Article

An Experimental Study on the Solubility of Betulin in the Complex Solvent Ethanol-DMSO

Gulbarshin K. Shambilova 1,2,*, Aigul S. Bukanova 1, Altynay S. Kalauova 1, Danagul Zh. Kalimanova 2, Amanegeli I. Abilkhairov 1, Igor S. Makarov 3,*, Markel I. Vinogradov 3, Georgy I. Makarov 3, Sergey A. Yakimov 4, Alexander V. Koksharov 4 and Egor M. Novikov 5

1 Institute of Petrochemical Engineering and Ecology named after N.K. Nadirov, Atyrau Oil and Gas University named after S. Utebayev, M. Baimukanov Street, 45A, Atyrau 060027, Kazakhstan; bukanova66@mail.ru (A.S.B.); skalauova@mail.ru (A.S.K.); a.abilkhayrov@mail.ru (A.I.A.)
2 Department of Chemistry and Chemical Technology, Kh. Dosmukhamedov Atyrau University, Studenchesky Ave., 1, Atyrau 060011, Kazakhstan; dana80_04@mail.ru
3 A.V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Leninsky Prospect, 29, 119991 Moscow, Russia; m.i.vinogradov1989@yandex.ru (M.I.V.); georgii.makarov@chemistry.msu.ru (G.I.M.)
4 Ilim Group, 42 Ul, Dybtsyna, 165651 Koryazhma, Russia; sergie.yakimov@krm.ilmgroup.ru (S.A.Y.); aleksandr.koksharov@krm.ilmgroup.ru (A.V.K.)
5 Department of Chemistry, New Mexico Highlands University, Las Vegas, NM 87701, USA; enovikov@live.nmhu.edu
* Correspondence: shambilova_gulba@mail.ru (G.K.S.); igormakarovtips@gmail.com (I.S.M.)

Abstract: Betulin is a promising natural organic substance due to its antibacterial, fungicidal, and antitumor properties, as are their derivatives. The particle size of betulin can reach several tens of micrometers, and its thickness is several microns. There are various ways of processing betulin, but the most promising are solution methods (applying thin layers, impregnation, etc.). Application or impregnation of various materials is carried out using betulin; however, currently known solvents do not allow obtaining solutions with the necessary content of it. Since a number of direct solvents are already known for betulin, which provides only low-concentration solutions, the use of complex systems based on two solvents can become the optimal solution to the problem. The literature data show that the use of mixtures of solvents allows for the preparation of homogeneous solutions, for example, for natural polymers like cellulose, etc. This approach to obtaining solutions has become the basis for the processing of betulin. The use of a mixed solvent based on ethanol and DMSO for the preparation of betulin solutions has been proposed for the first time. The solubility of betulin in a mixture system with a ratio of components of 50 wt.% to 50 wt.% was studied, and a solubility curve was plotted. It is shown that the use of a two-component solvent makes it possible to transfer up to 10% of betulin into solution, which is almost twice as much as compared to already known solvents. The rheological properties of the obtained solutions have been studied. The viscosity of betulin solutions in a complex solvent depends on its content and temperature, so for 7% solutions at 70 °C, it is approximately 0.008 Pa*s. Applying betulin to the surface of the cardboard increases its hydrophobic properties and repellency.

Keywords: betulin; DMSO; ethanol; complex solvent; solutions; temperature; solubility curve; morphology; rheology

1. Introduction

The search for new active substances in relation to bacteria, fungi, microbes, etc. is an urgent task of modern science. Among these substances, natural materials are of the greatest interest, for example, chitin, glucuronic acid, betulin, etc. Betulin (systematic name 3β, 28–dihydroxy–20 (29)–lupen or lup–20 (29)–en–3β, 28–diol) is one of the main components of extractive substances in birch bark and tar. After extraction, betulin is a fine
powder with a particle size of several microns. The crystalline organic substance of betulin is a pentacyclic triterpene alcohol of the lupan group [1]. The presence of an α-isopropyl (isopropylene) group in carbon atom C-19 A and a five-membered ring is a characteristic sign of belonging to this group [2,3]. The white color of the birch trunk is formed due to the accumulation of a light resinous mass of betulin in the cell cavities of the cork tissue of the tree [4]. According to the literature [5], the extractive compounds in industrial birch bark are betulin (78.1%), lupeol (7.9%), and betulin aldehyde (1.2%).

