

Optimal Design of Alternative Refrigerants via a Computer-Aided Molecular Design Approach

Iylia Bin Ismail, Klement Tam

Department of Chemical Engineering, Imperial College London

1. Introduction

With recent widespread concerns regarding global warming, the Kigali agreement came into force in October 2016, commencing the phase-down of manufacturing hydrofluorocarbons (HFCs). A key application of HFCs lies within refrigerants. Thus, this work aims to optimally identify 10 alternative refrigerants which can potentially level or even surpass the performance of a widely used HFC, R134a (tetrafluoroethane).

1.1 Refrigerant Cycle

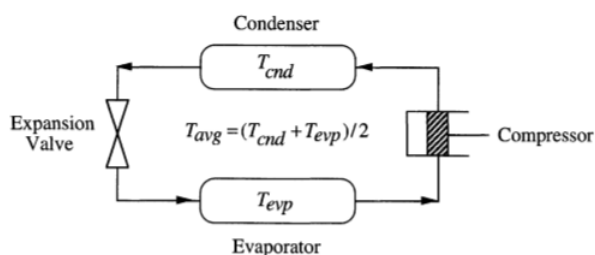


Figure 1: Typical vapour-compression refrigeration cycle (Sahinidis, 2003)

It is assumed that the refrigerant will be used in a typical vapour-compression refrigeration cycle as shown in Figure 1. The refrigerant enters the compressor as a saturated vapour before entering the condenser, where it is cooled by ambient air to the saturated liquid state. After expanding to the evaporator pressure via an expansion valve, it removes heat from the refrigerated space as it vaporises. The process conditions will be fixed at an evaporating temperature $T_{evp} = 272\text{K}$ and a condensing temperature $T_{cnd} = 316\text{K}$ to give an average process temperature $T_{avg} = 294\text{K}$.

1.2 Computer-Aided Molecular Design (CAMD)

The CAMD method was used to forecast promising molecular designs which can replace R134a. This involves solutions which meet specific target properties while satisfying molecular property specifications.

The problem is of a mixed integer nonlinear programming (MINLP) formulation, as decision variables comprise of both binary variables on whether to use certain functional groups, and continuous variables on constraints such as pressure and temperature. The nonlinearity arises from the objective function and some constraints. Globally optimal solutions were found by implementing the proposed algorithm using the BARON solver accessed via the GAMS modelling tool. Global optimization is used to ensure that the very best solutions are found within the astronomically vast possibilities of combinatorial molecular designs.

2. Optimization Formulation

2.1 Functional Groups

Table 1 shows the functional groups that were considered in this molecular design. These functional groups are all common in existing refrigerants. Cyclic groups were not examined and excluded from the list of functional groups due to the following reasons: (i) Most existing refrigerants are currently acyclic (Ashrae, 2019); (ii) Previous work that has been done on designing alternative refrigerants have shown very few cyclic molecules in the optimal solution set (Sahinidis et.al, 2003; Anderson and Digiulio, 2007). In the Table, (–) represents single bond, (=) represents double bond, (\equiv) denotes triple bond, and (>) denotes two single bonds.

Table 1: 28 Functional Groups are Considered to Design Alternative Refrigerants

Alkane Groups	Alkene Groups	Alkyne Groups	Halogen Groups	Oxygen Groups	Nitrogen Groups	Sulphur Groups
–CH ₃	= CH ₂	\equiv CH	–F	–OH	–NH ₂	–SH
–CH ₂ –	= CH –	\equiv C –	–Cl	–O –	> NH	–S –
> CH –	= C <		–Br	> C = O	> N –	
> C <	= C =		–I	O = CH –	–N =	
				–COOH	–CN	
				–COO –		
				= O		

2.2 Objective Function

The objective of this design is to find a efficient refrigerant. This objective function was proposed by Sahindis et.al, 2003 and is shown in Eq. (1).

$$\max_{s.t.} \frac{H_{ve}}{C_{pl}} \quad Eq. (1)$$

For the analytical evaluation of the efficiency of a refrigerant cycle, it is desirable for the refrigerants to have the following thermophysical properties: A high enthalpy of vaporisation (H_{ve}) and low liquid heat capacity (C_{pl}). A high enthalpy of vaporisation implies the required mass flowrate of refrigerant is lower to achieve the same cooling capacity. Subsequently, a low liquid heat capacity reduces the amount of refrigerant vapor generated in the expansion valve (Sahinidis et al., 2003). These two thermophysical properties are combined so as to maximize their ratio.

