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Chapter 14

Case Studies in Chemical Product Design – Use of CAMD Techniques

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14.1 Introduction

The objective of this chapter is to provide the reader with a selection of chemical product design related problems (case studies) highlighting the tasks where computer-aided molecular and mixture design (CAMD) techniques can be employed. Other computer-aided tools to be used are primarily methods for property prediction (product evaluation), product-process modeling (performance evaluation) and process simulation (design & verification). All computer-aided tools used in this case study were developed at CAPEC and are available as toolboxes within ICAS (Integrated Computer Aided System) – Gani (2002a). The solutions for all the problems presented in this chapter are not given. Interested readers can obtain the detailed solutions for all problems from the author.

14.1.1   Computer-Aided Molecular-Mixture Design: Brief Overview

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, CAMD technique [Gani et al. (1991)]is the reverse problem of property prediction, where, given the identity of the molecule (or the molecular structure) or a mixture, a set of target properties is calculated. In this chapter,

the Hybrid CAMD technique developed by Harper et al. (2001) and implemented in ProCAMD (2002b) will be used.

The solution of all CAMD problems, can in principle, 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).

14.2 Case Study 1: Solvent Design-Selection

A mixture of acetone and chloroform is to be separated into pure products [Hostrup et al. (1999)]. Since they also form an azeotrope, one alternative to satisfy the separation objective is to find a suitable solvent for separation by extractive distillation. This type of problem in product design is usually encountered during the purification or recovery of products, by-products, reactants or removal of undesirable products from the process. Also, it can be noted that failure to find a suitable solvent may result in the discard of the product. Alternatively, a functional chemical product manufacturer may be interested to find, design and develop a new solvent. In this case, the solvent is the chemical product.

14.2.1 Solvent Identification with ProCamd

First an analysis of the binary mixture of acetone and chloroform is made to obtain the relevant data. A selection of the most important data needed for this case study is listed in Table 1.

Table 1: Properties from analysis of the acetone-chloroform mixture

Property	Property Value	
	Acetone	Chloroform
T_b [K]	178.45	209.63
T_m [K]	329.44	334.33
δ_T [(MPa)$^{1/2}$]	19.73	18.92
Known solvents	Water, ethanol, ethyl ether	Ethanol, ethyl ether
Azeotrope composition at 1 atm and 345 K	0.344	0.656

Note that a high-boiling azeotrope is formed between acetone and chloroform. The above problem description and mixture analysis helps us to define the CAMD problem.

14.2.1.1 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 favorable EH&S properties.

14.2.1.2 Step 2

Since the solvent is selective to chloroform, a preliminary search in the database could be made to find known solvents for chloroform that are also miscible with acetone. Using the CAPEC database [Gani (2002a)], a list of known solvents, if satisfying the search criteria stated above, can be found. Figure 1 shows the solvents found within the database.

Figure 1: List of solvents from database search

Based on the above information, the CAMD problem definition is revised as follows – 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, the solvent must not form azeotrope with either acetone or chloroform, and, must be totally miscible with the binary mixture of acetone and chloroform.

14.2.1.3 Step 3

Set-up the solvent design/selection problem defined in step 2 in ProCAMD. In ProCAMD, the information related to the CAMD problem is organized in terms of the following types:

- General problem control: Define the type of molecules to be designed, the size of the molecules, to include isomers or not, etc.
- Non-temperature dependent: Specify upper, lower, and/or goal values only for the target properties (a collection of 26 properties are available)
- Temperature dependent property: Specify upper, lower, and/or goal values only for the target properties together with the temperature (a collection of 6 properties are available)

- Mixture property: Define the model to be used for liquid activity coefficient calculation, specify the binary mixture (composition, temperature, pressure), select the solute to be extracted, the type of phase equilibrium calculation (VLE or LLE) and finally, specify desired solvent performance related properties (solvent power, selectivity, etc.)
- Azeotrope/miscibility calculations: Specify if the solvent must or must nor form azeotropes, miscibility as a liquid solution, solid precipitation, etc.

