Solubility of D-Glucose in Water and Ethanol/Water Mixtures

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The solubility of D-glucose in water as a function of temperature in a mixture of ethanol/water containing (50, 60, 70, and 80) % ethanol was evaluated on the basis of the refraction index at 60 °C. The results obtained have shown that the solubility in water presents a linear increase with an increase in temperature, whereas for the solutions containing ethanol/water mixtures, this increase is represented by a second-order polynomial. Because glucose shows considerably high solubility, these data can be used to study the glucose crystallization process in mixtures containing antisolvents.

Introduction

Crystallization is one of the oldest purification techniques known, used in many cases when it is desired to obtain a solid product from a solution. Crystallization from solutions is an important process of separation and purification, regarding a large number of different industries.[1] The cost of the separation process is about (60 to 80) % of the total cost of the product manufacture. Besides, the products commercialized to be used by pharmaceutical and process industries are in the majority (around 70 %) of solids and require increases in structural perfection, homogeneity, and control of certain crystal quality.[2−5]

Crystallization is very efficient as a purification method due to the production of high purity and uniform crystals, which favors the subsequent steps of the process, such as filtration and drying. Thus, it results in a better appearance for the final product, an important factor related to the acceptance of the product by the consumer.[6]

The crystallization of sugars is a complex process, with difficult control, as both the shape and the size of the resulting crystals are generally unpredictable. When crystals of a particular size and shape are required, for example, for certain uses in the bakery industry, it is hard to produce, conveniently and consistently, the crystals with the required specifications.[7]

Glucose is the most available monosaccharide found in nature. It is widely used in the production of drugs and as the base product for the synthesis of other important substances such as ascorbic acid and sorbitol. Its purity is extremely important for these uses, and so it is generally produced through the hydrolysis of sucrose. In this case, it comes along with fructose, and this may complicate the crystallization process in its separation. It is known that glucose crystallization occurs very slowly, and this growth is even smaller when other sugars are present. In comparison to sucrose, there are only a few studies about the crystallization of monohydrate glucose, and almost nothing is known about the crystallization of anhydrous glucose.[8]

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Once the glucose is commercially crystallized from aqueous solution, many of its uses involve water systems, and thus the solubility of this hexose is an important property. The phase diagram of the system containing glucose/water shows the formation of binary compounds, and below the temperature of 100 °C, the stable crystal form is the α form, which crystallizes as a monohydrate below 50 °C. Above 100 °C, the β-anhydrous form is the most stable,[9] as the solubility of α-D-glucose is significantly affected by the presence of the β monomer in solution.[8]

The study of crystallization processes requires an assessment of the balance of a solid−liquid system. The study of phase balance holds generally to both the saturated and unsaturated status of the solution. However, it is another status of the solution, the supersaturation, that allows the crystallization.

Glucose, when in aqueous solutions at high temperatures, shows a high degree of dissolution, allowing excessive supersaturation because in the initial steps of crystallization very few crystals exist in suspension, on which the material may deposit to grow, implying an increase in supersaturation. As the water concentration increases, the glucose solubility increases rapidly, as this increase becomes slower in regions that are richer in water.[10] In these regions, the viscosity of the solutions increases, leading to the suspension of the solid α-D-glucose. Studies about the solubility of α-D-glucose, β-D-glucose, and α-D-glucose monohydrate, ranging from (−30 to +62) °C, did not reveal evidence of the existence of a eutectic point, corresponding to anhydrous α-D-glucose/ice. All the attempts to obtain this eutectic point resulted in the crystallization of the hydrated form.[11]

One of the ways of reducing supersaturation is to add seeds of solute at the beginning of the crystallization process, aiming the system stability, stimulating the nucleation, and promoting the crystallization. However, due to the high solubility of glucose, this method is not sufficient.

