

Predicting the solubility of active pharmaceutical ingredients in organic solvents using the SAFT- γ Mie group contribution approach

Vasileios Papaioannou, Thomas Pogiatis, Simon Dufal, Majid Sadeqzadeh,
Claire S. Adjiman, George Jackson and Amparo Galindo

Department of Chemical Engineering, Centre for Process Systems Engineering, South Kensington Campus, Imperial College London, SW7 2AZ, UK

v.papaioannou08@ic.ac.uk

Characteristics

The SAFT- γ Mie approach^[1] is a predictive thermodynamic methodology that combines the predictive capabilities of group-contribution methods with the accuracy of SAFT-type approaches.

Within SAFT- γ Mie :

- molecules are modelled based on functional/chemical groups
 - **transferable** group parameters
- a fused heteronuclear united-atom molecular model is employed
 - each chemical group is represented by a segment/set of identical segments
 - predictions for mixtures based on pure-component data alone
- the Mie intermolecular potential is used for the description of interactions
 - each chemical group is described by a set of parameters that define the form of the interaction potential
 - detailed potential allows for the simultaneous accurate description of a wide variety of thermodynamic properties^[1,2]

- high **predictive capabilities**

Solubility calculations :

Assuming that the solid phase consists of pure solute:

$$\ln x_{sl}^L = -\frac{\Delta h_{fus}}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right) + \frac{\Delta c_p}{R} \left(\frac{T_m}{T} - 1 \right) - \frac{\Delta c_p}{R} \ln \frac{T_m}{T} - \ln \gamma_{sl}^L(T, p, x^L)$$

$\ln x_{sl}^L$: mole fraction of solute
 Δh_{fus} : enthalpy of fusion
 R : gas constant
 T : temperature
 T_m : melting temperature
 Δc_p : heat capacity difference between phases
 γ_{sl}^L : activity coefficient of solute
 x^L : composition of liquid phase
 p : pressure

Δh_{fus} , T_m , Δc_p : from experimental data or a group-contribution method

Solubility predictions for active pharmaceutical ingredients (APIs)

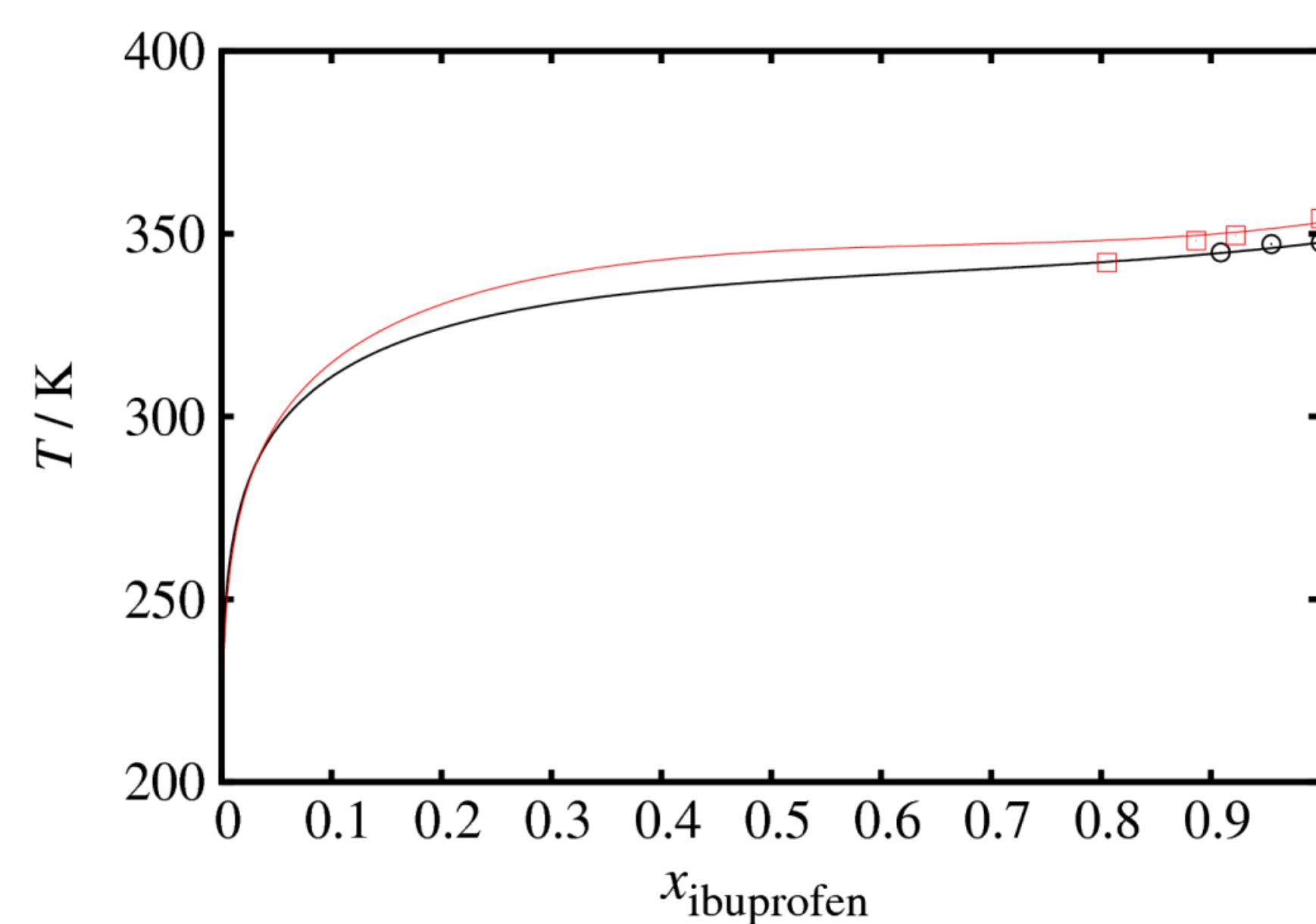
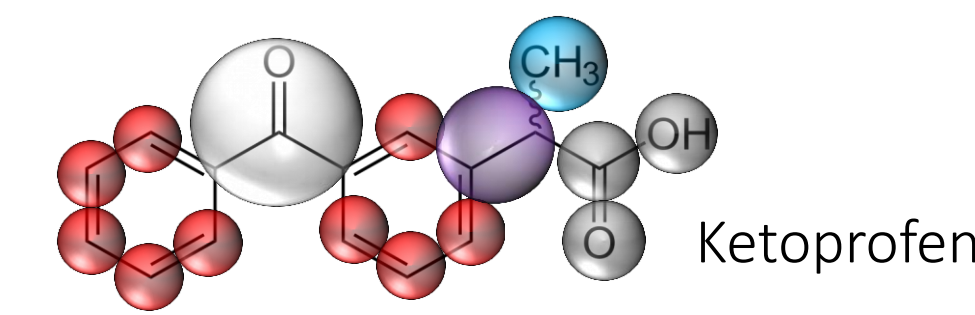
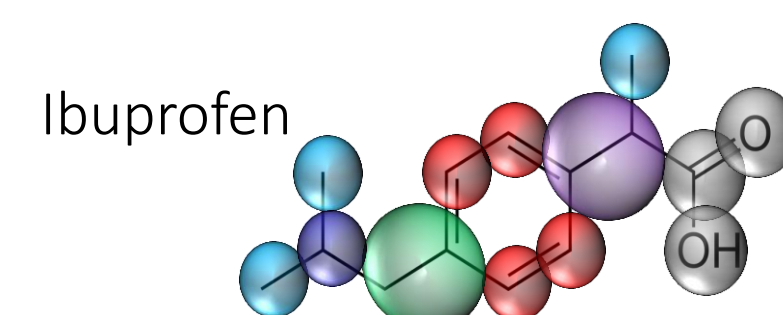


