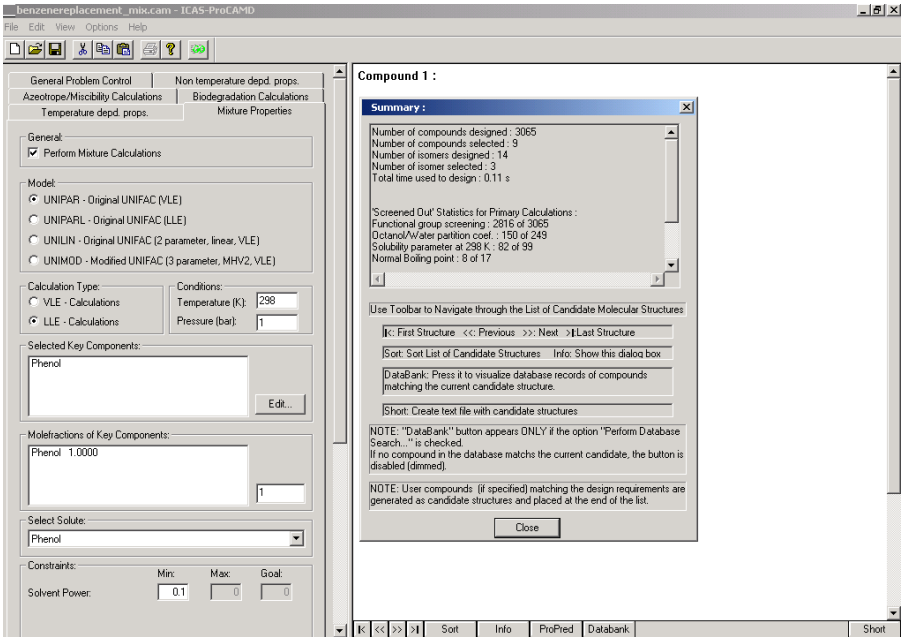
Compound substitution problem

Find all cyclic organic molecules with C, H & O atoms that have the same T_b, Hildebrand Solubility parameter, T_m as that of benzene but not the EH&S properties of benzene (Achenie et al. 2003, page 161)