The high biological activity of betulin makes it in demand in a number of industries; for example, the paper [6] shows the possibility of using betulin solutions for cellulose impregnating in order to improve the resistance of the polymer to the strain Aspergillus brasiliensis. In the medical industry, betulin is considered one of the main components of a number of promising pharmaceuticals with antitumor and antiviral activity, anti-inflammatory, antioxidant, hepatoprotective, or cytotoxic properties [7]. It is known that betulin can be used as a composite additive to obtain filled spinning solutions, with the subsequent formation of composite fibers from them with antifungal properties [8]. The antibacterial properties of betulin are used in the production of shampoos, soaps, and other perfumery and cosmetic products [9]. The constantly renewable raw material base, as well as the relative availability and functional properties of betulin, ensure constant interest in this substance both in its native state and for obtaining various transformation products, for example, betulinic acid [10].

Currently, a limited number of solvents are used to extract betulin from birch bark [2–4]. In work [5], the extraction rate of betulin was studied by infusing birch bark with fine grinding (particle size no more than 1.5 mm) in the following solvents: dichloromethane, methanol, isopropanol, ethanol, 2-butanol, and LIAV 200 hydrocarbon solvent at extraction temperatures up to 150 °C. It is shown that the use of these solvents allows for the extraction of 75 to 95% of the betulin contained in birch bark. Table 1 provides a generalized list of the described direct solvents.

### Table 1. List of direct betulin solvents.

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>C, %</th>
<th>T, °C</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-butanol</td>
<td>1.63</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>2</td>
<td>1-hexanol</td>
<td>0.552</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>3</td>
<td>1-nonanol</td>
<td>1.573</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>4</td>
<td>1-octanol</td>
<td>1.16</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>5</td>
<td>1-pentanol</td>
<td>0.861</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>6</td>
<td>2-butanol</td>
<td>0.885</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>8</td>
<td>acetone</td>
<td>1.74</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>9</td>
<td>acetonitrile</td>
<td>3.69</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>10</td>
<td>water</td>
<td>0.081</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>11</td>
<td>hexadecane</td>
<td>0.0229</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>12</td>
<td>dimethyl sulfoxide (DMSO)</td>
<td>0.0045</td>
<td>-</td>
<td>[12]</td>
</tr>
<tr>
<td>14</td>
<td>dichloromethane</td>
<td>0.517</td>
<td>25</td>
<td>[9]</td>
</tr>
<tr>
<td>15</td>
<td>diethyl ether</td>
<td>4.22</td>
<td>35</td>
<td>[13]</td>
</tr>
</tbody>
</table>
Table 1. Cont.

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>C, %</th>
<th>T, °C</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>dodecane</td>
<td>0.0117</td>
<td>55</td>
<td>[11]</td>
</tr>
<tr>
<td>17</td>
<td>methanol</td>
<td>0.549</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>18</td>
<td>methyl acetate</td>
<td>0.549</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>19</td>
<td>methyl formate</td>
<td>0.233</td>
<td>25</td>
<td>[9]</td>
</tr>
<tr>
<td>20</td>
<td>propanol</td>
<td>1.18</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>21</td>
<td>chloroform</td>
<td>1.905</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>22</td>
<td>cyclohexane</td>
<td>0.086</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>23</td>
<td>ethanol</td>
<td>5.44</td>
<td>78</td>
<td>[13]</td>
</tr>
<tr>
<td>24</td>
<td>ethyl acetate</td>
<td>1.54</td>
<td>35</td>
<td>[9]</td>
</tr>
<tr>
<td>25</td>
<td>ethyl formate</td>
<td>0.236</td>
<td>35</td>
<td>[9]</td>
</tr>
</tbody>
</table>

The table data show that the most active solvent for betulin is ethanol. The maximum concentration of betulin in ethanol reaches 5.44 mass percent at a temperature close to 80 °C.

However, using a mixture of solvents allows for improved dissolution; an increase in concentration leads to a decrease in temperature. For a number of polymers, the use of a mixture of several solvents is known; for example, a mixture of NMMO and DMSO can be used for cellulose [14]. The most interesting solvents for medicine have been selected, namely ethyl alcohol and dimethylsulfoxide. The use of this mixture is also due to the fact that betulin and its derivatives have great prospects for use in the medical field [15].