For the case study, the following specifications are needed:

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

Temperature dependent property
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 & Results from ProCAMD

After the execution has been completed, ProCAMD provides the results in terms of a "summary" of the molecular design based search as well as detailed results for each candidate solvent. Figure 2a shows the "summary" for the problem described above while Figure 2b shows the detailed results for one candidate solvent.
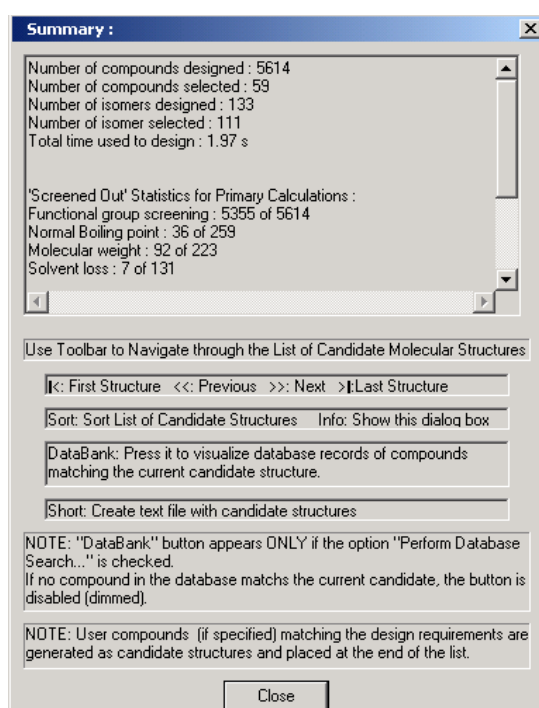
Figure 2a: Results summary from ProCAMD

It can be noted from Fig. 2a that ProCAMD needed only 1.97 seconds to generate 5614 molecular structures and after evaluating them ended-up with 111 feasible candidates. The time also includes the process calculations related to miscibility, azeotrope verification as well as solvent loss and selectivity.

Compound 110 :
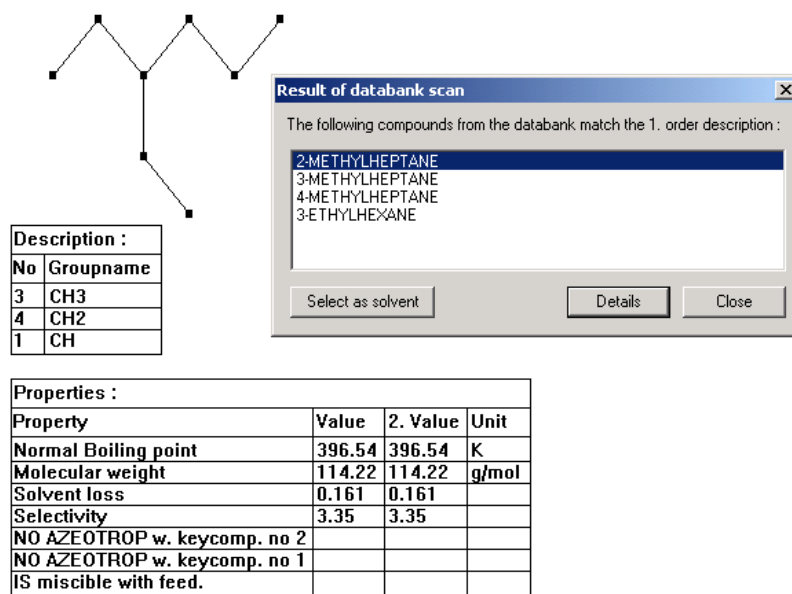
Figure 2b: Detailed results for a feasible solvent candidate found by ProCAMD