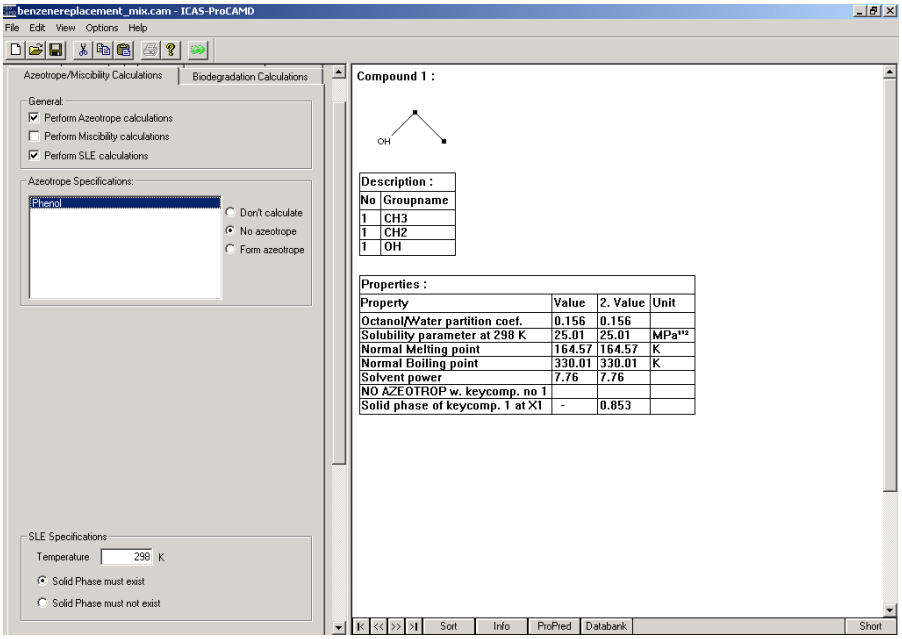
Screen shots from ProCamd



-a-



-b-



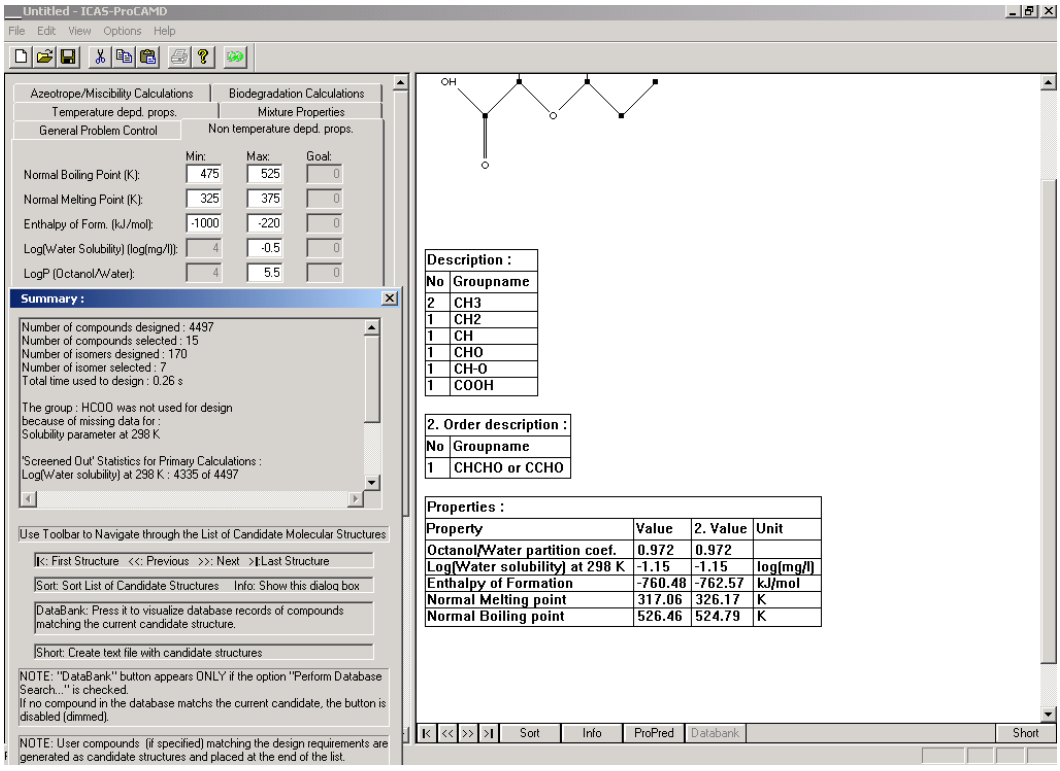
-c-

Find all compounds that match the following property constraints

475 K < normal boiling point < 525 K; 325 K < normal melting point < 375 K

-250 kJ/mol < heat of formation at 298 K < - 220 kJ/mol

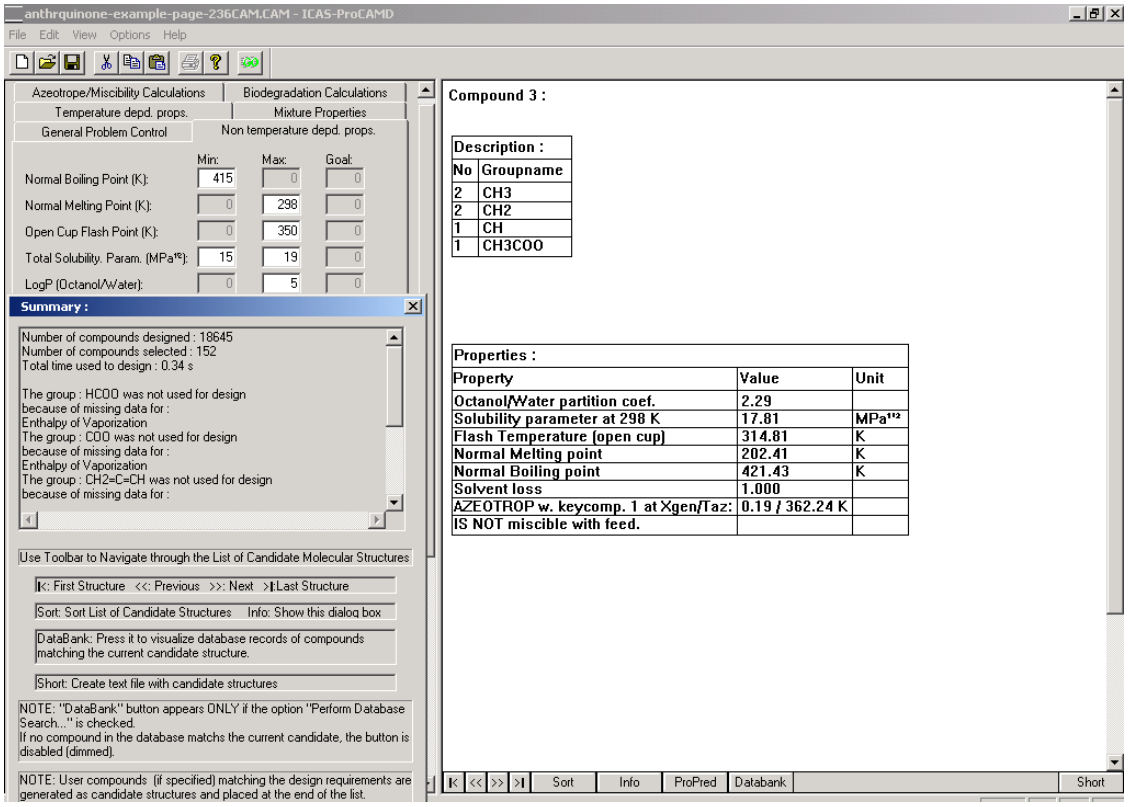
-0.75 < Log P < -0.50 ; 4.0 < log water solubility (log mg/L) < 5.5