Another way of reducing the supersaturation consists of the introduction of an antisolvent into the system. This antisolvent may be ethanol because this hexose is partially soluble in this alcohol. The solubility of D-glucose in the solution decreases with an increase in ethanol concentration.[10] According to these authors, an extensive analysis of D-glucose solubility in mixtures

10.1021/je700177n CCC: $37.00
Published on Web 09/22/2007

Table 1. Density, Viscosity, and Refraction Index of the Solutions, with Different Concentrations of Glucose in Water, at 60 °C

glucose concentration	density[a]		viscosity[a]			
%	$g \cdot cm^{-3}$	standard deviation	cps	standard deviation	refraction index[a]	standard deviation
0	–		–	–	1.326	0.005
10	1.022	0.001	29.4	1.0	1.341	0.010
20	01.063	0.001	34.8	1.0	1.359	0.010
30	1.109	0.001	43.8	0.9	1.375	0.012
40	1.157	0.005	63.0	1.1	1.395	0.009
50	1.207	0.001	107.1	1.4	1.416	0.011
60	1.268	0.001	264.6	1.1	1.432	0.007
70	1.334	0.002	409.2	1.3	1.455	0.009
80	1.376	0.002	430.8	1.5	1.477	0.013
90	–		–	–	1.506	0.015

[a] Each point is the average of three experimental runs at the same mixture.

containing ethanol/water was not reported yet, even though the importance of knowing this system is fundamental in many applications, both industrial and laboratorial.

A growing interest in biological molecules has revealed the need of studying the thermodynamic properties of mixtures involving biomolecules, and even though sugars have great importance, relatively few thermodynamic data are available for multicomponent mixtures involving these compounds.[10] And so, a wider study of glucose solubility in ethanol/water mixtures, at different concentrations of this alcohol, was undertaken.

Materials and Methods

Determination of the Curve of the Solubility of Glucose in Water. The glucose used was SIGMA (99 % purity). The glucose was characterized by humidity and had its fusion point determined.

The study of glucose solubility in water as a function of temperature was undertaken in a bench crystallizer, with a volume of 100 mL, jacketed and equipped with a helix impeller, both made of borosilicate glass. The crystallizer had two top entrances, one for feeding and the other for collection of samples and temperature measurements. The system utilizes an agitator with variable agitation speed IKA RW 20.n (IKA Works do Brasil Ltda.) and a thermostatic bath, equipped with a refrigeration system, with an operating range of (−30 to +200) °C (JULABO HP, Germany), for temperature control.

Initially, solutions with a known concentration of glucose (from (10 to 90) % in mass) were prepared, and the refraction index (RI) of these solutions was determined at 589.3 nm, by a Refractometer RE 40 (METTLER TOLEDO), at a temperature of 60 °C. Subsequently, solutions with an excess of glucose were transferred to the crystallizer, and the solubility was determined after agitation of these solutions over 48 h at 450 rpm. The concentration of glucose at equilibrium in the solutions at the different conditions of temperature (from (0 to 60) °C) was controlled by the measurement of the refraction index (RI).

Both curves for glucose mass % as a function of the refraction index and glucose solubility as a function of temperature were adjusted by the least-squares method. The polynomium that showed the lower error percentage was considered as the best fit of the experimental data.

Determination of the Solubility Curve of Glucose in an Ethanol/Water Mixture. The study of glucose solubility in an ethanol/water mixture as a function of temperature was done using mixtures containing (50, 60, 70, and 80) % ethanol (99.7 %), using the same methodology previously described.

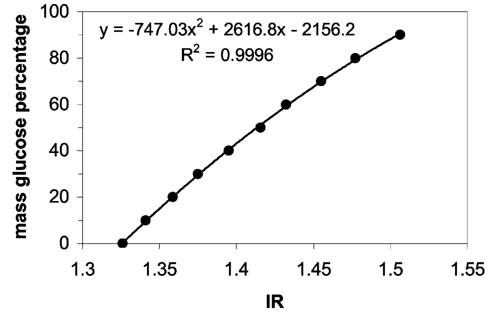

Figure 1. Schematic representation of the variation of glucose mass % in water as a function of refraction index (RI) at 60 °C. % mass = $-747.03 \cdot RI^2 + 2616.8 \cdot RI - 2156.2$.

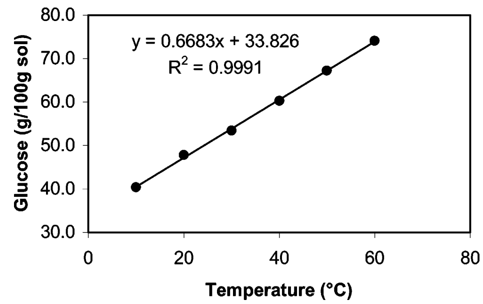

Figure 2. Glucose solubility in water (g of glucose/100 g of solution).

