A Modified NRTL Equation For The Solubility Of Sterols In Supercritical Carbon Dioxide.

I. Kikic[1], N. De Zordi[1], A.Vetere[2], A. Cortesi[1], M. Moneghini[3], D. Solinas[1]

[1] Dept. Engineering and Architecture, University of Trieste, V. A. Valerio 6/a,c 34127 Trieste (Italy)
[2] Viale Gran Sasso 20, 20131, Milano (Italy)
[3] Dept. Chemical and Pharmaceutical Sciences, University of Trieste, V. L. Giorgieri 1, 34127 Trieste (Italy)

ABSTRACT

The evaluation of the solubility of solid solutes in supercritical carbon dioxide is of paramount interest for the optimization of different supercritical based technologies. Most of the proposed approaches, at the end, give a method for the correlation only of the solubility and not a tool for the prediction. In this study, a modified NRTL equation, that includes the ratio of molar volumes of the two components, is used for the evaluation of the activity in the supercritical phase. Furthermore, the model is applied in the one parameter form according to the method already proposed by Tassios. The remaining cross interaction parameter is correlated to the difference of well know properties of pure compounds.
The method is applied with satisfactory results to the description of the solubility of sterols in supercritical carbon dioxide in a wide range of temperature and pressure.

Keywords: solubility, supercritical fluids, sterols

INTRODUCTION

For the optimization of the different processes based on the supercritical fluid technology the knowledge of the solubility of the compounds involved is essential. Experimental methods are developed, to cover different ranges of pressures and temperatures. A series of excellent reviews [1-5] with the description of the experimental techniques used and the list of the systems studied were published in the last twenty years. For supercritical carbon dioxide solubility data are reported in [6].
The problem of the
Different classes of models were proposed:

- Empirical density dependence models (mainly derived from the modification of Chrastil equation;
- Equation of state models;
- Activity coefficient models.

Literature reports many correlations or predictions of solid solutes solubility in SCO2 using equations of state [7 - 9], or semi empirical equations [10 - 15].
Most of these approaches, at the end, gives a method for the correlation only of the solubilities and not a tool for the prediction. Few tentative were done to their modification in predictive models. For example the equation of state and activity coefficient models, referring

to the group contribution concept (mainly the UNIFAC method), can be used for the prediction. The main difficulty found is the characterization of drug solutes with complicated structure through the defined groups.
Recently quantum mechanics approaches were suggested for the prediction of the solubility of drugs in supercritical carbon dioxide using bot equation of state or activity coefficient models. The main limitation of these methods is represented by the relatively complexity of the calculation. A simplified version of these approaches, based on the solvation theory using a series of descriptors was also recently presented [16]
The semi empirical models require the enthalpy and temperature of fusion for the solid and the activity coefficient of the solute in solution. Enthalpies of fusion data are abundant in the literature [17], or they can be quickly measured with a differential scanning calorimeter (DSC). Since the solubility of solids in liquids is usually insensitive to the quality of the solution model, an ideal solution model often performs adequately. For solids of low solubility solute–solvent interactions are significant, and an appropriate activity coefficient model must be chosen.
In this study a modified NRTL equation [18], that includes the ratio of molar volumes of the two components, is used for the evaluation of the activity in the supercritical phase. Furthermore the model is applied in the one parameter form according to the method already proposed by Tassios [19]. The remaining cross interaction parameter is correlated to the difference of well know properties of pure compounds.

METHOD

The formalism considers the supercritical fluid rich phase as a subcooled liquid. The condition for equilibrium is that the fugacity of each component f_i must be equal in both phases. The subscript numbers 1 and 2 will be referred to CO_2 and pharmaceutical compound, while the superscripts S and L stand for solid and liquid, respectively. The solubility Y_2 in terms of standard state fugacities f_2^0 is:

$$Y_2 = \frac{1}{\gamma_2}\frac{f_2^{0S}\left(P^0,T\right)}{f_2^{0L}\left(P^0,T\right)} \tag{1}$$

where γ_2 is the activity coefficient of the solute (the drug) in solution.
The ratio of the standard state fugacities depends on the properties of the solute and can be calculated, neglecting the terms containing the differences between solid and liquid state heat capacities and molar volumes, following Prausnitz [20]:

$$\frac{f_2^{0S}\left(P^0,T\right)}{f_2^{0L}\left(P^0,T\right)} = \mathrm{EXP}\left[\frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f}-\frac{1}{T}\right)\right] \tag{2}$$

where ΔH_2^f is the solute enthalpy of fusion.
Combining the equation (1) with equation (2) and assuming that the activity coefficient is independent from concentration and equal to the value at infinite dilution:

$$\ln Y_2 = \frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f}-\frac{1}{T}\right) - \ln\gamma_2^{\infty} \tag{3}$$