2.3 Modelling of Physical Properties

2.3.1 Group contribution methods

A group-contribution method is used to estimate physical properties of pure components and mixtures from molecular structure. They provide the important advantage of quick estimates without requiring substantial computational resources. Generally, the properties are calculated from the contributions of three types of groups: first order groups, second order groups, and third order groups (Constantinou and Gani, 1994). The first order groups describe a wide variety of organic compounds, while the second order groups can distinguish isomers and

provide more structural information of compounds. Third order groups were not introduced as these groups describe molecular fragments in polycyclic compounds and cyclic molecules were excluded from the list of functional groups. The most straightforward form of a group-contribution method is the first order group that is based on additive principle and is commonly used method of Joback and Reid (1987). For simplicity, this paper focuses solely on first order approach even though second order approach tends to give more accurate prediction.

2.3.2 Predicting physical properties

5 important physical and thermodynamic properties such as boiling temperature (T_b), critical temperature (T_c), critical pressure (P_c), ideal heat capacity of gas at average temperature (C_{p0}), and enthalpy of vaporisation at boiling temperature (H_{vb}) were estimated from Joback and Reid (1987). Consequently, these values were used in empirical correlations to calculate liquid heat capacity at average temperature (C_{pl}) using Rowlinson's modification of Bondi's equation. Additionally, heat of vaporisation at evaporating temperature (H_{ve}) and vapour pressures (P_{vpe} & P_{vpc}) were calculated using Watson's method and Riedel-Plank-Miller equation respectively. The series of equations were adapted from Sahinidis et al. (2003) and are shown in *Appendix B.2*.

2.4 Safety Constraints

2.4.1 Toxicity level

One concern that has emerged with the introduction of alternative refrigerants is toxicity. Acute toxicity, which refers to the impact of a single exposure or multiple short-term exposures, is a key risk for operators as they may be exposed from opening a compressor or removing a gasket with refrigerant trapped below it. Therefore, an additional safety constraint was imposed to eliminate molecules past a LC_{50} of 0.01 mg L^{-1} , an industrial standard (Ashrae, 2019). LC_{50} is an expression for acute toxicity which measures the concentration that is lethal for 50% of exposed population. The LC_{50} of the molecules were calculated using the GC method developed by Martin and Young (2001):

$$-\log(LC_{50}) = \sum_i^N n_i \text{Tox}_i, \quad \text{Eq. (2)}$$

where Tox_i is the toxicity contribution of functional group i .

2.5 Structural Constraints

2.5.1 Constraints from literature review

A series of structural constraints were enforced to eliminate combinations of groups which do not meet molecular bonding requirements and thus cannot be physically formed. These includes the constraints developed by Joback and Stephanopoulos (1995), Odele and Macchietto (1993). In addition, new structural constraints proposed by Sahinidis et al. (2003) were used to further tighten the structural feasibility formulations. Detailed formulations can be found in *Appendix B.4*.

2.5.2 Additional constraints based on chemical insights

Some new constraints were included based on the chemical insights that were thought of in this paper. More detailed explanations on these constraints can be found in *Appendix B4.4*.

2.5.2.1 *Design space*: Since viable refrigerants are thermodynamically restricted to small molecules (McLinden, 1990), the size of the design space N_{max} was confined to 10 functional groups, i.e.

$$\sum_i n_i \leq N_{max} \quad Eq. (3)$$

2.5.2.2 *Halide-amine constraint*: Low-boiling compounds that contain halides and amines have large tendencies to explode (Gani et. al, 1991). Thus, molecular designs with both functional group types were prevented from being formed with the following constraint:

$$n_F + n_{Cl} + n_{Br} + n_I + N_{max} \cdot (n_{NH_2} + n_{NH} + n_N) \leq N_{max} \quad Eq. (4)$$

2.5.2.3 *Limit on unsaturated bonds*: Refrigerants with unsaturated bonds tend to have lower stability (Karnaz, 2013). Thus, only one unsaturated bond is allowed in the molecule with the constraints as shown:

$$n_{CH_2db} + n_{CHdb} + n_{Cdb} + n_{CHtb} + n_{Ctb} \leq 2 \quad Eq. (5)$$

$$n_{Cdbdb} \leq 1 \quad Eq. (6)$$

2.5.2.4 *Ether adjacent to alkane groups*: For the functional group $-O-$ to exist in the design, an ether group must exist, i.e. an oxygen atom connected to two alkyl groups. The following constraint ensures this:

$$n_O \leq 0.99 \cdot (n_{CH_3} + n_{CH_2} + n_{CH} + n_C) \quad Eq. (6)$$

2.6 Property Targets

The maximum vapour pressure at condensing temperature and minimum vapour pressure at evaporating temperature allowed are given to be 14 bar and 1.1 bar respectively, i.e. $P_{vpc} \leq 14$ bar and $P_{vpe} \geq 1.1$ bar.