14.2.1.4 Step 4

Here, process simulation needs to be performed to verify the solvent performance. ICAS [Gani (2002a)] provides tools for design of the extractive distillation columns (PDS-tool) as well as rigorous simulation and optimization (ICASSim & ICAS-opt). In this case study, only the final flowsheet obtained through PDS-tool and the simulation results obtained through ICASSim are highlighted. Note that this part could, in principle, be done through any other process simulation software. Figures 3a and 3b show the flowsheet and the corresponding simulation results. It can be noted from Fig. 3b that the desired separation has been achieved.
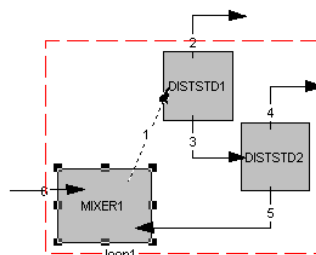
Figure 3a: Designed flowsheet for the acetone-chloroform separation

```
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
==================  ==========   ==========
```

Figure 3b: Verification by simulation of the flowsheet of Fig. 3a.

14.2.2 Related Problems

a. *Find solvents to separate acetone from methanol separation (VLE separation) – replace chloroform with methanol, identify the mixture properties and then set-up the solvent design-selection problem as highlighted above.*

b. *Find solvents for methyl acetate from methanol separation (VLE separation)* – here replace acetone with methyl acetate in the mixture from problem a and follow the same procedure.

c. *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* – here, solvents are not being searched. Instead, all compounds that are totally miscible with ethanol and forms an azetrope with ethanol at 1 atm are being sought. This is a simple example of mixture design.

d. *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.* – this problem is similar to the case study and problems a & b with the only difference that liquid-liquid phase equilibria is involved instead of VLE.

e. *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* – this problem is also similar to the above problem but here, solid-liquid equilibria is involved instead of LLE or VLE. Other similar problems, find solvents (anti-solvents) to extract by crystallization, the following compounds – Naphthalene, Ibuprofene (see chapter 4), Diuron (CAS number 330-54-1) and Crabazole (CAS number 86-74-8).

f. *Solvents for organic synthesis* – A good collection of problems on this topic can be found in Gani et al (2005) and Gani et al. (2006).

14.3   Case Study 2: Backbone Generation

In this case study, we will start with a known molecule (for example, Corticosterone), use the property estimation features in ProPred [Marerro (2002)] to create free attachments in the molecule (that is, create a backbone). The Backbone is then transferred to ProCamd, where terminated structures will be generated. In this way structures of "synthetic candidates" of a lead biologically active compound may be identified through molecular design.

14.3.1   Step 1

Start ProPred from ICAS and draw the molecule (or import the mol-file of the molecular structure or specify the SMILES string)

14.3.2   Step 2

ProPred draws the molecule and predicts the properties (as shown in Figure 4a)
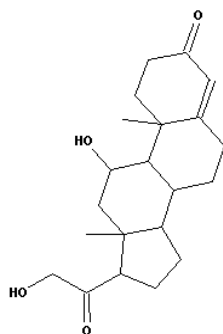
Figure 4a: Molecular structure of Corticosterone (000050-22-6)

| Summary | Marrero and Gani | Constantinou and Gani | Joback and ◀ | ▶ |

Property Values estimated by using methods
included in ProPred

Compound Name   : Corticosterone
Compound CAS   : 000050-22-6
Compound Smiles : OCC(=O)C1CCC2C3CCC4=CC(=O)CCC4(C)C3C(O
Compound Formula : C21H30O4
Mw (g/mol)   : 346.46

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

WARNING:
Accuracy of some estimated properties (e.g. Hansen parame
might be poor if the melting point is far above 298 K