The activity coefficient is expressed with the modified NRTL equation proposed by Vetere [18]:

$$\ln\gamma_2 = x_1^2\left[\tau_{12}\left(\frac{G_{12}\,V_1/V_2}{x_2 + x_1 G_{21}\,V_1/V_2}\right)^2 + \frac{G_{21}\tau_{21}\,V_2/V_1}{\left(x_1 + x_2 G_{21}\,V_2/V_1\right)^2}\right] \quad (4)$$

Where V_1 and V_2 are the molar volume of the two components and

$$G_{ij} = \exp\left(-\alpha_{ij}\tau_{ij}\right) \qquad \text{and} \quad \tau_{ij} = \frac{g_{ij} - g_{jj}}{RT}$$

α_{ij} is the non-randomness parameter usually set to values between 0.2 and 0.3; g_{ij} is the energy of interaction between molecules of the two components i and j and g_{ii} is the interaction between molecules of the same component.
At infinite dilution the expression of the activity coefficient is given by:

$$\ln\gamma_2^{\infty} = \tau_{12} + \tau_{21}G_{21}\,V_2/V_1 \quad (5)$$

In this paper α_{ij} is assumed equal to 0.2; g_{ii} is calculated with the method suggested by Tassios [19]:

$$g_{ii} = -\left(\Delta H_v - RT\right) \quad (6)$$

Where ΔH_v is the energy of vaporization of the component i.
The interaction between molecules of the two components is calculated from:

$$g_{12} = g_{21} = K_{12}\left(g_{11}g_{22}\right)^{0.5} \quad (7)$$

The empirical constant K12 which characterizes the binary system considered can be generalized for a family of mixtures as a linear function of the difference between the Hildebrand solubility parameters, namely:

$$K_{12} = a + b\left(\delta_1 - \delta_2\right) \quad (8)$$

Substituting the previous expression in the equation (3):

$$\ln Y_2 = \frac{\Delta H_2^f}{R}\left(\frac{1}{T_2^f} - \frac{1}{T}\right) - \tau_{12} + \tau_{21}G_{21}\,V_2/V_1 \quad (9)$$

The effect of pressure on the activity coefficient is expressed following the suggestions reported by Eckert et al. [21] adding in the equation (9) a term containing a constant A and the carbon dioxide reduced density. The constant A is calculated by:

$$A = c + d\frac{T_f}{T} + e\frac{\delta_{CO_2}}{\delta_{drug}} \quad (10)$$

RESULTS

The method was applied to the correlation of solubility data of six sterols. The experimental data are taken from [6] and cover a range of temperatures between 308 and 348 K and pressures between 90 and 355 bar. Melting point and heats of fusion are from [17].
The solubility parameter of the sterols are calculated following the classical definition of the solubility parameter:

$$\delta = \left(\frac{\Delta U}{V}\right)^{0.5} = \left(\frac{\Delta H_v - RT}{V}\right)^{0.5} \quad (11)$$

And it is considered independent from the pressure.
The solubility parameter of carbon dioxide that depends strongly from pressure and temperature was evaluated following the suggestion reported in [22]:

$$\delta^2 \approx \left(\frac{\partial E}{\partial V}\right)_T = T\left(\frac{\partial P}{\partial T}\right)_V - P \quad (12)$$

and using the Bender equation of state [23] for the calculation of the derivative of the pressure.
In Figure 1 the solubility parameter of carbon dioxide is reported as function of pressure for