Characterization of Glucose. The glucose used in the crystallization experiments had its humidity determined in a titrator (Karl Fisher DL38, METTLER TOLEDO). Its fusion point was determined through differential and exploratory calorimetry in a DSC 822^e (METTLER TOLEDO), operating with STAR^e software, by sampling 2 g of material.

The water/glucose solutions with known concentration (from (10 to 90) % in mass) had their density and viscosity determined at 60 °C, using a densimeter DE40 (METTLER TOLEDO) and a viscosimeter DV-II (BROOKFIED), equipped with a cryostat bath with digital detection of temperature (LACTEA APARELHOS CIENTÍFICOS).

Results and Discussion

The glucose used in the crystallization experiments had a humidity of 0.231 % and a fusion point of 157.19 °C (a three-replicate average). Values for density and viscosity, as well as the values for refraction index (RI), of the glucose/water mixtures at the concentrations of (10 to 90) % are displayed in Table 1.

The evaluation of glucose mass percentage in the aqueous solutions as a function of RI is shown in Figure 1. It can be verified that the correlation between mass % of glucose in water and the RI at 60 °C is determined by a second-degree polynomial.

Table 2 contains the values of the refraction index and the corresponding solubility of the glucose in water solutions at the saturation temperatures studied. Figure 2 shows the glucose solubility in water as a function of temperature. It can be observed that the curve of the SIGMA analytical purity glucose solubility increases linearly with the temperature increase, with a correlation coefficient (R^2) equal to 0.9991. The increase of D-glucose solubility in a linear manner also was observed by Perez and Macedo.[12]

The determination of the glucose solubility in water was done with the objective to study the crystallization process of this hexose. However, the system glucose/water presents greater complexity than other systems containing water and sugar

Table 2. Refraction Index and Solubility of Glucose in Water (g of Glucose/100 g of Solution) as a Function of the Temperature

T (°C)	refraction index[a]	standard deviation	solubility[a]	standard deviation
10	1.395	0.001	40.4	0.7
20	1.409	0.001	47.8	0.6
30	1.420	0.001	53.4	0.7
40	1.434	0.002	60.3	0.8
50	1.449	0.002	67.2	0.8
60	1.465	0.003	74.1	0.2

[a] Each point is the average of three experimental runs at the same mixture.

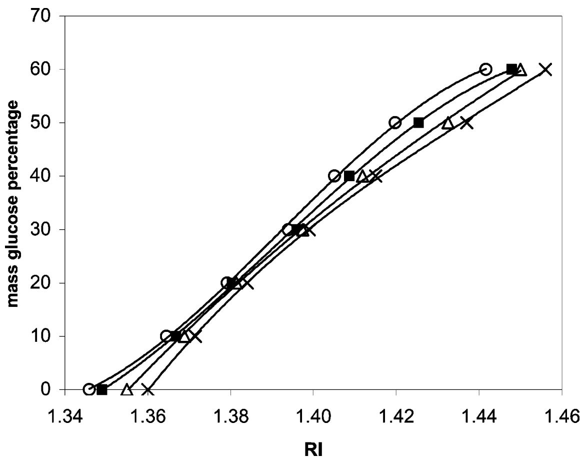

Figure 3. Representation of the variation of glucose mass percentage (glu %) in ethanol/water as a function of the refraction index (RI) at 60 °C: ◇, (50 to 50) %; ■, (60 to 40) %; △, (70 to 30) %; and ×, (80 to 20) %.

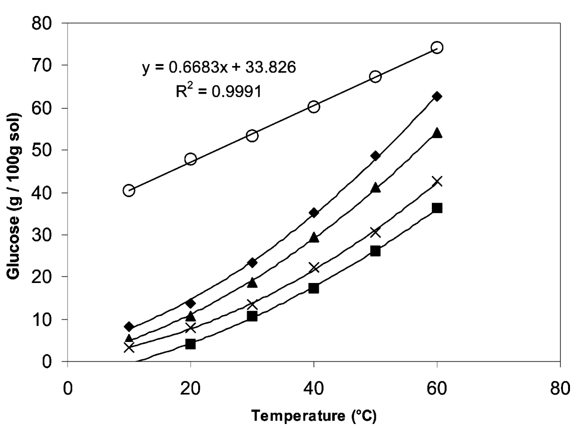

Figure 4. Glucose solubility in water (○) and ethanol/water (g of glucose/100 g of solution): ◆, (50 to 50) %; ▲, (60 to 40) %; ×, (70 to 30) %; ■, (80 to 20) %.