Figure: Isobaric (T-x) phase diagram of the solid-liquid equilibria of ibuprofen + myristic acid (circles) and ibuprofen + stearic acid (squares) (P = 101 kPa).

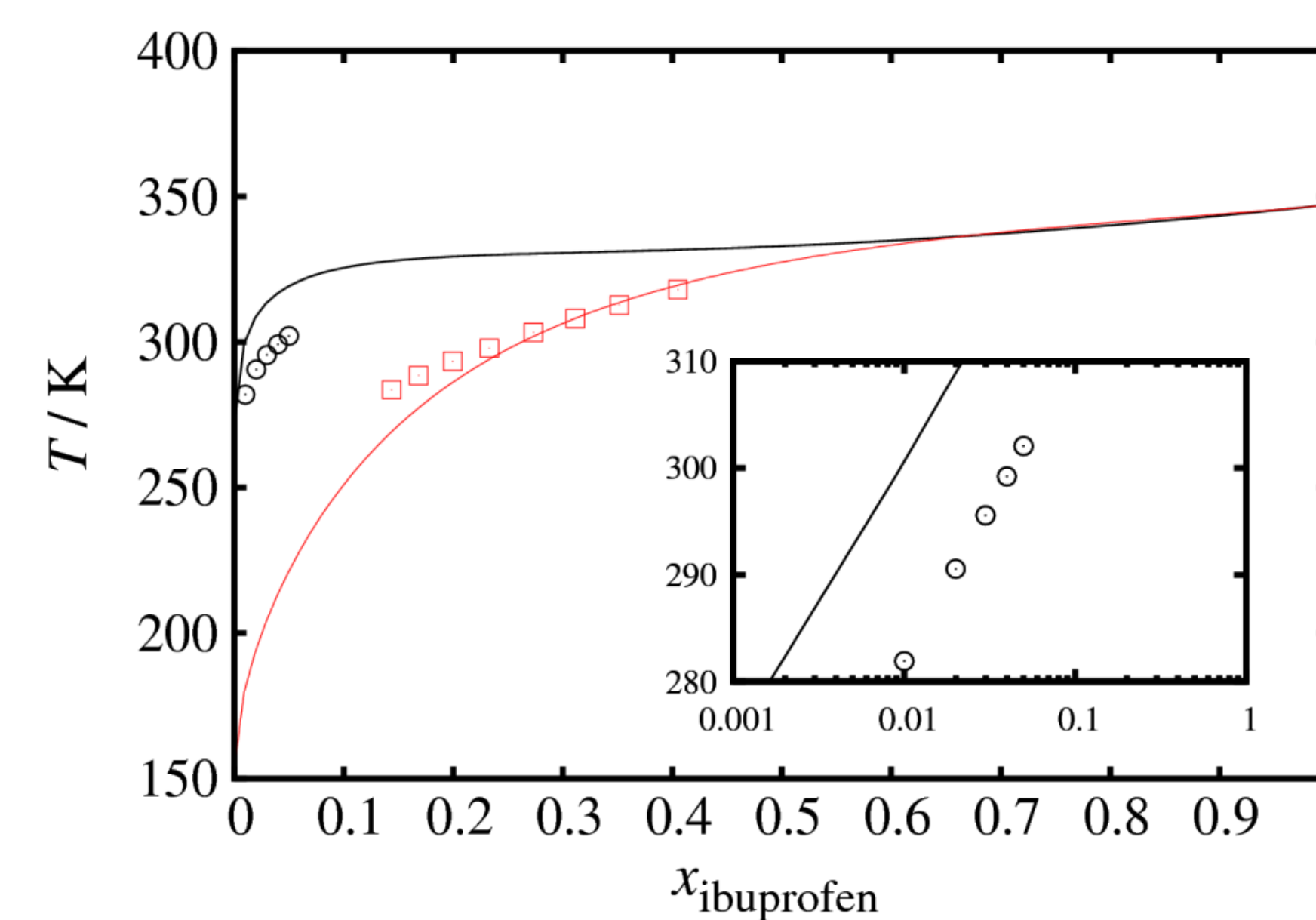


Figure: Isobaric (T-x) phase diagram of the solid-liquid equilibria of ibuprofen + heptane (circles) and ibuprofen + acetone (squares) (P = 101 kPa).