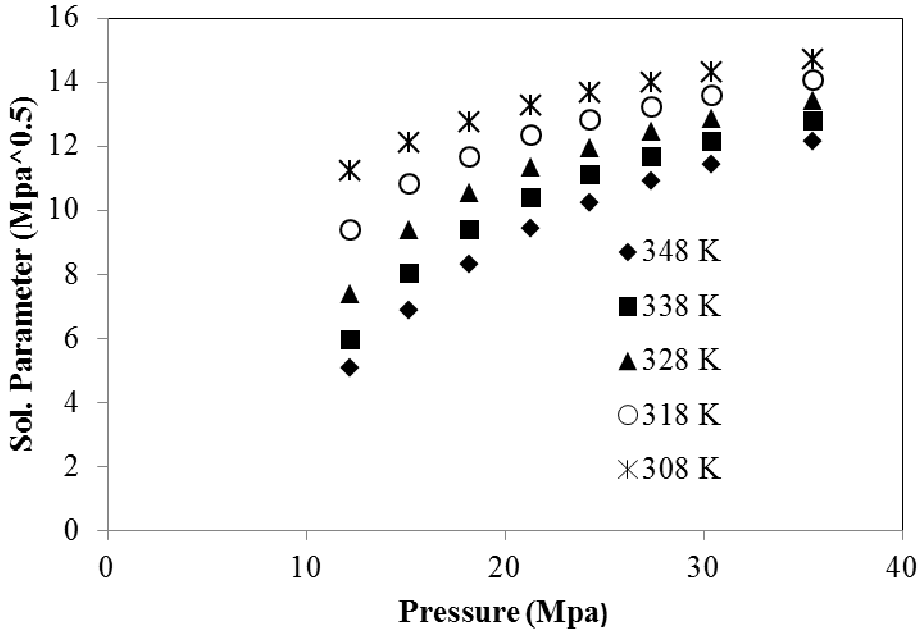

Figure 1: Solubility parameter of carbon dioxide.

the different temperatures. At constant pressure the solubility parameter decreases increasing temperature but these variations are lower at higher pressures.
In Figure 2 is reported the logarithm of the calculated as a function of the logarithm of the experimental solubilities showing an AAD ln Y_2 % of 7.957
.

$$AAD = \frac{100}{n}\left|\frac{\ln Y_2^{calc} - \ln Y_2^{exp}}{\ln Y_2^{exp}}\right| \quad (13)$$

The maximum deviations are presented for the data of progesterone and stigmasterol which present deviations that reach 25 %.

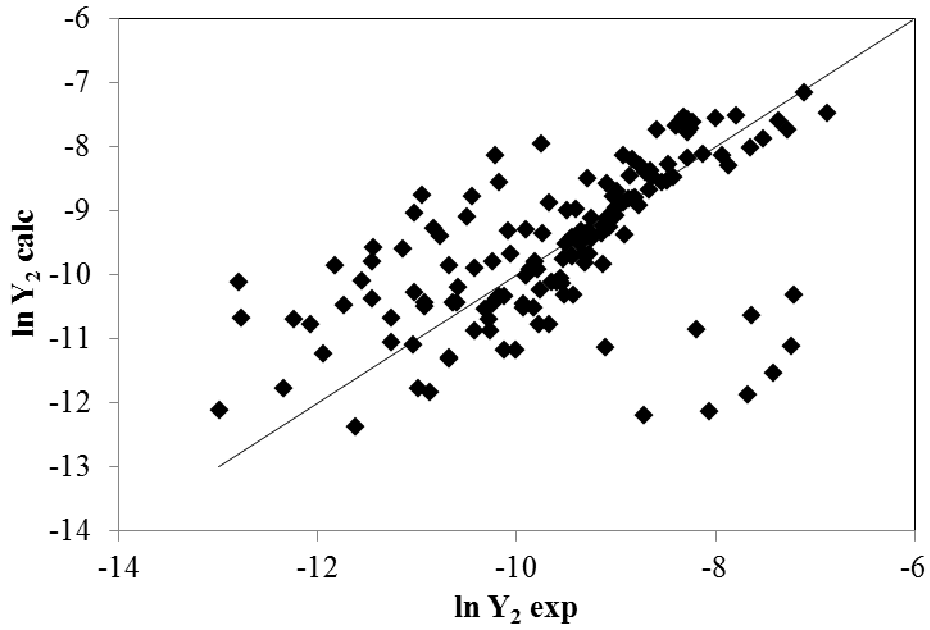

Figure 2: Comparison between experimental and calculated solubilities.

In figure 3 the results obtained with cyproterone acetate at 318 K are reported.