Property	Method	Unit	Est.Value	Exp.V
Tm	MG	K	455.30	454.1
Tb	MG	K	690.57	N/A
Tc	MG	K	922.59	N/A
Pc	MG	bar	18.82	N/A
Vc	MG	cm³/mol	1083.09	N/A
Zc	MG		0.266	N/A
Gf[298K]	MG	kJ/mol	−404.20	N/A
Hf[298K]	MG	kJ/mol	−911.63	N/A
omega	CG		1.324	N/A
Hv[298K]	******	kJ/mol	N/A	N/A
Hv[Tb]	MG	kJ/mol	128.18	N/A
Hfus	MG	kJ/mol	45.80	N/A
Sfus	MG	J/(mol*K)	100.86	N/A
Vm[298K]	******	cm³/mol	N/A	N/A
Vm[Tb]	MG	cm³/mol	431.69	N/A
Sol. Par.[298K]	MG	MPa½	25.62	N/A
Refractive Index	MG		1.89	N/A
Molar Refraction	******		N/A	N/A
Surf.Tens.[298K]	******	dyn/cm	N/A	N/A
G.T. Temp.	******	K	N/A	N/A
Log(Kow)	MG		2.41	1.94
Log(Ws)	MG	Log(mg/L)	1.82	2.29
Closed Flash Temp.	CG	K	534.57	N/A
Open Flash Temp.	CG	K	606.27	N/A
Hansen Disp. sol.	CG	MPa½	16.49	N/A

Figure 4b: Predicted properties of Corticosterone

14.3.3 Step 3

Using the drawing tools in ProPred, remove the OH group connection from the molecular structure at the two locations (as shown in Figure 4c).
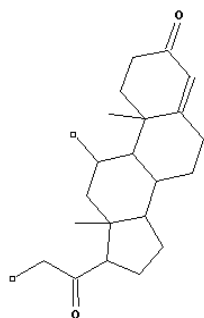

Figure 4c: Backbone with two-free attachments.

14.3.4 Step 4

Launch ProCamd from ProPred from the tools menu in ProPred.

14.3.5 Step 5

Fill-out the necessary problem definition pages in ProCamd (general problem control, non-temperature dependent properties) as shown below in Figure 4d.

14.3.6 Step 6

Terminate the backbone by clicking on "GO". Among the 10 different candidates, compound 2 (which is Corticosterone) is shown in Figure 4e.

Figure 4d: ProCAMD problem formulation for generating completed structures for the specified backbone.

Compound 2 :

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

Figure 4e: Completed backbone in ProCAMD

14.3.7   Related Problems

- *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. All the generated structures will also need to satisfy a set of property targets (melting point, solubility parameter and the octanol-water partition coefficient).
- *Design a large molecule having the following properties, $M_w > 300$; $T_b > 400 K$; $T_m > 300 K$* – This problem is solved with ProCAMD in the first step by simply asking for all types of molecules satisfying only the three specified property targets. Once these are generated, it is possible to work further with these through ProPred, where manually other atoms and bonds are added to evaluate the properties of the generated molecules.

14.4   Case Study 3: Polymer Design

A polymer film is needed to protect an electronic device [Seider et al. (2003)]. The device will operate at temperatures below 333 K and must be protected by a fairly dense layer that absorbs small concentrations of water. A design team has prepared the following quality specification: density = 1.5 g/cm³, glass transition temperature = 383 K (50 degrees above the operating temperature), and water absorption = 0.005 g/g polymer. As stated initially by Derringer and Markham (1985), candidate molecular groups, together with their group contributions (for target property estimations) are given in Table 2.

Table 2: Group contribution values for estimation of the polymer properties

Group number	Group name	Y_i	V_i	H_i	M_i
1	CH2	2700	15.85	0.000033	14
2	CO	27000	13.4	0.11	28
3	COO	8000	23	0.075	44
4	O	4000	10	0.02	16
5	CONH	12000	24.9	0.75	43
6	CHOH	13000	19.15	0.75	30
7	CHCl	20000	29.35	0.015	48.5

In the above table, M_i, V_i, Y_i and H_i are the contributions for group i for estimating the molecular weight, the molar volume, the glass-transition temperature, and the water absorption, respectively. The model equations for each of these properties are as follows:

Molecular weight, M (gm/mol)

$$M = \sum_{i=1}^{7} M_i n_i$$

Molar volume, V (cm^3/mol)

$$V = \sum_{i=1}^{7} V_i n_i$$

Density $\rho = 1/V$

Glass transition temperature, T_g (K)

$$Y = \sum_{i=1}^{7} Y_i n_i$$

$$T_g = Y / M$$

Water absorption, W (gm$_{water}$/gm$_{polymer}$)

$$H = \sum_{i=1}^{7} H_i n_i$$

$$W = 18H / M$$

14.3.1 Step 1

Generate polymer repeat units with minimum 2 groups and maximum 4 groups.

14.3.2 Step 2

Estimate the target properties for each generated polymer repeat units and eliminate those that do not match the target property values. For the remaining polymers, evaluate them in terms of the following selection criteria:

$$\left(\frac{\rho - \rho^{spec}}{\rho} \right) + \left(\frac{Tg - Tg^{spec}}{Tg} \right) + \left(\frac{w - w^{spec}}{w} \right)$$

The polymer repeat unit with the smallest value is the best polymer, in this simple polymer design problems. Table 3 highlights the values for the target properties and the selection criteria for 6 polymer repeat units and the best polymer is highlighted.

Table 3: Designed polymers with the group contribution method

Polymer	ρ	T_g	W	Selection criteria
-CH2-CHCl-	1.383	363.2	0.0043	0.026766
-(CHCl)2-	1.652	412.5	0.0056	0.029073
-CH2-(CHCl)2-	1.489	384.7	0.0049	0.000748
-(CHCl)3-	1.652	412.4	0.0056	0.029073
-(CH2)2-(CHCl)2-	1.383	363.2	0.0043	0.026766
-(CHCl)4-	1.652	412.4	0.0056	0.029073

14.3.3 Related Problem

Simultaneous design of membrane-based gas separation and the design of the polymeric membrane – In this problem, a membrane-based pervaporation model is used to calculate the target properties for the design of the polymeric membrane. This step actually also designs the pervaporation processes as for a given mixture to separate and a specified product recovery, the details of the polymeric membrane in terms of its properties (permeability, surface area, volume, etc.) are calculated. Using these calculated values as targets, in the next step, a polymer design problem (similar to the one given above but with different properties) is formulated and solved. A detailed solution of problems of this type can be found in Soni et al. (2006), who highlights an application example for selective recovery of oxygen from air through pervaporation with

polymeric membranes. Soni et al. (2006) found several polymers that satisfy the target properties. A detailed solution of the problem can also be obtained from the author.

14.4 Case Study 4: Refrigerant Design

It is desired to find a replacement for Freon-12 as an alternative refrigerant [Duvedi & Achenie (1996)]. The objective is to find replacements that have the same refrigerant related properties as Freon-12 but without the harmfull environmental properties (such as the Ozone depletion potential) - The new refrigerant must absorb heat at temperatures as low as –1.1°C and reject heat at temperatures as high as 313 K. It must also respect the following characteristics:

- Must not polymerize.
- Be nonflammable.
- Assure that if there are leaks, they are from the refrigeration system.
- Allow a compression ratio below 10.
- A small amount of refrigerant must allow a transfer of the heat.
- A small amount of refrigerant must flash into the valve.
- Choice of the specifications for ProCAMD

The following specifications are necessary to solve the problem through ProCAMD:

- To ensure that the refrigerant does not polymerize, compounds that have double or triple bonds will be avoided.
- To ensure that the refrigerant is nonflammable, compounds involving both nitrogen and halides will be avoided.
- To ensure that if there are leaks, they are from the refrigeration system, desirable refrigerant must have a vapor pressure greater than 1.4 bars (0.4 bar of security are taken with the atmospheric pressure). As vapor pressure increases with temperature, solvent must verify: P_s(271 K) >1.4 bars.
- A compression ratio below 10 means that the following expression is checked: P_s(43.3°C)<14 bars.