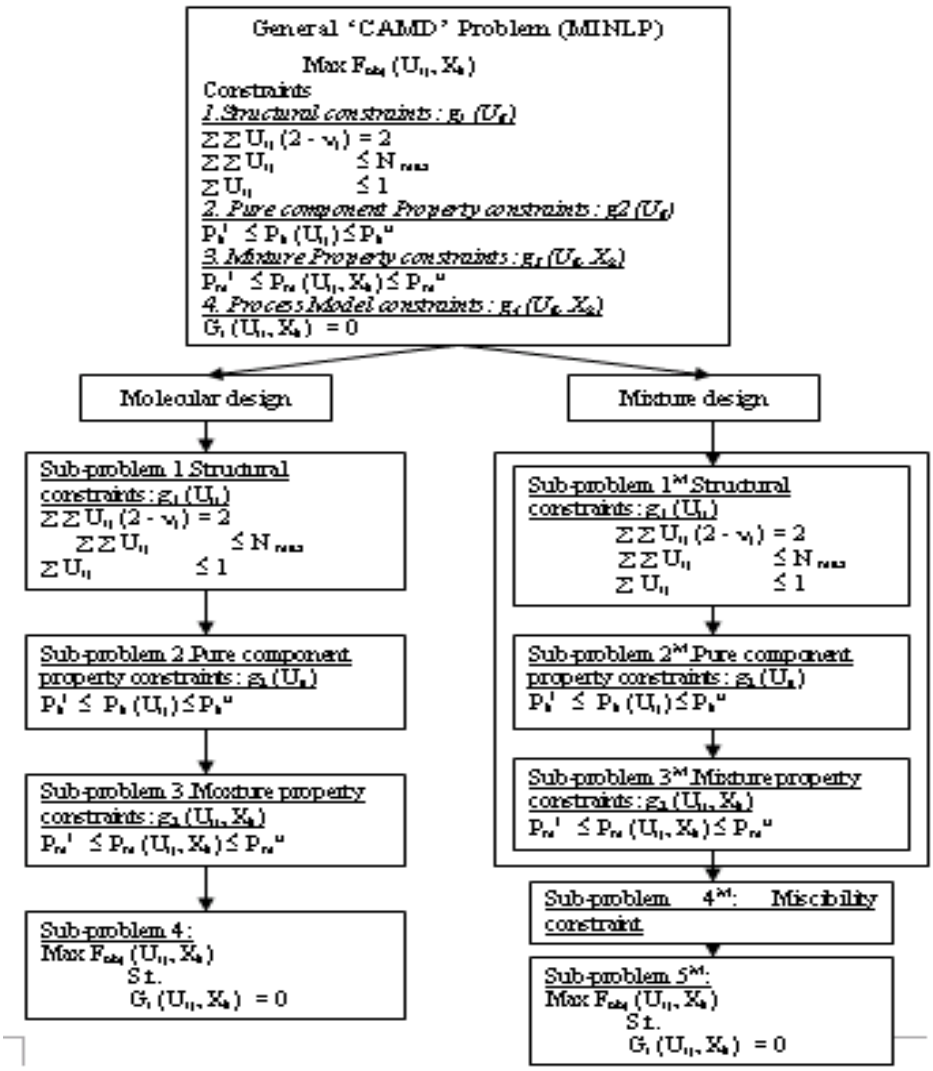
Case Study: Anthraquinone recovery **-** Solvent selection problem statement (Achenie et al. 2003, page 236-242)

Based on the processing constraints, the following desired properties for the solvent are needed.