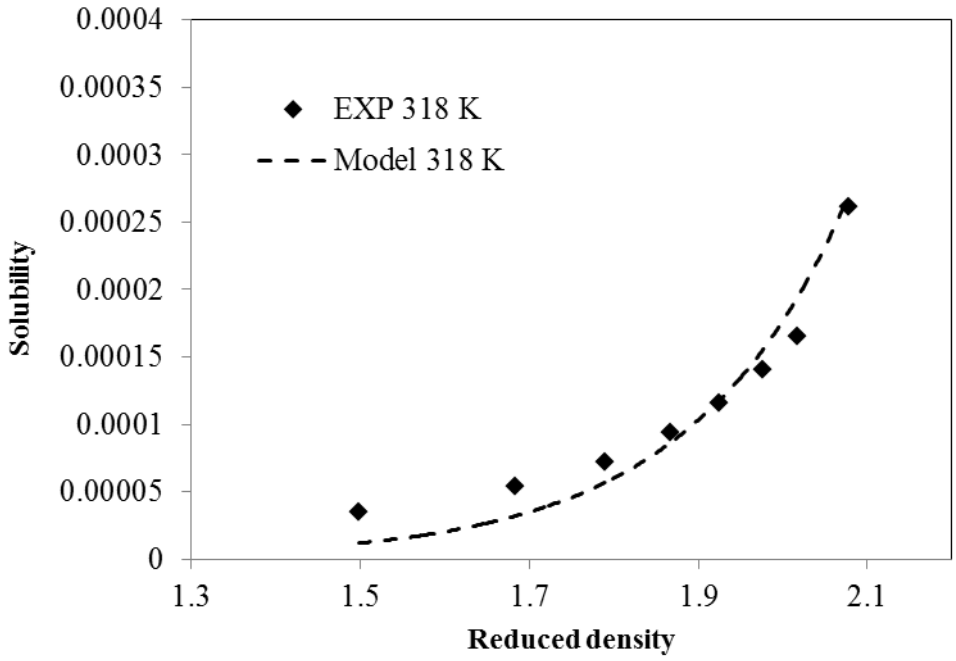

Figure 3 Calculated (model) and experimental solubilities for cyproterone acetate

It is interesting to observe that the agreement is better at the higher density (corresponding to 35.5 MPa) that to the lower (corresponding to 12 MPa). The AAD ln Y_2 % for these data at 318 K is 4.585

In the Figure 4 and 5 a comparison between experimental and calculated data are presented for Cholesterol and cholesteryl acetate at two different temperatures.