mixtures because the glucose is an organic substance that, when in aqueous solution, presents high viscosity and a high degree of dissolution at high temperatures. Such a fact also is observed for fructose. The crystallization in aqueous solution of this sugar is difficult because of its high solubility in water, which not only affects the yield but also produces a solution with very high viscosity. Because crystalline fructose can be obtained employing ethanol as antisolvent,[13] this methodology was employed.

In this way, curves of solubility for glucose have been obtained in ethanol−water mixtures containing (50, 60, 70, and 80) % of ethanol. Table 3 presents the values of the refraction index (RI) of the glucose−ethanol−water solutions in the concentrations of (10 to 60) % of glucose at the temperature of 60 °C.

The evaluation of the mass glucose percentage (glu %) in solutions of ethanol−water as a function of RI is shown in Figure 3. It is verified that the correlation of glucose % in ethanol−water and RI at 60 °C is determined by a third-degree polynomial, independent of the concentration of ethanol in the solution.

$$\text{glu }\%_{50\%\text{et}} = -64\,373\cdot\text{RI}^3 + 268\,811\cdot\text{RI}^2 - 373\,394\cdot\text{RI} + 172\,558 \quad R^2 = 0.9994$$

$$\text{glu }\%_{60\%\text{et}} = -44\,094\cdot\text{RI}^3 + 183\,981\cdot\text{RI}^2 - 255\,165\cdot\text{RI} + 117\,655 \quad R^2 = 0.9997$$

$$\text{glu }\%_{70\%\text{et}} = 5204\cdot\text{RI}^3 - 23\,576\cdot\text{RI}^2 + 36\,040\cdot\text{RI} - 18\,496 \quad R^2 = 0.9993$$

$$\text{glu }\%_{80\%\text{et}} = 23\,524\cdot\text{RI}^3 - 101\,822\cdot\text{RI}^2 + 147\,394\cdot\text{RI} - 71\,300 \quad R^2 = 0.9997$$

In Table 4, the values of the refraction index (RI) and the corresponding glucose solubilities are presented in ethanol/water solutions at the studied temperatures of saturation.

Figure 4 shows glucose solubility in water in comparison with the solubility in solutions of ethanol/water [(50, 60, 70, and 80) %] as a function of temperature. It is observed that although the solubility of the glucose in water increases in a linear way with an increase in temperature, as already demonstrated, the solubility of the glucose in ethanol/water solution is better represented by a polynomial of second degree, independent of the ethanol concentration in the solution. For all the evaluated ethanol concentrations, the glucose solubility considerably increases as the temperature increases. On the other hand, with an increase of the concentration of ethanol from (50 to 80) %, the solubility of this hexose is reduced by about 50 %. Such a fact was also observed by Bockstans et al.[10] According to these authors, the D-glucose solubility in ethanol/water solutions follows a logical progression with high solubility in water-rich regions and very low solubility in ethanol-rich regions. The equations that represent the solubility of the glucose in ethanol/water as a function of temperature are presented with their respective coefficients of correlation (R^2) as follows

$$\%\text{ Glucose}_{50\%\text{et}} = 0.0103\cdot T^2 + 0.3858\cdot T + 2.7845 \quad R^2 = 0.9991$$

$$\%\text{ Glucose}_{60\%\text{et}} = 0.0092\cdot T^2 + 0.3435\cdot T + 0.6987 \quad R^2 = 0.9994$$

$$\%\text{ Glucose}_{70\%\text{et}} = 0.0086\cdot T^2 + 0.1792\cdot T + 0.6987 \quad R^2 = 0.9993$$

$$\%\text{ Glucose}_{80\%\text{et}} = 0.0064\cdot T^2 + 0.2856\cdot T - 3.9723 \quad R^2 = 0.9997$$

There are few works dealing with the growth or dissolution rate of α-D-glucose crystals, and in general, they describe the growth or dissolution of α-D-glucose monohydrated in agitated suspensions, there being scarce data relating solutions of glucose in a mixture of solvents. According to Sadovyi, cited in Kraus and Nyvlt,[14] the growth rate of monohydrated D-glucose crystals is directly proportional to the supersaturation and had significant solubility reduction in the presence of other sugars.