Typically, refrigerants have a critical temperature of 343K and 385K. The lowest operating temperature of the condenser is approximately 300K and refrigerants with a critical temperature below that would operate within a supercritical cycle. This requires a higher operating pressure and advanced process control (Kazakov et al., 2012). A higher critical temperature of up to 550K is set to allow a wider range of solutions. Thus, critical temperature is bounded between 300K and 550K, i.e. $300K \leq T_c \leq 550K$.

To meet a performance level at least that of the replaced HFC refrigerant, the new refrigerants are required to have a heat of vaporisation greater than or equal to R134a, i.e. $H_{ve} \geq H_{vb}^{R134a}$, and a liquid heat capacity at average process temperature less than or equal to R134a, i.e. $C_{pl} \leq C_{pl}^{R134a}$.

2.7 Integer Cuts

10 alternative refrigerant solutions were then attained by using integer cuts. The nonlinear cut constraint presented by Sahinidis et al. (2003) was applied:

$$\sum_i |n_i^k - n_i| \geq 1, \quad \forall k \in [1, 2, \dots, 10] \quad Eq. (7)$$

By introducing a *LOOP* function in GAMS, the MINLP optimization problem was solved 10 times, with each consecutive iteration having integer cuts inserted to exclude the previous iterations' optimal solutions.

3. Results & Discussion

3.1 Computational Results

The MINLP model used in this paper were solved by the global optimization solver BARON accessed via the GAMS modelling tool. The algorithm took approximately 20 minutes of CPU time to derive a final solution set of 10 optimal molecules, as displayed in *Table 2*.

Table 2: Optimal Solution Set of Alternative Refrigerants to R134a

	Molecular Structure	$\frac{\Delta H_{ve}}{C_{pl}}$ [10^3 K]	T_c [K]	Expt. T_c [K]	Rel. Abs. Error (RAE) %
R134a	F – CH₂ – CF₃	0.141	369.61	374.21	1.24
1	F – N = O	0.308	415.95	349.40	16.00
2	F – Br	0.286	436.66	449.00	2.83
3	Cl – CH = O	0.282	405.18	–	–
4	F – SH	0.279	438.04	–	–
5	CH ₃ – Cl	0.268	428.09	416.24	2.77
6	(F –)(Cl –) > C = O	0.243	398.20	324.00	18.63
7	F – S – F	0.233	433.49	–	–
8	CH ₃ – CH = C = O	0.230	420.20	–	–
9	CH ₃ – C \equiv CH	0.222	429.23	402.00	6.34
10	Cl – CH ₂ – F	0.220	417.06	455.00	9.10

3.2 Analysis of Solution

Among the 10 solutions in *Table 2*, 8 of them are on the complete set of solutions attained by Sahinidis et al., 2013. The objective values are also in line with what was attained from this model. This demonstrates that the model is properly formulated.

F – Br, F – SH and F – S – F can be immediately eliminated as these 3 molecules are known to be highly unstable. This also indicates that the model can be enhanced with further granularity in its constraints to filter out such unstable molecules. CH₃ – Cl (R40) and Cl – CH₂ – F (R31) were previously widely used refrigerants but these are chlorofluorocarbons (CFCs) that have already been phased out via the Montreal Protocol due to its contribution to depletion of the ozone layer. In fact, HFCs like R134a were meant to replace them, until its strong greenhouse effects were realised.

Therefore, further investigation can be made on the remaining 5 molecules, with a priority on $F - N = O$, $CH_3 - CH = C = O$ and $CH_3 - C \equiv CH$ as these do not contain Cl. The halogen is known to cause higher ozone depleting potentials.

3.3 Model Validation

To validate the accuracy of thermophysical property predictions using Joback and Reid's GC method, the T_c values obtained from the model was compared to experimental values in NIST webbook. Only 6 of the 10 molecules had T_c values available and these are shown in *Table 2*.

The predictions of R134a, $F - Br$, $CH_3 - Cl$, and $CH_3 - C \equiv CH$ are very reliable with RAE% of less than 7%, indicating that there is a low degree of error between predicted and experimental values. The mean RAE% is 9.04%, with $(F -)(Cl -) > C = O$ having the largest contributor of RAE% of 18.63% and $F - N = O$ having the second largest RAE% of 16.00%. These deviations may be attributed to second order contributions between the functional groups that were excluded in this study, However, the mean RAE% is considered to be within an acceptable range. Therefore, the use of Joback and Reid method is reasonably accurate.

3.4 Model Limitations

One limitation of this model is it cannot distinguish isomers. The positions of functional groups were self-determined after the model generated the number of each group. Isomers can have slightly varied thermophysical properties which could have different efficiencies as refrigerants.