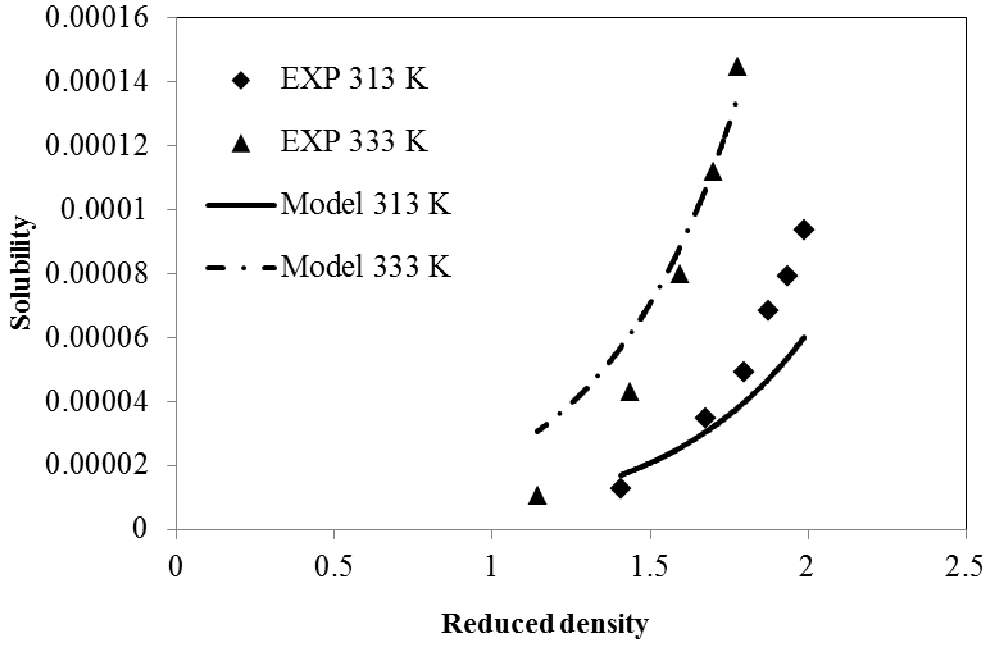

Figure 4 Calculated (model) and experimental solubilities for cholesterol

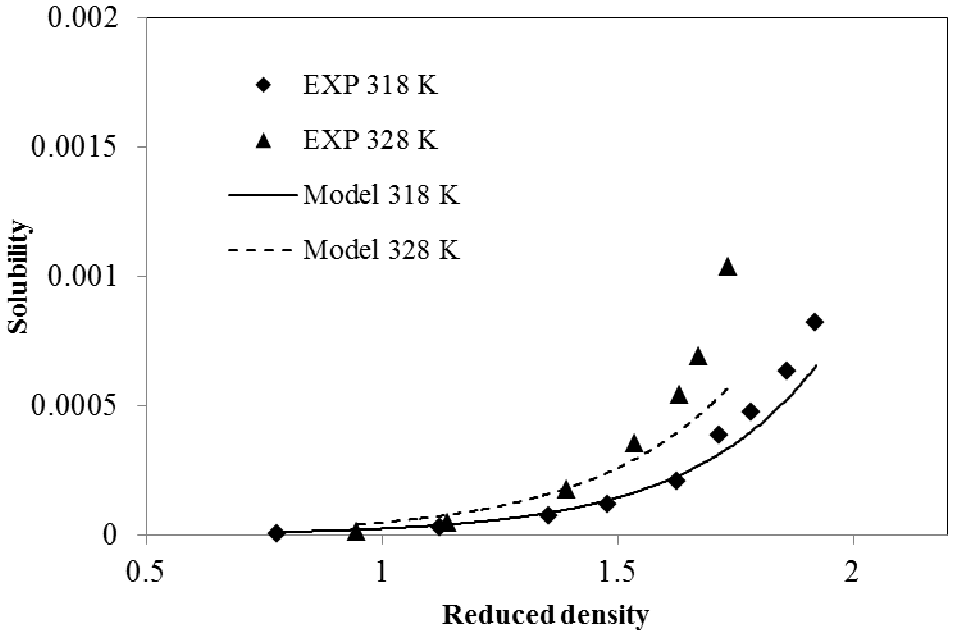

Figure 5 Calculated (model) and experimental solubilities for cholesteryl acetate

In the case of cholesterol the data at 333 K are modelled satisfactory with larger deviations at the lower densities whereas the contrary happens for the data at 313 K where the deviations are quite important for reduced density higher than 1.8.

The experimental data of cholesteryl acetate at 318 and 328 K are reproduced with very low deviations for the lower reduced densities. Increasing the density the deviations increase specially for the case of the higher temperature.

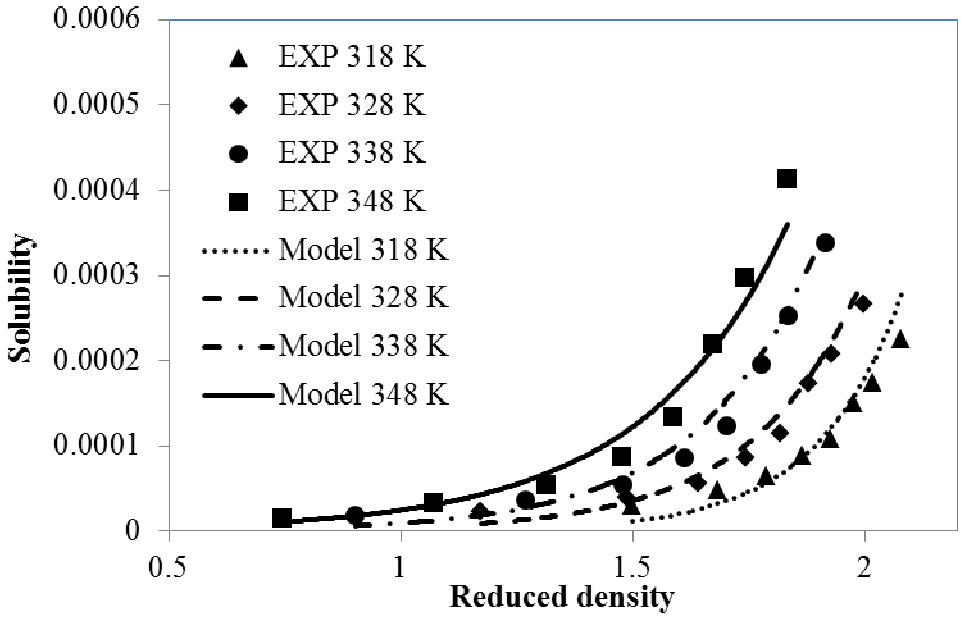

Figure 6 Calculated (model) and experimental solubilities for medroxyprogesterone acetate

In the case of Figure 6 the results obtained for medroxyprogesterone acetate at different temperatures are reported. In this case the agreement is very good at all the temperatures considered in all the range of density.
The AAD ln Y_2 % for these data is 3.314.