Table 3. Refraction Index of the Solutions in Different Concentrations of Glucose [Glu] in Ethanol/Water Solution, at 60 °C

	refraction index[a]							
[Glu] (%)	(50 to 50) %	SD[b]	(60 to 40) %	SD[b]	(70 to 30) %	SD[b]	(80 to 20) %	SD[b]
0	1.346	0.002	1.349	0.005	1.355	0.014	1.360	0.007
10	1.365	0.002	1.367	0.005	1.369	0.005	1.372	0.005
20	1.379	0.001	1.380	0.004	1.381	0.004	1.384	0.005
30	1.394	0.004	1.396	0.005	1.397	0.005	1.399	0.010
40	1.405	0.002	1.409	0.004	1.412	0.023	1.415	0.015
50	1.420	0.001	1.425	0.004	1.433	0.003	1.437	0.018
60	1.442	0.002	1.448	0.003	1.450	0.010	1.456	0.015

[a] Each point is the average of three experimental runs at the same mixture. [b] SD = Standard Deviation.

Table 4. Refraction Index (RI) and Glucose Solubilities S_{GLU} (g of Glucose/100 g of Solution) in Ethanol/Water Solutions, as a Function of Temperature[a]

	(50 to 50) %			(60 to 40) %			(70 to 30) %			(80 to 20) %		
T (°C)	RI	S_{GLU}	SD[b]	RI	S_{GLU}	SD[b]	RI	S_{GLU}	SD[b]	RI	S_{GLU}	SD[b]
10	1.361	8.2	0.7	1.360	5.2	0.3	1.361	3.3	0.3	–	–	–
20	1.370	13.7	0.5	1.369	10.8	0.4	1.367	7.8	0.2	1.365	4.2	0.3
30	1.383	23.4	0.4	1.380	18.6	0.5	1.374	13.6	0.4	1.373	10.7	0.4
40	1.398	35.1	0.5	1.395	29.5	0.6	1.387	22.2	0.4	1.381	17.4	0.4
50	1.417	48.5	0.5	1.412	41.3	0.4	1.400	30.6	0.9	1.394	26.2	0.4
60	1.450	62.6	0.2	1.435	54.0	0.6	1.420	42.6	0.51	1.410	36.2	0.4

[a] Each point is the average of three experimental runs at the same mixture. [b] SD = Standard Deviation of glucose solubility.

The α-D-glucose monohydrate crystallization is presented as slow and is dependent on different parameters. Among these parameters are the nucleation, the D-glucose molecular transport to the growing nucleus, adsorption, and orientation of the surface of the crystal besides the phenomenon of mutarotation.[15] According to these authors, the temperature, as much as the concentration, has an influence on the relative growth rate of crystals, due to limited saturation. As the concentration of α-D-glucose in solution is high, the interactions between individual molecules of the sugar become more significant, until crystallization occurs. Moreover, regarding α-D-glucose crystallization, the transformation also includes mutarotation. It is known that α-D-glucose crystallization monohydrate occurs very slowly, and this rate is more reduced in the presence of other sugars. However, little information exists about how this rate is influenced by mutarotation, a characteristic property of D-glucose.

Le Barc'h et al.[15] have evaluated the influence of temperature on the composition of D-glucose solutions in the range (30 to 45) °C, varying the saturation degree. According to these authors, the ratio of the α anomer in the mixture increases significantly the equilibrium with an increase in concentration and temperature. Arkipovitch and Peruschevskii, cited in Kraus and Nyvlt,[14] reported that, for low concentration solutions, the mutarotation phenomenon could not be a limiting kinetic factor for the growth of D-glucose crystals. However, because of the known equatorial conformation of the α-D-glucose and the strong structure of the water around the solute, it is possible to foresee that the step of dehydration, previous to the crystallization, would be very slow. The equatorial group hydroxyl of the β-D-glucose is more strongly hydrated than the axial group. Consequently, the β-D-glucose predominance in the solution can explain the growth rate of α-D-monohydrated glucose crystals.[15]

Conclusions

The solubility of glucose in water was compared with the solubility in ethanol/water solutions as a function of temperature. Although the solubility of glucose in water increases linearly with an increase in temperature, the solubility of this hexose in ethanol/water solution is better represented by a second-degree polynomial. The increase in temperature causes an increase of glucose solubility, independent of the ethanol concentration; however, this solubility is reduced as a function of the increase of the ethanol concentration.