Also, to reduce the amount of refrigerant needed, the latent heat of vaporization must be as high as possible. The latent heat of vaporization of Freon12 is 18.4kJ/mol, so to assure that the new refrigerant is at least as good as the

Freon12 and knowing that the latent heat of vaporization decreases with temperature, the refrigerant must check:

ΔHv(271 K) > 18.4 kJ/mol.
Cpl(293 K) < 134.6 J /(mol K)

The problem can be solved using the discretization method discussed in chapter 4 of this book. First candidates are generated using the normal boiling points and the normal boiling point. In the next stage, the remaining properties are calculated only for the molecules that have not been discarded.

As reported by ProCAMD, it generated 1206 replacement candidates, out of which 565 were initially selected. This gave rise to 559 structures, out of which 289 were found to be acceptable.

The generated list of compounds that could be potential replacements of Freon-12 are given in Table 4.

Table 4: Feasible refrigerant replacement solvents.

	Ps (bars) at 271 K	Cpl (J/(mol K)) at 293 K	Ps (bars) at 313 K	Hv (kJ/mol) at 298 K
CCl2F2 = FREON 12	3.08	117.8	11.28	19.4
CH3Cl	2.19	79.4	9.00	21.80
C2H2F4	2.69	134.8	10.16	19.7
C2H6O	3.16	109.3	12.66	20.8
C2H3ClF2	1.60	123.4	10.28	27.9
C2H5FO	1.34	123.1	5.02	20.6
C2H2ClF3	1.46	137.1	5.18	19.5
C3H7F	2.12	125.2	6.97	18.1
C4H10	1.50	138.9	5.81	20.8

Finally, the Ozone Depletion Potential (ODP) can be calculated with the following models:

Molecules that have one carbon atom:

$$ODP = 0.585602 n_{Cl}^{-0.0035} e^{M/238.563}$$

Molecules that have two carbon atoms:

$$ODP = 0.0949956 n_{Cl}^{-0.0404477} e^{M/83.7953}$$

Based on the above model for ODP, CH3Cl is removed from the list of refrigerant alternatives together with all other compounds with chlorine. Finally, the two compounds C2H6O and C4H10 are kept for further studies as possible replacements.

14.5   Other Problem Definitions

14.5.1   Active Ingredient Design/Selection

α-chloroacetamideochloroacetanilides is a herbicide that have the remarkable property of stunting the growth of turf grass without killing the grass while enriching the green texture of the turf. These compounds are referred to as "turf retardants". Experiments have been performed to measure the biological activities measured as the decrease in vertical growth of the turf grass tall fiscue. These activities were then correlated to the LogP of the various relatives of α-chloroacetanilide. Table A in appendix lists the values of the activities and the corressponding LogP of the molecules.

Determine the following:

a) Use the values given in the table to estimate the coefficients for the following correlation

   $A = d + eLogP + f(LogP)^2$

b) Generate completed structures from the backbone of the α-chloroacetamideo-chloroacetanilides given below (generate at least 15 structures). R1 could be hydrocarbons (acyclic and cyclic) while R2 and R3 should be only acyclic hydrocarbons with 1-3 carbon atoms.
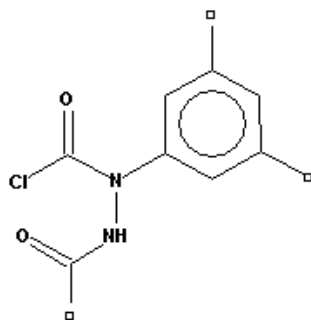
c) Estimate the LogP of the generated completed structures
d) Identify the structure with the highest activity

14.5.2 Drug Design

The drug barbiturate is a well-known drug. It has different forms, mostly different types of barbituric acid - a list of barbituric acids are given below together with the CAS-numbers.