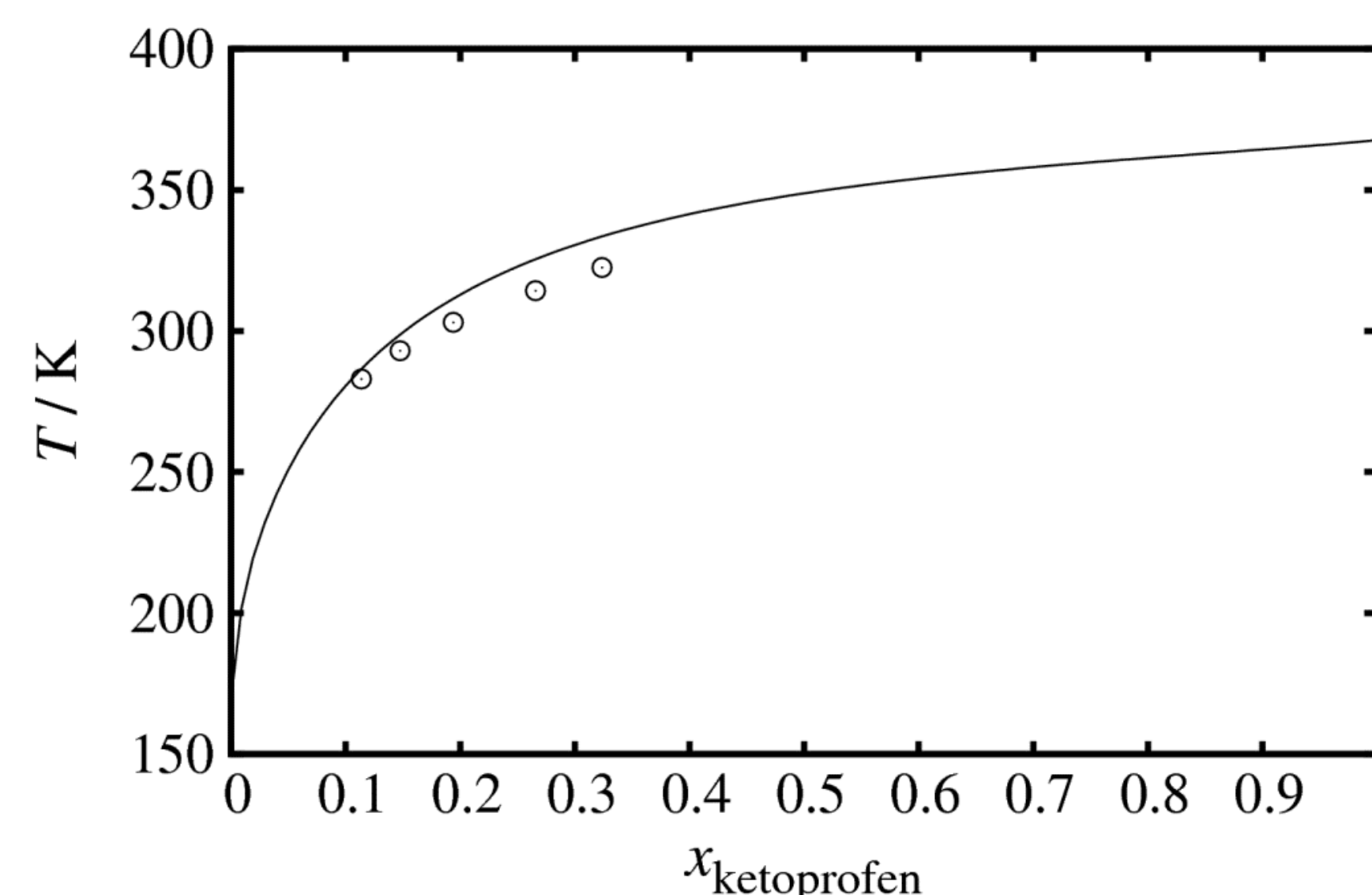


Figure: Isobaric (T-x) phase diagram of the solid-liquid equilibrium of ketoprofen + acetone (P = 101 kPa).

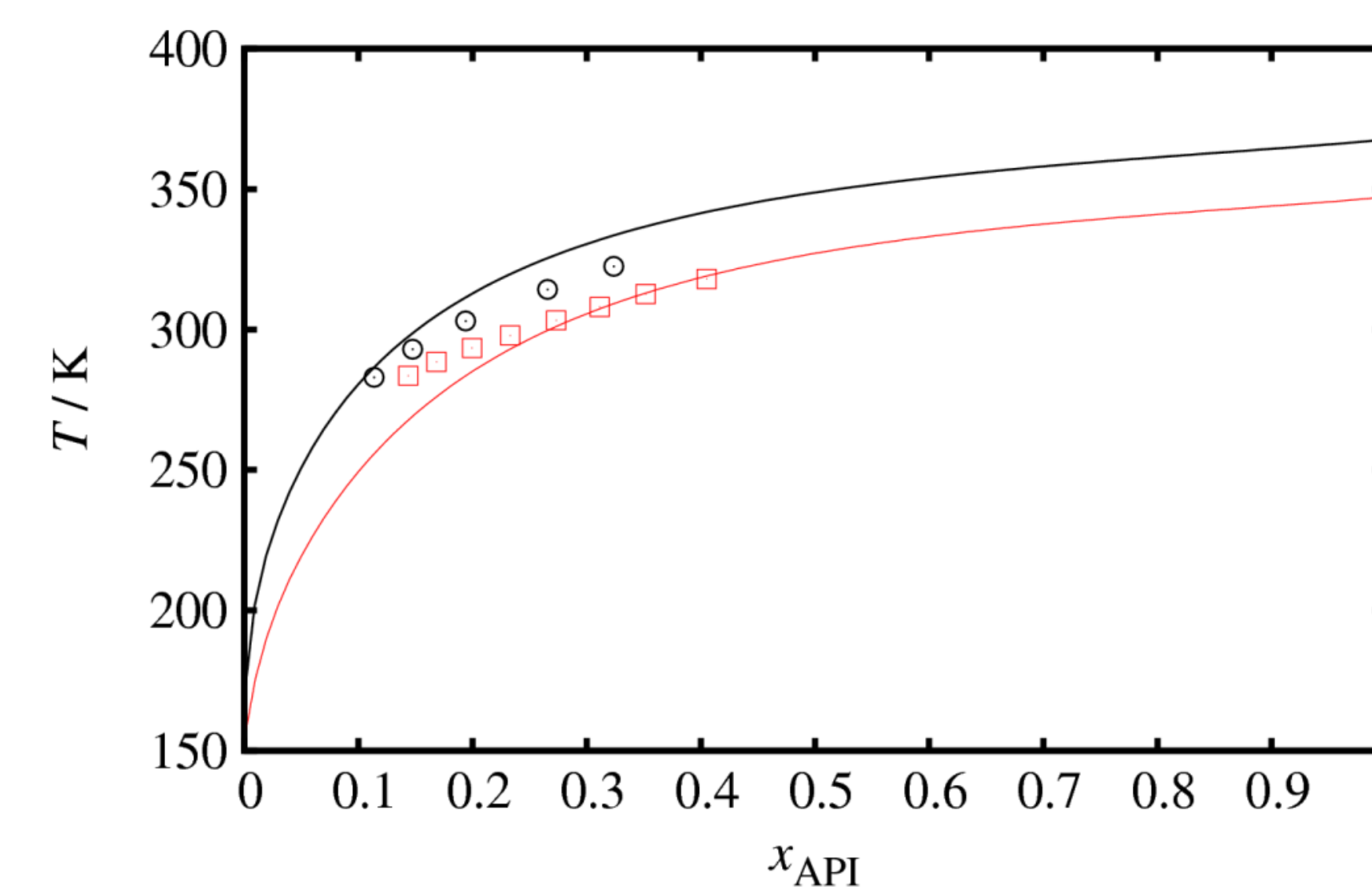


Figure: Isobaric (T-x) phase diagram of the solid-liquid equilibria of ibuprofen + acetone (circles) and ketoprofen + acetone (squares) (P = 101 kPa).