CONCLUSION

A modified NRTL equation has been used to describe the dependence of the solubility of sterols in supercritical carbon dioxide on the density of the fluid phase, considering 6 substances in the temperature range from 308 to 348 K and pressures ranging from 9 to 35 MPa. The method can be extended to estimate, on the basis of common pure component properties the solubility of active compounds of pharmaceutical interest.

REFERENCES

[1] FORNARI, R. E., ALESSI, P., KIKIC, I., Fluid Phase Equilibria, Vol. 57, **1990**, p. 1
[2] DOHRN, R., BRUNNER, G., Fluid Phase Equilibria, Vol. 106, **1995**, p. 213
[3] CHRISTOW, M., DOHRN, R., Fluid Phase Equilibria, Vol. 202, **2002**, p. 153
[4] DOHRN, R., PEPER, S., FONSECA, J. M.S., Fluid Phase Equilibria, Vol. 288, **2010**, p. 1
[5] FONSECA, J. M. S., DOHRN, R., PEPER, S., Fluid Phase Equilibria, Vol. 300, **2011**, p. 1
[6] GUPTA, R. B., SHIM, J.-J., Solubility in Carbon Dioxide, CRC Press, Boca Raton , Fl., **2007**

[7] COIMBRA, P., DUARTE, C. M. M., DE SOUSA, H. C., Fluid Phase Equilibria, Vol. 239, **2006**, p. 188
[8] SHAMSIPUR, M., FASIHI, J., KHANCHI, A., YAMINI, Y., J. Supercritical Fluids, Vol. 47, **2008**, p. 154
[9] BOZORGMEHR, M. R., HOUSAINDOKHT M. R., Chemical Engineering & Technology, Vol. 29, **2006**, p. 1481
[10] BUSHH, D., ECKERT, C. A., Fluid Phase Equilibria, Vol. 15-151, **1998**, p. 479
[11] SHIMOYAMAA, Y., IWAI, Y., J. Supercritical Fluids. Vol. 50, **2009**, p. 210
[12] ZHAO,Y, LIU, W., WU, Z., Industrial & Engineering Chemistry Research, Vol. 49, **2010**, p. 5952
[13] HOJIATI, M., YAMINI, Y., KHAJEH, M., VETANARA, A., J. Supercritical Fluids, Vol. 41, **2001**, p. 187
[14] SPARKS, D. I., HERNANDEZ, R., ESTEVEZ, L. A., Chemical Engineering Science, Vol. 63, **2008**, p. 4292
[15] SAUCEAU, M., LETOURNEAU, J. J., RICHON, D., FAGES, J., Fluid Phase Equilibria, Vol. 208, **2003**, p. 99
[16] DE ZORDI, N., KIKIC, I., MONEGHINI, M., SOLINAS, D., J. Supercritical Fluids, Vol. 66, **2012**, p. 16
[17] SU, C. A., CHEN, Y.-P., Fluid Phase Equilibria, Vol. 254, **2007**, p. 167
[18] VETERE, A., Fluid Phase Equilibria, Vol. 218, **2004**, p. 33
[19] TASSIOS, D., American Institute of Chemical Engineering J., Vol. 17, **1971**, p. 1367
[20] PRAUSNITZ, J. M., LICHTENTHALER, R. N., DE AZEVEDO, E. G., "Molecular ther modynamics of Fluid Phase Equilirbia", third ed., Prentice-Hall, Englewood Cliffs, NJ, **1999**
[21] ECKERT, C. A., ZIGER, D. H., JOHNSTON, K. P., KIM, S., J. Physical Chemistry, Vol. 90, **1986**, p. 2738
[22] WILLIAMS, L. L., RUBIN, J. B., EDWARDS, H. W., Industrial & Engineering Chemistry Research, Vol. 43, 2004, p. 4967
[23] BENDER, E., Proceedings of the 5th Symposium on Thermophysical Properties, American Society of Mechanical Engineers, New York, 1970