Another limitation of this model is regarding the safety constraint using LC_{50} as a basis. The LC_{50} data for some functional groups were not obtainable so the LC_{50} values for molecules containing these functional groups were assumed to be zero.

In addition to these, there are other factors such as safety, environmental, and economical aspects that can be considered in this model and are discussed below in the model outlook.

4. Model Outlook

4.1 Flammability Limit

In order to reduce the risk of fire or explosion when handling refrigerants in confined space, the concentration of refrigerants in air need to be in accordance with the safety classifications of ASHRAE standard (Ashrae, 2019). This standard focuses on the lower limit of flammability (*LFL*). This is defined as the minimum concentration of refrigerant that can propagate a flame when mixed homogeneously in air in the presence of an ignition source. The recommended *LFL* required by ASHRAE is $LFL > 0.10 \text{ kgm}^{-3}$. Frutiger *et al.* (2016) has developed a novel group contribution model for *LFL* with a 95% confidence interval of the prediction. The *LFL* group contribution and safety limit can be implemented in GAMS to ensure that the refrigerants proposed are safer to handle.

$$\log \frac{LFL}{4.53} = \sum_{i=1}^N n_i LFL_i \quad Eq. (8)$$

$$LFL > 0.10 \text{ kgm}^{-3} \quad Eq. (9)$$

4.2 Ozone Depletion Potential

Ozone Depletion Potential (ODP) is defined as the amount of degradation a compound can cause to the ozone layer. ODP can be estimated from the molecular structure of CFC's with one or two carbon atoms and was developed by Duvedi and Achenie (1996). The ODP constraints shown below can be enforced in GAMS to account for the environmental impact of the refrigerants. The upper bound considered is based on an ODP band provided by Linde Group (2015).

$$ODP = 0.585602n_{cl}^{-0.0035} \exp\left(\frac{MW}{238.563}\right) \text{ for CFCs containing 1 carbon} \quad Eq. (10)$$

$$ODP = 0.0949956n_{cl}^{-0.0404477} \exp\left(\frac{MW}{83.7953}\right) \text{ for CFCs containing 2 carbons} \quad Eq. (11)$$

$$ODP < 0.03 \quad Eq. (12)$$

4.3 Equipment Cost

The choice of a refrigerant does not solely depend on safety and environmental impacts, but also the cost incurred by implementing it. The process of refrigeration cycle needs to be operated as economical as possible. The total capital cost comprises the compressor, condenser, and evaporator. The condenser and evaporator are fixed costs as they are independent of refrigerant used and dependent on the equipment area. The area can be calculated from the operating condition T_{cond} and T_{evap} . The compressor cost is a function of vapour capacity. Thus, the volumetric flowrate of the refrigerant must be calculated as shown:

$$V_r = \frac{Q}{H_{ve} - C_{pl}(T_c - T_e)} V_m, \quad Eq. (13)$$

$$\text{Compressor Cost} = f(V_r) \quad Eq. (14)$$

where Q is the cooling capacity and V_m is the molar volume.

V_r can be included in GAMS as a constraint by setting an upper bound based on a budget. This will ensure the optimal refrigerants are financially feasible.

5. Conclusion

In this paper, an optimisation model was developed with integer cuts via a CAMD approach to streamline the process of identifying alternative refrigerants to R134a. The model comprises of a mixed integer nonlinear programming algorithm that provides molecular designs at least as efficient as a refrigerant than R134a, while satisfying pre-determined physical conditions and structural feasibility constraints.

Valuable insights can be attained from this study. Firstly, the model shows a few CFCs in its optimal solution set. Unfortunately, these were already phased out before HFCs under the Montreal Protocol due to its contribution to ozone depletion. This indicates a possible trade-off between refrigerant effectiveness and environmental issues. Optimization of the two factors is

necessary and essential. Secondly, after manual elimination of the 10 solutions attained, $F - N = O$, $CH_3 - CH = C = O$ and $CH_3 - C \equiv CH$ appears to be the most promising molecules that could serve as alternative refrigerants. Further scientific experiments can be done to test and assess their use in practical application.

In terms of model enhancement, the model includes a safety constraint by assessing the toxicity of refrigerants to protect industrial workers. However, other factors like flammability limit, ozone depletion potential and equipment cost can also be considered to further address concerns specific to the use of refrigerants. With these, a leap towards a sustainable future can be achieved.

References

Anderson, I. J. and Digiulio, C. D. (2007) 'Incorporating Product Design into the Development of New Refrigerants'.

Ashrae (2019) *ANSI/ASHRAE 34-2019, Designation and Safety Classification of Refrigerants*. Available at: <https://www.ashrae.org/technical-resources/standards-and-guidelines/ashrae-refrigerant-designations> (Accessed: 12 December 2019).