Thermodynamic properties and phase behaviour description^[3]

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CH ₃	CH ₂	CH	C	aCH	aCCH ₂	aCCH	CH ₂ =	CH=	cCH ₂	COOH	CH ₃ COCH ₃	COO	H ₂ O	aCCOaC

Table: Groups available for use in the SAFT- γ Mie approach: the green shading indicates the group-group interaction parameters that were regressed to experimental data, while the grey shading indicates the parameters that are calculated using combining rules.

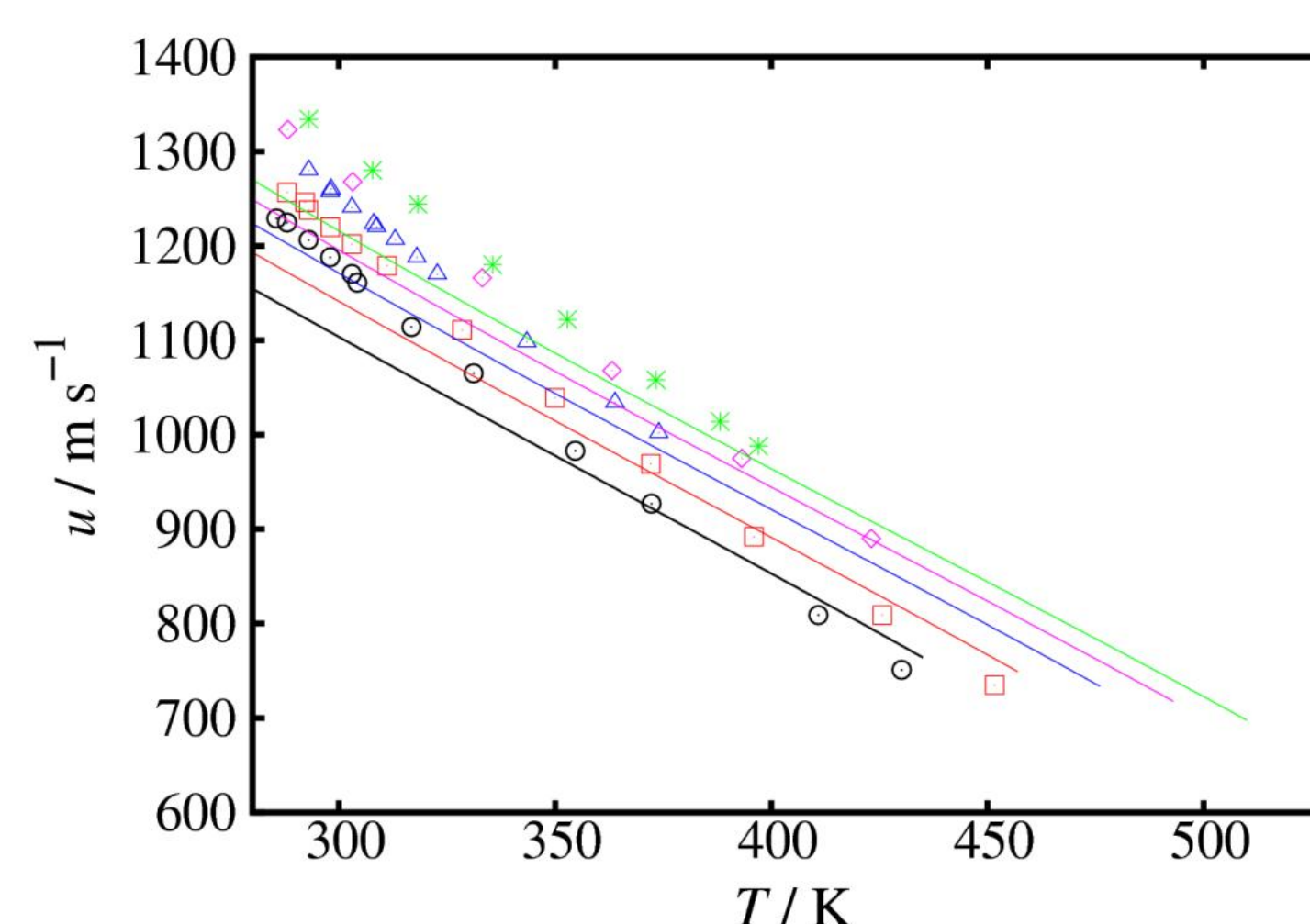


Figure [predicted]: Speed of sound of pure carboxylic acids: butanoic acid (circles), pentanoic acid (squares), hexanoic acid (triangles), heptanoic acid (diamonds) and octanoic acid (asterisks) (P = 101 kPa).