1. Anthracene has to be soluble in the solvent at 145°C. The solubility is approximately 0.27 by mass fraction in the existing solvent at the reaction temperature. So ideally we prefer the new solvent to have solubility greater than that.
2. Recovery of Anthraquinone, the product, from the solvent. Ideally prefer to achieve greater recovery of the product than in the current solvent. Also need to ensure that no eutetic is formed when the product is crystallised.
3. Solubility of Nitric Acid in the solvent needs to be high in order for the instantaneous reaction between the Nitric Acid and Anthracene to take place.
4. Reactivity of the solvent with Nitric Acid, Anthracene and Anthraquinone will need to be known. The solvent in this case is simply a reactant carrier and does not appear in the reaction mechanism. Therefore the solvent should not participate in the reaction.
5. Solvent used needs to be immiscible with water. The process is designed to treat such solvents. Therefore the solvent chosen should form an azeotrope with water, where the liquid splits into two liquid phases with different compositions.
6. The chosen solvent should have a minimum boiling point of 145°C because the reaction temperature is 145°C. At this temperature the solvent should be a liquid for liquid phase reaction.
7. The chosen solvent should have a maximum melting point of 25°C because the product is crystallised at 25°C. This will minimise the chance of solvent to be crystallised out with the product.
8. The solvent will be released to the environment via the effluent stream and via vents. Therefore we want a solvent, which is environmentally friendly.
9. The solvent used should also be economically favourable. This factor should not be of a great concern as long as a majority of the solvent is being recovered. If the solvent used requires addition of make-up of fresh solvent feed for each batch of reaction, then the cost of the solvent would be a major criterion.


anthrquinone-example-page-236CAM.CAM - ICAS-ProCAMD
File Edit View Options Help
Azeotrope/Miscibility Calculations
Biodegradation Calculations
Temperature depd. props.
Mixture Properties
General Problem Control
Non temperature depd. props.
Min: Max: Goal:
Normal Boiling Point (K): 415 0 0
Normal Melting Point (K): 0 298 0
Open Cup Flash Point (K): 0 350 0
Total Solubility. Param. (MPa^½): 15 19 0
LogP (Octanol/Water): 0 5 0
Summary :
Number of compounds designed : 18645
Number of compounds selected : 152
Total time used to design : 0.34 s
The group : HCOO was not used for design
because of missing data for :
Enthalpy of Vaporization
The group : COO was not used for design
because of missing data for :
Enthalpy of Vaporization
The group : CH2=C=CH was not used for design
because of missing data for :
Use Toolbar to Navigate through the List of Candidate Molecular Structures
|<: First Structure <<: Previous >>: Next >|Last Structure
Sort: Sort List of Candidate Structures Info: Show this dialog box
DataBank: Press it to visualize database records of compounds matching the current candidate structure.
Short: Create text file with candidate structures
NOTE: "DataBank" button appears ONLY if the option "Perform Database Search..." is checked.
If no compound in the database matchs the current candidate, the button is disabled (dimmed).
NOTE: User compounds (if specified) matching the design requirements are generated as candidate structures and placed at the end of the list.
Compound 3 :
Description :
No Groupname
2 CH3
2 CH2
1 CH
1 CH3COO
Properties :
Property Value Unit
Octanol/Water partition coef. 2.29
Solubility parameter at 298 K 17.81 MPa^½
Flash Temperature (open cup) 314.81 K
Normal Melting point 202.41 K
Normal Boiling point 421.43 K
Solvent loss 1.000
AZEOTROP w. keycomp. 1 at Xgen/Taz: 0.19 / 362.24 K
IS NOT miscible with feed.
|< << >> >| Sort Info ProPred Databank Short

Appendix D: Decomposition Strategy for CAMD



Solvent design problem formulation

$$Max \quad PR\% = \frac{100}{1-X_1} * \left(1 - \frac{X_1}{X_2}\right) \tag{11}$$

$$\sum_i \sum_j u_{ij}(2 - v_j) = 2 \tag{12}$$

$$\sum_i \sum_j u_{ij} = N_{max} \tag{13}$$

$$\sum_j u_{ij} = 1 \tag{14}$$

$$17 \le \delta \le 19 \quad \text{MPA}^{1/2} \tag{15}$$

$$\delta_H \ge 8 \quad \text{MPA}^{1/2} \tag{16}$$

$$T_f = 3.63 * \sum_i \sum_j N_i T_{fj} + 0.409 * T_b + 8843 \ge 323 \text{ K} \tag{17}$$

$$-Log(LC_{50}) \le 3.3 \tag{18}$$

$$T_m = 102.425 * \sum_i N_i T_{mi} + \sum_j M_j T_{mj} \le 270 \text{ K} \tag{19}$$

$$T_b = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \ge 340 \text{ K} \tag{20}$$

$$\mu \le 1 \quad \text{cp} \tag{21}$$

$$\ln x_1^{Sat} - \frac{\Delta_{fus} H}{T_m}\left(1 - \frac{T_m}{T}\right) + \ln \gamma_1^{Sat} = 0 \tag{22}$$

$$x_1 + x_2 = 1 \tag{23}$$

$$260 \le T \le 320 \tag{24}$$

Solvent-Antisolvent mixture design

$$\text{Max } PR\% = \frac{100}{1-X_1} * \left(1 - \frac{X_1}{X_2}\left(1 + \frac{M_{w,r}}{M_r}\right)\right) \quad (25)$$