Constantinou, L. and Gani, R. (1994) 'New group contribution method for estimating properties of pure compounds', *AIChE Journal*, 40(10), pp. 1697–1710. doi: 10.1002/aic.690401011.

Duvedi, A. P. and Achenie, L. E. K. (1996) 'Designing environmentally safe refrigerants using mathematical programming', *Chemical Engineering Science*, 51(15), pp. 3727–3739. doi: 10.1016/0009-2509(96)00224-2.

Frutiger, J. *et al.* (2016) 'Group-contribution based property estimation and uncertainty analysis for flammability-related properties', *Journal of Hazardous Materials*. Elsevier B.V., 318, pp. 783–793. doi: 10.1016/j.jhazmat.2016.06.018.

Gani, R., Nielsen, B. and Fredenslund, A. (1991) 'A group contribution approach to computer-aided molecular design', *AIChE Journal*, 37(9), pp. 1318–1332. doi: 10.1002/aic.690370905.

Joback, K. G. and Reid, R. C. (1987) 'Estimation of Pure-Component Properties from Group-Contributions', *Chemical Engineering Communications*, 57(1–6), pp. 233–243. doi: 10.1080/00986448708960487.

Karnaz, J. (2013) 'Compressor and system energy efficiency improvements through lubricant optimization'. doi: 10.1533/9781782421702.3.163.

Kazakov, A., McLinden, M. O. and Frenkel, M. (2012) 'Computational design of new refrigerant fluids based on environmental, safety, and thermodynamic characteristics', *Industrial and Engineering Chemistry Research*, 51(38), pp. 12537–12548. doi: 10.1021/ie3016126.

Linde Group (2015) 'Refrigerants Environmental Data', *Refrigerants Environmental Data*, (2006), p. 2. doi: 10.1016/j.applthermaleng.2007.07.018.

Martin, T. M. and Young, D. M. (2001) 'Prediction of the acute toxicity (96-h LC50) of organic compounds to the fathead minnow (*Pimephales promelas*) using a group contribution method', *Chemical Research in Toxicology*, 14(10), pp. 1378–1385. doi: 10.1021/tx0155045.

McLinden, M. O. (1990) 'Optimum Refrigerants for Non-Ideal Cycles: An Analysis Employing Corresponding States', *International Refrigeration and Air Conditioning Conference*, pp. 69–79.

Odele, O. and Macchietto, S. (1993) 'Computer Aided Molecular Design: A Novel Method for Optimal Solvent Selection', 82(2), pp. 78–79.

Sahinidis, N. V., Tawarmalani, M. and Yu, M. (2003) 'Design of alternative refrigerants via global optimization', *AIChE Journal*, 49(7), pp. 1761–1775. doi: 10.1002/aic.690490714.

Appendix

Appendix A: Nomenclature

Sets

i Functional group [CH₃, CH₂...]

Integer Variables

$n(i)$ Number of functional group i in a molecule

Z_{sb} Integer variable modelling structural requirement for single bonds

Z_{db} Integer variable modelling structural requirement for double bonds

Z_{tb} Integer variable modelling structural requirement for triple bonds

Variables

α Intermediate variable used to calculate acentric factor

β Intermediate variable used to calculate acentric factor

ω Acentric factor

G Intermediate variable used to for Riedel-Plank-Miller equation

h Intermediate variable used to for Riedel-Plank-Miller equation

k Intermediate variable used to for Riedel-Plank-Miller equation

LC_{50} Lethal concentration which kills 50% of population [mol L⁻¹]

Positive Variables

C_{p0} Ideal gas heat capacity at average temperature [J mol⁻¹K⁻¹]

C_{pl} Liquid heat capacity at average temperature [J mol⁻¹K⁻¹]

MW Molecular weight [g mol⁻¹]

H_{vb} Heat of vaporisation at boiling temperature [kJ mol⁻¹]

H_{ve} Heat of vaporisation at evaporating temperature [kJ mol⁻¹]

P_c Critical pressure [bar]

P_{vpc} Vapour pressure at condensing temperature [bar]

P_{vpcr} Reduced vapour pressure at condensing temperature

P_{vpe} Vapour pressure at evaporating temperature [bar]

P_{vper} Reduced vapour pressure at evaporating temperature

T_{avgr} Reduced average temperature [K]

T_b Boiling temperature [K]

T_c Critical temperature [K]

T_{cndr} Reduced condensing temp. [K]

T_{evpr} Reduced evaporating temp. [K]