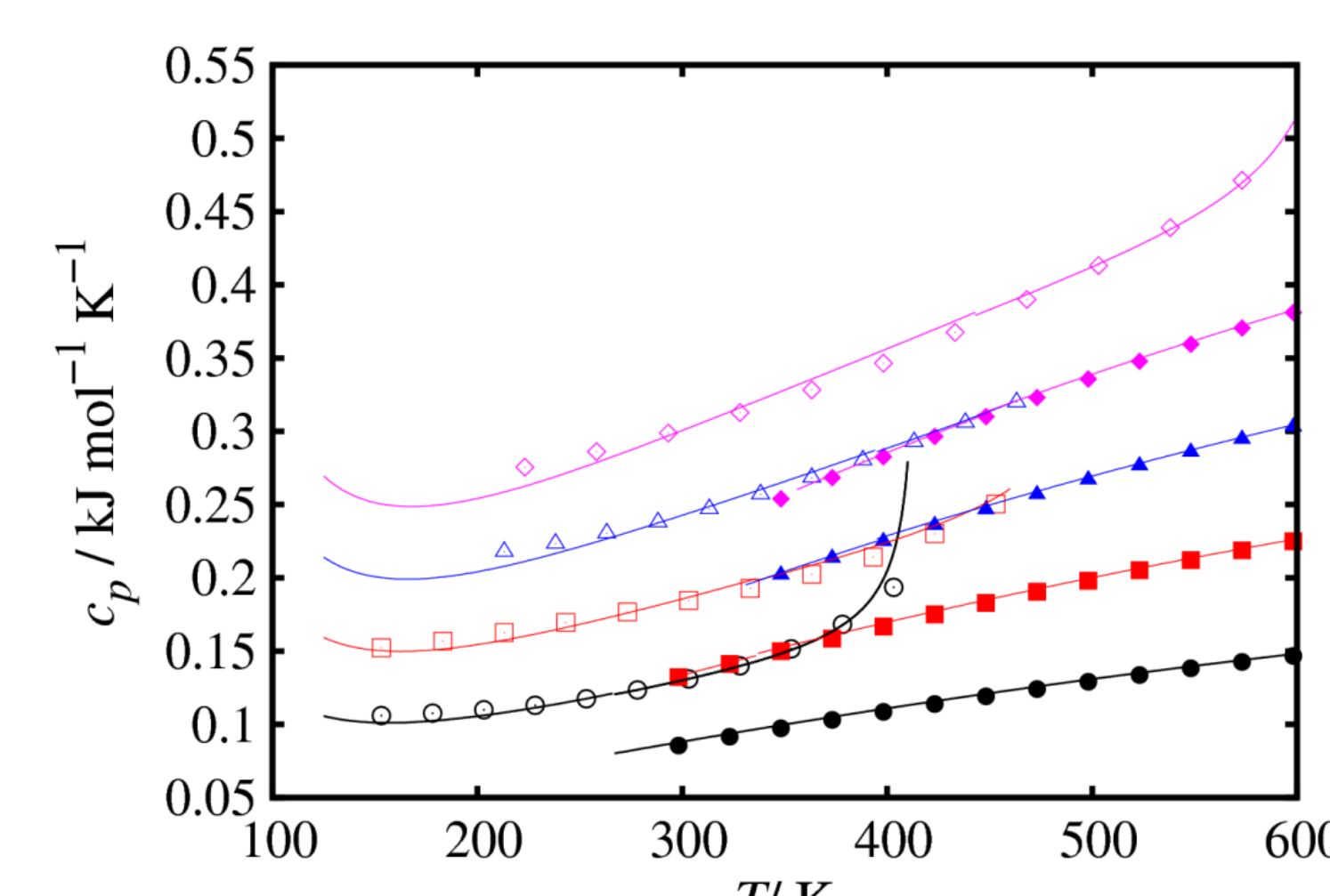


Figure [predicted]: Isobaric heat capacity of n-alkenes in the liquid phase (open symbols) and the gaseous phase (filled symbols): 1-butene (circles), 1-hexene (squares), 1-octene (triangles) and 1-decene (diamonds) (P = 101 kPa).

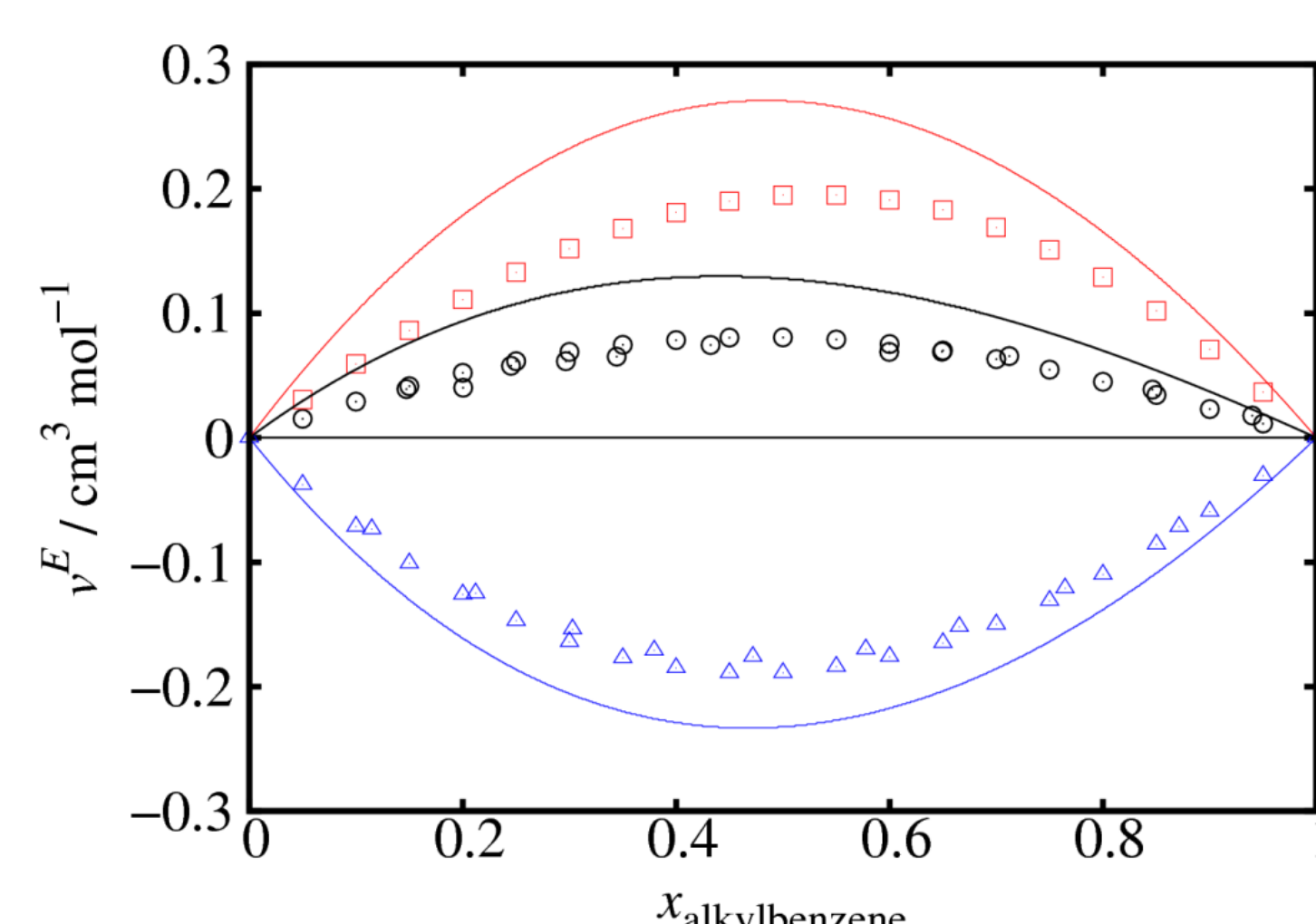


Figure [predicted]: Excess volume of propylbenzene + octane (circles), propylbenzene + nonane (squares) and butylbenzene + heptane (triangles) (T = 298.15 K, P = 101 kPa).