The solubility of one or more sugars in water has been reported with frequency in the literature; however, little has been described on the solubility of sugars in a mixture of solvents. Therefore, more experiments aiming to verify the glucose solubility in the presence of antisolvent are necessary for a better understanding of the crystallization process of this hexose.

Literature Cited

(1) Sgualdino, G.; Vaccari, G.; Mantovani, G.; Aquilano, D. Implications of Crystal Growth Theories for Mass Crystallization: Application to Crystallization of Sucrose. *Prog. Cryst. Growth Ch.* **1996**, *32*, 225−245.

(2) Scheel, H. J. Historical Aspects of Cristal Growth Tecnology. *J. Cryst. Growth* **2000**, *211*, 1−12.

(3) Birmingham, S.; Bruinsma, D.; Kramer, H.; Van Rosmalen, G.; Witkamp, G.; Derenzo, S.; Giulietti, M.; Secker, M. M.; Re, M. I.; Cekinski, E. *Industrial Crystalization and Precipitation*; IPT-TU DELFT, 2001.

(4) Giulietti, M.; Seckler, M.; Derenzo, S.; Ré, M. I.; Cesinski, E. Industrial Crystallization and Precipitation from Solutions: State of the Technique. *Braz. J. Chem. Eng.* **2001**, *18* (4), 423−440.

(5) Van Rosmalen, G. M.; Bermingham, S.; Bruinsma, D.; Kramer, H.; Derenzo, S.; Seckler, M.; Rê, M. I.; Cekinski, E.; Giulietti, M. "Lectures on Industrial Crystallization and Precipitation", IPT-TU DELFT, 2003.

(6) Belter, P.; Cussler, E. L.; Hu, W. *Bioseparation Dowstream Process for Biotechnology*; John Wiley & Sons: New York, 1988.

(7) Beckett, S. T.; Miller, M. M.; Grimes, S.; Donaldson, J. Crystallization of Sugars, Patent US 6579375 B2, 17 june 2003.

(8) Kraus, J.; Nývlt, J. Crystallization of Anhydrous Glucose. I. Mutarotation Rate and Solid-Liquid Phase Equilibria. *Zuckerindustrie* **1994a**, *119* (1), 298−303.

(9) Glucose and Glucose-Containing Syrups. *Ullmanns Encyclopedia Of Industrial Chemistry*, 6th ed.; Electronic Release, 1998.

(10) Bockstanz, G. L.; Bufa, M.; Lira, C. T. Solubilities of α-Anhydrous Glucose in Etanol/Water Mixtures. *J. Chem. Eng. Data* **1989**, *34*, 426−429.

(11) Young, F. E. D-Glucose-Water Phase Diagram. *J. Phys. Chem.* **1957**, *61*, 616−619.

(12) Perez, A. M.; Macedo, E. A. Measurement and modeling of Solubilities of D-glucose in Water/Alcohol and Alcohol/Alcohol Systems. *Ind. Eng. Chem. Res.* **1997**, *36*, 2816−2820.
(13) Flood, A. E.; Puagsa, S. Refractive Index, Viscosity, and Solubility at 30 °C, and Density at 25 °C for the System Fructose + Glucose + Ethanol + Water. *J. Chem. Eng. Data* **2000**, *45*, 902−907.
(14) Kraus, J.; Nývlt, J. Crystallization of Anhydrous Glucose. III. Shape Factors and Growth Rates of Crystals. *Zuckerindustrie* **1994b**, *119* (4), 298−303.
(15) Le Barc'h, N.; Grossel, J. M.; Looten, P.; Mathlouthi, M. Kinetic Study of the Mutarotation of D-Glucose in Concentrated Aqueous Solution by Gas-Liquid Chromatography. *Food Chem.* **2001**, *74*, 119−124.

Received for review April 4, 2007. Accepted August 3, 2007.

JE700177N