Binary Variables

Y_{SDx} 1 if groups w/ both single and double bonds are present, 0 otherwise

Y_{SDy} 1 if groups w/ only single bonds are present, 0 otherwise

Y_{SDz} 1 if groups w/ only double bonds are present, 0 otherwise

Y_h 1 if higher-bonded groups are present, 0 otherwise

Parameters

a_i	Number of atoms in group i
$C_{p0,i}$	Ideal gas heat capacity parameter a, b, c, d for group i
DB_i	Number of double bonds in group i
H_{vb}^i	Contribution of group i to enthalpy of vap. at boiling temp. [kJ mol ⁻¹]
N	Total number of groups in model
N_{max}	Maximum number of groups allowed
$P_{c,i}$	Contribution of group i to critical pressure [bar]
SB_i	Number of single bonds in group i
$T_{b,i}$	Contribution of group i to boiling temperature [K]
$T_{c,i}$	Contribution of group i to critical temperature [K]
T_{avg}	Average temperature [K]
T_{cnd}	Condensing temperature [K]
T_{evp}	Evaporating temperature [K]
Tox_i	Contribution of group i to toxicity
v_i	Valency of group i

Appendix B: Complete Mathematical Formulations**B.1 Objective Function**

$$\max_{s.t.} \frac{H_{ve}}{C_{pl}} \quad Eq. (B1)$$

B.2 Physical Properties Constraints**B.2.1 Joback and Reid**

$$T_b = 198.2 + \sum_{i=1}^N n_i T_{b,i} \quad Eq. (B2)$$

$$T_c = \frac{T_b}{0.584 + 0.965 \sum_{i=1}^N n_i T_{c,i} - (\sum_{i=1}^N n_i T_{c,i})^2} \quad Eq. (B3)$$

$$P_c = \frac{1}{(0.113 + 0.0032 \sum_{i=1}^N n_i a_i - \sum_{i=1}^N n_i P_{c,i})^2} \quad Eq. (B4)$$

$$C_{p0} = \sum_{i=1}^N n_i C_{p0a,i} - 37.93 + \left(\sum_{i=1}^N n_i C_{p0b,i} + 0.21 \right) T_{avg} + \left(\sum_{i=1}^N n_i C_{p0c,i} - 3.91 \times 10^{-4} \right) T_{avg}^2 + \left(\sum_{i=1}^N n_i C_{p0d,i} + 2.06 \times 10^{-7} \right) T_{avg}^3 \quad Eq. (B5)$$

$$H_{vb} = 15.3 + \sum_{i=1}^N n_i H_{vb,i} \quad Eq. (B6)$$

$$T_{br} = \frac{T_b}{T_c} \quad Eq. (B7)$$

$$T_{avgr} = \frac{T_{avg}}{T_c} \quad Eq. (B8)$$

$$T_{cndr} = \frac{T_{cndr}}{T_c} \quad Eq. (B9)$$

$$T_{evpr} = \frac{T_b}{T_c} \quad Eq. (B10)$$

B.2.2 Rowlinson's modification of Bondi's equation

$$\alpha = -5.97214 - \ln\left(\frac{P_c}{1.013}\right) + \frac{6.09648}{T_{br}} + 1.28862 \ln(T_{br}) - 0.169347 T_{br}^6 \quad Eq. (B11)$$

$$\beta = 15.2518 - \frac{15.6875}{T_{br}} + 13.4721 \ln(T_{br}) - 0.43577 T_{br}^6 \quad Eq. (B12)$$

$$\omega = \frac{\alpha}{\beta} \quad Eq. (B13)$$

$$C_{pl} = C_{p0} + 8.314 \left[1.45 + \frac{0.45}{1 - T_{avgr}} + 0.25\omega \left(17.11 + 25.2 \frac{(1 - T_{avgr})^{\frac{1}{3}}}{T_{avgr}} + \frac{1.742}{1 - T_{avgr}} \right) \right] \quad Eq. (B14)$$

B.2.3 Watson's method

$$H_{ve} = H_{vb} \left(\frac{1 - \frac{T_{evpr}}{T_c}}{1 - \frac{T_b}{T_c}} \right)^{0.38} \quad Eq. (B15)$$

B.2.4 Riedel-Plank-Miller

$$h = \frac{T_{br} \ln\left(\frac{P_c}{1.013}\right)}{1 - T_{br}} \quad Eq. (B16)$$

$$G = 0.4835 + 0.4605 T_{br} \quad Eq. (B17)$$

$$k = \frac{\frac{h}{G} - (1 + T_{br})}{(3 + T_{br})(1 - T_{br})^2} \quad Eq. (B18)$$

$$\ln P_{vpcr} = \frac{-G}{T_{cndr}} \left[(1 - T_{cndr}^2 + k(3 + T_{cndr})(1 - T_{cndr})^3) \right] \quad Eq. (B19)$$