Subject to

$$\sum_i \sum_j u_{ij}(2 - v_j) = 2 \quad (26)$$

$$\sum_i \sum_j u_{ij} = N_{atoms} \quad (27)$$

$$\sum_j u_{ij} = 1 \quad (28)$$

$$T_b(solvent) = 102425 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \leq 270 \text{ K} \quad (29)$$

$$T_c(solvent) = 204359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \geq 340 \text{ K} \quad (30)$$

$$T_f(solvent) = 3.63 * \sum_i \sum_j N_i T_{bj} + 0.409 * T_c + 8843 \geq 323 \text{ K} \quad (31)$$

$$17 \leq \delta(solvent) \leq 19 \text{ MPA}^{0.5} \quad (32)$$

$$T_c(anti-solvent) = 204359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \geq 340 \text{ K} \quad (33)$$

$$T_b(solvent) = 102425 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \leq 270 \text{ K} \quad (34)$$

$$T_f(anti-solvent) = 3.63 * \sum_i \sum_j N_i T_{bj} + 0.409 * T_c + 8843 \geq 250 \text{ K} \quad (35)$$

$$\delta(anti-solvent) \geq 30 \text{ MPA}^{0.5} \quad (36)$$

$$\frac{1}{x_2} + \frac{\partial \ln \gamma_2}{\partial x_2} \geq 0 \quad (37)$$

$$\ln x_i^{sat} - \frac{\Delta_{sol} H}{T_m}\left(1 - \frac{T_m}{T}\right) + \ln \gamma_i^{sat} = 0 \quad (38)$$

$$x_1 + x_2 + x_3 = 1 \quad (39)$$

Appendix E: Target property selection for solvent-based separation

Table 2: List of important properties for some separation techniques

Properties	Solvent Design									
	L-L Extraction		Extractive Distillation		Azeotropic Distillation		Solid Separation		Gas Absorption	
Pure	**E**	**D**	**E**	**D**	**E**	**D**	**E**	**D**	**E**	**D**
δ	√	√	√	√	√	√		√		√
τ		√								√
μ		√								√
T_b	√		√		√		√		√	
T_m	√		√		√		√			
ρ					√					
P^v			√							
H_{vap}				√		√				
Mixture	*1 E*	**D**	**E**	**D**	**E**	**D**	**E**	**D**	**E**	**D**
Selectivity		√		√		√		√	√	
SL		√				√			√	
SP		√		√		√	√		√	
DC		√		√		√				
Phase-split	√		√		√		√			
Azeotrope				√	√					
ρ_m	√									
μ_m	√									
H										√

Note: E is Essential; D is Desirable; L-L is liquid-liquid; the definitions of property variables in column 1 are given in Nomenclature.

Table 3: List of properties for addressing EH&S considerations

Properties		Environmental Concern		
		Health	Safety	Environment
Implicit	Toxicity	√		√
	Biological persistence			√
	Chemical stability	√	√	
	Reactivity		√	
Explicit	Biodegradability		√	√
	P_v	√	√	√
	H (in water)			√
	Log P	√		√
	Log W_s	√		√
	Flash point		√	
	BOD			√
	ρ (vapor)	√	√	
	Evaporation rate	√	√	√
	LD50	√		√
	ODP			√

Evaluation of Primary Solvent Properties for Liquid Extraction

Property (mass basis)	**Estimate**
Solvent Selectivity	$\beta = \frac{\gamma^{\infty}_{B,S} MW_A}{\gamma^{\infty}_{A,S} MW_B}$
Solvent Power	$S_P = \frac{MW_A}{\gamma^{\infty}_{A,S} MW_B}$
Solute Distribution Coefficient	$m = \frac{\gamma^{\infty}_{A,B}}{\gamma^{\infty}_{A,S}} \frac{MW_B}{MW_S}$
Solvent Loss	$Sl = \frac{1}{\gamma^{\infty}_{S,B}} \frac{MW_S}{MW_B}$