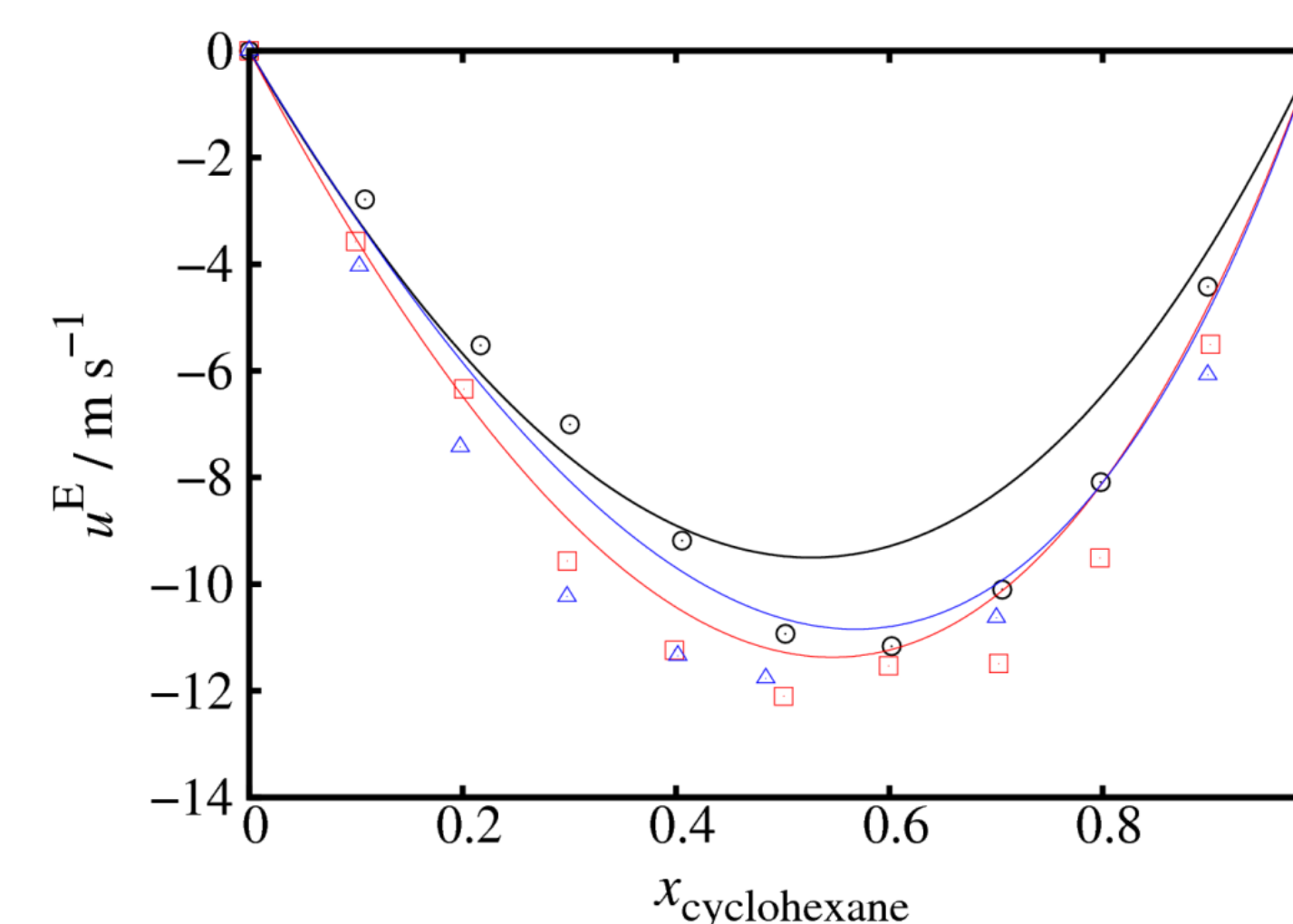


Figure [predicted]: Excess speed of sound of cyclohexane + hexane (circles), cyclohexane + heptane (squares) and cyclohexane + octane (triangles) (T = 303.15 K, P = 101 kPa).

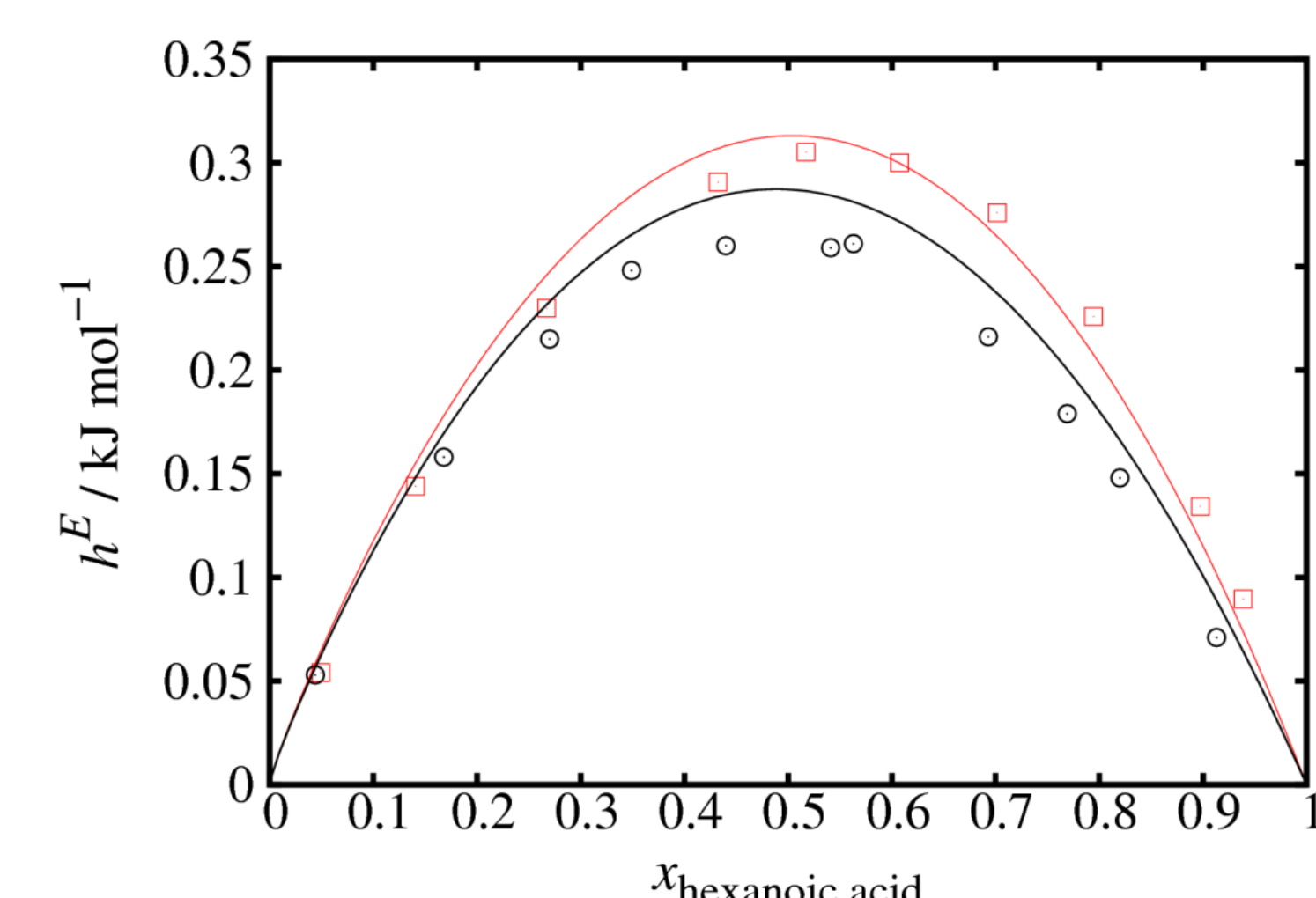


Figure [fitted]: Excess enthalpy of hexane + hexanoic acid (circles) and heptane + hexanoic acid (squares) (T = 298.15 K, P = 101 kPa).