$$\ln P_{vper} = \frac{-G}{T_{evpr}} \left[(1 - T_{evpr}^2 + k(3 + T_{evpr})(1 - T_{evpr})^3) \right] \quad Eq. (B20)$$

$$P_{vpc} = P_{vpcr}P_c \quad \text{Eq. (B21)}$$

$$P_{vpe} = P_{vper}P_c \quad \text{Eq. (B22)}$$

B.3 Safety Constraints

B.3.1 Toxicity level

An additional safety constraint was imposed to eliminate molecules past a LC_{50} of 0.01 mg L^{-1} . The GC method developed by Martin et al. (2001) was employed as such:

$$-\log(LC_{50}) = \sum_i^N n_i \text{Tox}_i \quad \text{Eq. (B23)}$$

Since the LC_{50} contribution data from each functional group are given in units of $10^{-3} \text{ mol L}^{-1}$, multiplying the molecular weight of the molecule gives the desired units of mg L^{-1} .

$$MW = \sum_i^N n_i MW_i \quad \text{Eq. (B24)}$$

$$MW \cdot LC_{50} \geq 0.01 \quad \text{Eq. (B25)}$$

For functional groups without toxicity data, the LC_{50} values are inserted as 0.

B.4 Structural Constraints

B.4.1 Joback-Stephanopoulos

At least 2 functional groups are required to form a molecule. The maximum design space (N_{max}) for this problem was set at 10 since refrigerants are deemed to be small and volatile molecules.

$$2 \leq \sum_i n_i \leq 10 \quad \text{Eq. (B26)}$$

The number of bonds formed in the molecule, which is equivalent to half of the number of total available bonds from each group, must be at least equal to the number of groups minus one.

$$\sum_i^N \frac{n_i b_i}{2} \geq \left(\sum_i^N n_i - 1 \right) \quad \text{Eq. (B27)}$$

If there exist together two types of groups – groups with single bonds but no double bonds and groups with double bonds but no single bonds, there needs to be a transition group containing both single and double bonds between these 2 groups. To ensure this rule, the following constraints with binary variables are imposed.

$$Y_{SDx} \leq \sum_{i \in SD} n_i \leq N_{max} \cdot Y_{SDx} \quad \text{Eq. (B28)}$$

$$Y_{SDy} \leq \sum_{i \in \frac{S}{D}} n_i \leq N_{max} \cdot Y_{SDy} \quad \text{Eq. (B29)}$$

$$Y_{SDz} \leq \sum_{i \in \frac{D}{S}} n_i \leq N_{max} \cdot Y_{SDz} \quad \text{Eq. (B30)}$$

$$Y_{SDy} + Y_{SDz} - 1 = Y_{SDx}, \quad \text{Eq. (B31)}$$

where SD are groups with both single and double bonds, S/D are groups with single but no double bonds, and D/S are groups with double but no single bonds.

Since every bond that is formed in the molecule requires a pair of the same bond type, there must be an even number of the same bond type (single, double and triple bonds). This is ensured using the non-negative integer variables Z_D and Z_T .

$$\sum_i n_i \cdot SB_i = 2Z_S \quad \text{Eq. (B32)}$$

$$\sum_i n_i \cdot DB_i = 2Z_D \quad \text{Eq. (B33)}$$

$$\sum_i n_i \cdot TB_i = 2Z_T \quad \text{Eq. (B34)}$$

B.4.2 Odele-Macchietto

The following constraints were adapted to ensure structural feasibility in the octet rule and that two adjacent groups are only linked by no more than one bond.

$$\sum_i (2 - v_i) \cdot n_i = 2 \quad \text{Eq. (B35)}$$

$$\sum_i^N n_i \geq n_j \cdot (v_j - 1), \quad \forall i \neq j \quad \text{Eq. (B36)}$$

B.4.3 Sahinidis et al.

As pointed out by Sahinidis et al. (2003), the Joback-Stephanopoulos and Odele-Macchietto constraints are insufficient to eliminate all infeasible group combinations, such as $1(>\text{CH}-)$, $3(=\text{O})$ and $1(=\text{N}-)$. Thus, more structural constraints between one-bonded and higher-bonded groups were also adapted from Sahinidis et al. (2003). A “one bonded group” ($i \in \mathcal{O}$) is defined as a group with only one (single, double, triple) bond while a “higher-bonded group” ($i \in \mathcal{H}$) is a group with more than one bond. Together with the binary variable Y_h , Eqs. (B38) – (B39) ensures that if present, the number of one-bonded groups must be less than or equal to the available bonds contained in higher-order groups.