Candidate 1: 000077-02-1
Candidate 2: 061346-87-0
Candidate 3: 000076-94-8
Candidate 4: 091430-64-7
Candidate 5: 001953-33-9
Candidate 6: 007391-69-7
Candidate 7: 090197-63-0
Candidate 8: 017013-41-1
Candidate 9: 027653-63-0

Analyze each of the compounds and calculate their Octanol-Water partition coefficients. Use the following two models to estimate the molar concentration (C) of the compound,

- To produce a 1:1 complex with protein (binding to bovine serum albumin)

$Log_{10}(1/C) = 0.58 \log_{10}P + 0.239$

- To calculate the hypnotic activity of the compound in rabbits after subcutaveous injection

$$Log_{10}(1/C) = 2.09 \log_{10}P - 0.63 (\log_{10}P)^2 + 1.92$$

Find which form of barbituric acid has the best (lowest concentrations) in both cases. For the best barbiturate molecule, find a solvent which is miscible with water.

14.5.3 Mixture Design (Additive for Paints)

For a specific paint application, a mixture of solvents is needed. The mixture is going to be identified by its ability to mix with water (total miscibility), normal boiling point (determines the solvent evaporation rate), the solubility parameter (determines if it is soluble in the paint) and molecular weight (size the candidate molecule).

For mixture properties, use the following linear mixing rules:

Molecular weight: $M_{Wm} = \Sigma\, x_i\, M_{Wi}$

Boiling point: $T_{bm} = \Sigma\, x_i\, T_{bi}$

Hildebrand solubility parameter: $\delta_{Tm} = \Sigma\, x_i\, \delta_{Ti}$

In the above equations, subscript i indicates compound i and subscript m indicates the mixture value.

For following upper and lower bounds for each property as well as the target values, find how many binary mixture satisfy the target and find the minimum cost binary mixture.

Molecular weight: $41 < M_{Wm} = 85 < 151$
Boiling point: $350 < T_{bm} = 370 < 559$
Hildebrand solubility parameter: $20 < \delta_{Tm} = 25 < 34$

The cost function can be defined as,

$$F = \Sigma\, x_i\, C^*\rho_i$$

Where, C is a cost factor (=1000 $) and ρ_i is the density of compound i.

Note: To generate the candidate molecules, you may use any database of your choice. Out of the compounds found, if the following 5 compounds appear, select them in the short list of 10 compounds.

Acetonitrile
Ethyleneglycol
Morpholine
2-Butoxyethanol
Triethyleneglycol

14.5.4 Mixture Design

For some process application, it is necessary to find mixtures that are not miscible in water, is liquid at the operating condition (around 300 K and 1 atm) and can absorb heat (that is, has a high heat capacity). Find the mixture with the highest heat capacity (in the liquid phase).

Determine the following:

a) Formulate the general mixture design problem as an optimization problem providing all relevant equations for the objective function and constraints.
b) Suggest a decomposition scheme
c) Solve each decomposed sub-problem (before the final optimization sub-problem)
d) Order the binary mixtures with respect to their heat capacities to identify the optimal solution.

The mixture is going to be identified by its ability to not mix with water (total immiscibility), normal boiling point (each compound in the mixture has a T_b above 350 K so the mixture will be a liquid), normal melting point (each compound in the mixture has a T_m below 250 K so the mixture will be a liquid), the Hildebrand solubility parameters of each of the compounds should be between 18-22 MPa$^{1/2}$ (so the two compounds are mutually miscible).

For mixture properties, use the following linear mixing rules:

Molecular weight: $M_{Wm} = \Sigma\, x_i\, M_{Wi}$

Boiling point: $T_{bm} = \Sigma\, x_i\, T_{bi}$

Boiling point: $T_{mm} = \Sigma x_i T_{mi}$

Hildebrand solubility parameter: $\delta_{Tm} = \Sigma x_i \delta_{Ti}$

In the above equations, subscript i indicates compound i and subscript m indicates the mixture value.