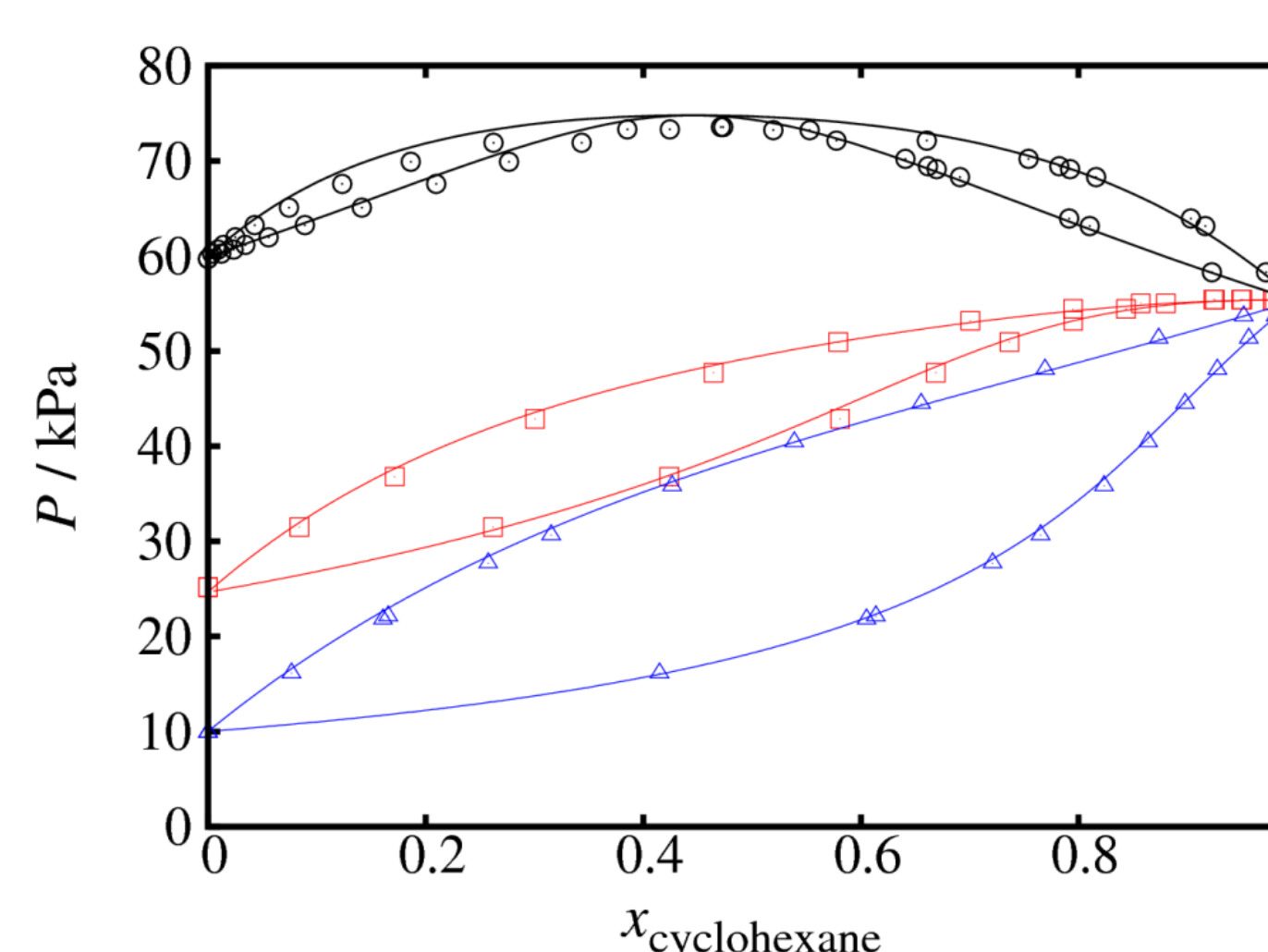


Figure [predicted]: Isothermal (P-x) phase diagram of cyclohexane + ethyl acetate (circles), cyclohexane + propyl acetate (squares) and cyclohexane + butyl acetate (triangles) (T = 335 K).