$$Y_h \leq \sum_{i \in \mathcal{H}} n_i \leq N_{\max} \cdot Y_h \quad \text{Eq. (B37)}$$

$$\sum_{\substack{i \in \mathcal{O}, \\ \text{single-bonded}}} n_i \leq \sum_{i \in \mathcal{H}} n_i SB_i^H + N_{\max} \cdot (1 - Y_h) \quad \text{Eq. (B38)}$$

$$\sum_{\substack{i \in \mathcal{O}, \\ \text{double-bonded}}} n_i \leq \sum_{i \in \mathcal{H}} n_i DB_i^H + N_{\max} \cdot (1 - Y_h) \quad \text{Eq. (B39)}$$

Finally, to prevent two one-bonded groups from forming a molecule even though there are other molecules present, the following constraint is imposed.

$$\sum_{i \in \mathcal{H}} n_i \cdot (S_i^H + D_i^H) - \sum_{i \in \mathcal{O}} n_i = 2 \left(\sum_{i \in \mathcal{H}} n_i - 1 \right) \quad \text{Eq. (B40)}$$

B.4.4 Additional constraints based on chemical insights

B.4.4.1 Halide-Amine constraint: Low-boiling compounds that contain halides and amines have large tendencies to explode (Ga. Thus, molecular designs with both functional group types were prevented from being formed with the following constraint:

$$n_F + n_{Cl} + n_{Br} + n_I + Nmax \cdot (n_{NH_2} + n_{NH} + n_N) \leq Nmax \quad \text{Eq. (B41)}$$

Through Eq. (B41), if any of the halides are present, i.e. $n_F + n_{Cl} + n_{Br} + n_I \geq 1$, then the amine groups $n_{NH_2} + n_{NH} + n_N$ must be equal to 0 to meet the inequality constraint. The same works vice versa.

B.4.4.2 Limit on saturated bonds: Refrigerants with unsaturated bonds tend to have lower stability (Karnaz, 2013). Thus, only one unsaturated bond is allowed in the molecule with the constraint as shown:

$$n_{CH_2db} + n_{CHdb} + n_{Cdb} + n_{CHtb} + n_{Ctb} \leq 2 \quad \text{Eq. (B42)}$$

$$n_{Cdbdb} \leq 1 \quad \text{Eq. (B43)}$$

Eqs. (B42)-(B43) limits the total sum of carbon groups containing double or triple bonds to 2. In this way, not more than one unsaturated bond can be present in the molecule.

B.4.4.3 Ether adjacent to alkane groups: For the functional group $-O-$ to exist in the design, an ether group must exist, i.e. an oxygen atom connected to two alkyl groups. The constraint in below ensures this.

$$n_O \leq 0.99 \cdot (n_{CH_3} + n_{CH_2} + n_{CH} + n_C) \quad \text{Eq. (B44)}$$

Thus, if an ether groups is present, i.e. $n_O \geq 1$, there has to be at least 2 times of alkyl groups for this constraint to be satisfied.

B.5 Process Conditions and Property Targets

For the typical vapour-compression refrigerant cycle considered, the evaporating temperature, condensing temperature and average process temperature were fixed with the equality constraints below.

$$T_{evp} = 272 \text{ K} \quad \text{Eq. (B45)}$$

$$T_{cnd} = 316 \text{ K} \quad \text{Eq. (B46)}$$

$$T_{avg} = \frac{T_{evp} + T_{cnd}}{2} = 294 \text{ K} \quad \text{Eq. (B47)}$$

The maximum vapour pressure at condensing temperature and minimum vapour pressure at evaporating temperature allowed are given to be 14 bar and 1.1 bar respectively. Additionally, the heat of vaporisation must be greater than or equal to R134a and a liquid heat capacity at average process temperature must be less than or equal to R134a. These are satisfied by the inequality constraints.

$$P_{vpc} \leq 14 \text{ bar} \quad \text{Eq. (B48)}$$

$$P_{vpe} \geq 1.1 \text{ bar} \quad \text{Eq. (B49)}$$

$$H_{ve} \geq H_{ve}^{R134a} \quad \text{Eq. (B50)}$$

$$C_{pl} \leq C_{pl}^{R134a} \quad \text{Eq. (B51)}$$

B.6 Variable Bounds

Table 3 shows additional bounds on continuous and integer variables that were implemented after rounds of preliminary testing to expedite the MINLP solver.

Table 3: Variable Bounds

Symbol	Lower Bound	Upper Bound	Symbol	Lower Bound	Upper Bound
α	-5.4	6100	T_{avgr}	—	1
β	-16000	0	T_b	50	1000
C_{p0a}	1	135	T_{br}	—	1
ΔH_{vb}	10	110	T_{cndr}	—	1
ΔH_{ve}	18.4	100	T_{evpr}	—	1
P_{vpcr}	—	1	ω	-1	1.3
P_{vper}	—	1	z	—	1