14.6 Conclusions

A collection of case studies for chemical product design highlighting some of the tasks where systematic model-based approaches can be applied, has been presented. All the case studies have been solved by the author and his coworkers using the methods and software tools developed in-house. Interested readers can obtain the detailed solutions from the author as well as licenses for the software tools used. It can also be noted that the process related issues have not been highlighted in the case studies. This is intentional as the objective for the case studies presented in this chapter has been to highlight mainly the product related issues through the use of CAMD techniques. As many of the unit operations found in the food processing, pharmaceutical and agrochemical industries, for example, are still not available, the objective of current and future work is to fill this gap.

References

Duvedi, A. Achenie, L. E. K, 1996, Designing environmentally safe refrigerants using mathematical programming, Chemical Engineering Science, 15, 3727-3739.

Gani, R., Nielsen, B., Fredenslund, Aa., 1991, A Group Contribution Approach to Computer-Aided Molecular Design, AIChE Journal, 37 (9), 1318-1332.

Gani, R. 2002a, *ProCAMD Manual*, PEC03-25, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).

Gani, R, 2002b, *ICAS Documentation*, PEC02-14, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).

Gani, R., Jimenez-Gonzalez, C., Constable, D. J. C., 2005, Method for selection of solvents for promotion of organic reactions, Computers & Chemical Engineering, 29, 1661-1676.

Gani, R., Jimenez-Gonzalez, C., ten Kate, A., Crafts, P. A., Jones, M., Powell, L., Atherton, J. H., Cordiner, J. L., 2006, A modern approach to solvent selection, Chemical Engineering, March, 30-43.

Harper, P. M., Gani R., Kolar, P., Ishikawa, T., 1999, Computer aided molecular design with combined molecular modelling and group contribution, *Fluid Phase Equilibria*, 160, 337-347.

Marrero, J., 2002, *ProPred Manual*, PEC02-15, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).

Seider, W. D. Seider, Seader, J. D., Lewin, D., 2003, *Product & Process Design Principles Synthesis, Analysis, ad Evaluation,* (2nd edition), Wiley.

Soni, V., Abildskov, J., Jonsson, G., Gani, R., 2006, Structural design of polymers for membrane based separation processes using reverse simulation approach, Computer Aided Chemical Engineering, (in press).

Appendix

Table A: List of measured biological activity of the turf versus the LogP of the API

A	LogP	A	LogP	A	LogP
62	3.29	53	4.04	74	3.21
0	4.88	26	4.14	67	2.99
70	3.22	5	5.32	65	3.22
53	4.28	14	7.11	70	2.84
10	6.05	28	4.66	70	2.73
56	4.05	19	7.99	13	4.55
30	3.84	16	4.46	65	2.70
49	4.06	7	6.28	64	2.68
0	6.40	53	4.15	61	2.46
46	3.82	3	4.62	60	2.52
65	3.75	0	4.69	68	2.46
0	4.93	0	1.99	0	5.34
35	4.13	49	3.56	3	7.46
65	3.52	49	1.73	42	4.81
42	1.52	62	2.40	36	2.91
33	3.56	60	1.44	34	3.96
71	2.70	57	1.97	0	5.87
49	3.82	52	3.79	47	3.39
60	3.49	52	3.26	21	2.29
63	3.09	72	1.97	36	2.23
67	2.17	66	3.02	3	5.52
67	3.85	66	2.49	15	4.73
72	3.05	41	0.79	54	3.08
44	2.76	63	3.02	38	3.61
72	3.52	75	1.48	8	4.99
42	4.02	65	2.49	43	3.17
30	4.00	70	1.95	28	3.73
40	4.02	61	1.79	0	6.05
74	3.74	53	2.36	44	3.67
21	3.56	58	2.89	50	2.56
16	6.93	60	2.89	5	2.63
37	3.69	41	3.42	53	2.91
69	3.26	12	0.87	34	1.15
46	3.96	28	0.88	52	2.93
61	2.75	21	2.59	45	1.5
65	2.76	50	2.47	58	2.03