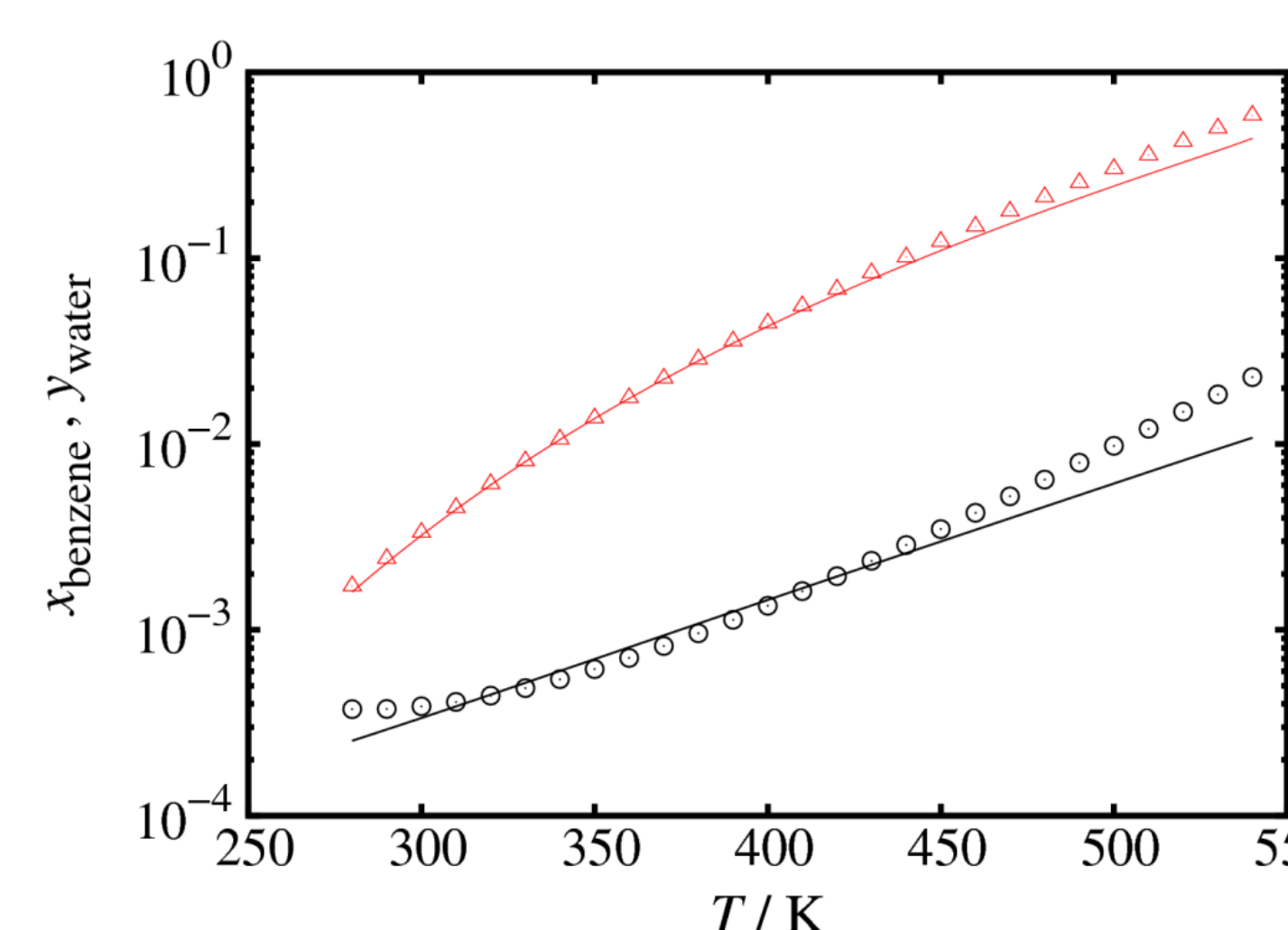


Figure [predicted]: Orthobaric (T-x) phase diagram of the liquid-liquid equilibrium of water + benzene: water-rich phase (circles) and benzene rich phase (triangles).

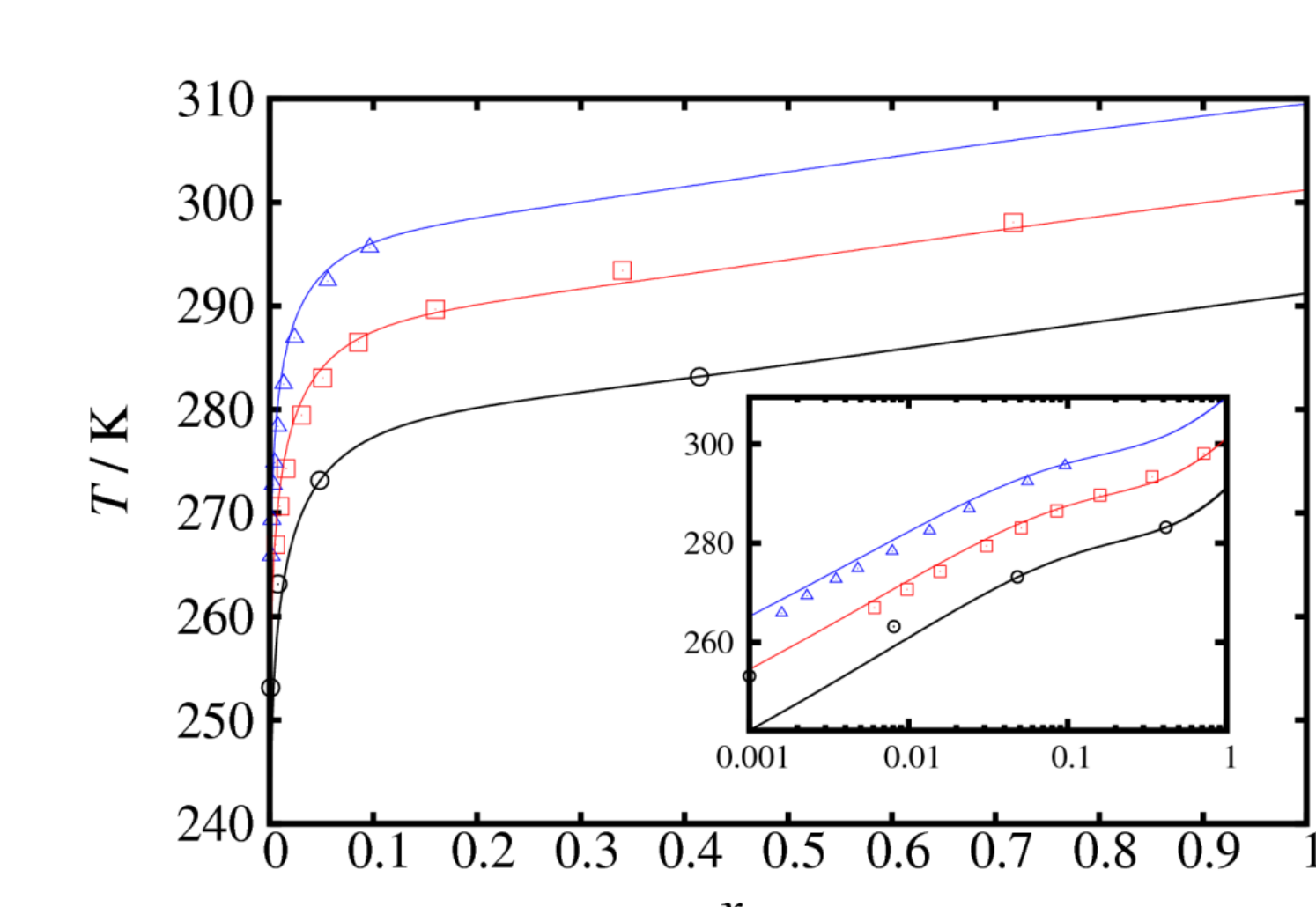


Figure [predicted]: Isobaric (T-x) phase diagram of the solid-liquid equilibria of butyl acetate + hexadecane (circles), butyl acetate + octadecane (squares) and butyl acetate + eicosane (triangles) (P = 101 kPa).

Conclusions

- The SAFT- γ Mie EoS is shown to accurately describe the phase behaviour and thermodynamic properties for a wide variety of systems.
- The method is used to the **predict** the solubility of active pharmaceutical ingredients:
 - no solid-liquid equilibrium data are included in the development of the group parameters;
 - based on transferable parameters obtained from experimental data of simpler molecules and mixtures;
 - good agreement with experimental solubility data.

References

- [1] V. Papaioannou, T. Lafitte, C. Avendaño, C. S. Adjiman, G. Jackson, E. A. Müller, and A. Galindo, *J. Chem. Phys.*, **140**, 054107 (2014).
- [2] T. Lafitte, A. Apostolou, C. Avendaño, A. Galindo, C. S. Adjiman, E. A. Müller, and G. Jackson, *J. Chem. Phys.*, **139**, 154504 (2013).
- [3] S. Dufal, V. Papaioannou, M. Sadeqzadeh, T. Pogiatis, A. Chremos, C. S. Adjiman, G. Jackson and A. Galindo, *J. Chem. Eng. Data*, submitted. (2014).

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