Dimethyl sulfoxide is a commercially important and safe product commonly used in laboratories and industry. This effective liquid solvent formulation is most in demand for the production of fibers, active ingredients, paints, salts, etc., in cosmetology, the pharmaceutical industry, and other industries. An excellent aprotic solvent (DMSO) has been intensively studied for its pharmacological activity, as it has many effects. For example, it has been found to alleviate the symptoms of arthritis, secondary amyloidosis associated with rheumatoid arthritis, bursitis, and myositis [16]. Semipolar sulfur-oxygen bonds in DMSO have a full or partial positive charge on sulfur and a negative charge on the oxygen atom. Therefore, strongly polarized S-O bonds can interact with or bind to various reagents both through sulfur and oxygen atoms. DMSO is capable of accepting and forming hydrogen bonds with water (two H-bonds with water molecules), alcohols, phenols, proteins, carbohydrates, nucleic acids, and other H-donor compounds in living systems [17]. The molecular and crystal structures of DMSO were described in detail by Thomas [18]. Thus, along with ethyl alcohol, DMSO is a widely studied and used compound in medicine. Accordingly, the purpose of this work was to study the solubility of betulin in a mixture of ethanol and DMSO at different temperatures, the morphology of the solutions, and their rheological properties. We hypothesized that the resulting betulin solutions could be used to create functional layers in order to change the hydrophilic (hydrophobic) properties of surfaces.

2. Experimental

Chemically pure DMSO of the company “Ecos 1” (Ecos-1, Moscow, Russia) with a moisture content of no more than 0.1%, ethyl alcohol with a moisture content of about 5%, and betulin (C₃₀H₅₀O₂, CAS No. 479-98-3) of the company “Cortex” (Tyumen, Russia) with purity ~96% were used in order to obtain betulin solutions in the mixture. Anhydrous components are not used due to their inexpediency in production.

To obtain solutions of betulin in complex (multicomponent) solvents, a mixture of dimethyl sulfoxide and alcohol was first prepared in the required mass ratio. Betulin was added to the mixture in portions and heated, then stirred in a controlled manner until optical dissolution. A magnetic stirrer from IKA (IKA, Staufen, Germany) was used for
heating and mixing. To avoid solvent evaporation, the experiment was carried out in a hermetically sealed container.

To apply betulin to the surface of cellulose samples, they were immersed in a betulin solution in a complex solvent (50% ethanol and 50% DMSO). After a few seconds of exposure to the betulin solution, the sample was removed and dried at 50 °C to a constant weight.

The morphology of the solutions was studied using the method of polarization microscopy (microscopes “Boetius”, VEB Kombinat Nadema, Ruhla, former GDR, and Micromed MS-2-ZOOM Digital, St.-Petersburg, Russia).

The rheological behavior of mixed solutions was studied on a HAAKE MARS 60 rheometer (Thermo Fisher Scientific, Dreieich, Germany). As working units, cone-plane pairs with a diameter of 50 mm and an angle between the cone and the plate of 1 degree were used under conditions of continuous deformation at constant shear stress \( \tau \). To prevent the rapid evaporation of alcohol, an atmosphere with a high alcohol vapor content was created by pouring alcohol around the cone-and-plate geometry. The tests were carried out at a dissolution temperature and shear rates of \( 10^{-3} \)–\( 10^{3} \) s\(^{-1}\).

FTIR spectra of the betulin powder in the attenuated total reflectance mode were recorded in the HYPERION-2000 IR microscope coupled with the IFS-66 v/s Bruker IR-Fourier spectrometer (crystal—Ge, scan. 50, resolution 2 cm\(^{-1}\), range 4000-600 cm\(^{-1}\)).

To analyze the morphology of betulin particles, a JSM-6490 microscope (JEOL USA Inc., Peabody, MA, USA) was utilized in scanning mode with an accelerating voltage of 5÷20 kV and an electron beam current of ~1 nA.

To change the hydrophilicity of the paper surface, a betulin solution was applied to cardboard (white liner 100 ± 2 (1 m\(^2\), g)) and kraftliner (single-layer, 2 K-90) produced by Ilim (Ilim Group, Koryazhma, Russia).

3. Results and Discussions

The study of the morphology of betulin has just recently gained attention. According to [19], hydrogen bonding allows primary betulin crystals to produce supraparticles. The process is the sequential formation of betulin particles from its solution during precipitation, where the solvent and coagulation conditions of betulin play an important role [20]. Further, the precipitated betulin particles can form more complex structures. Figure 1 shows micrographs of the initial betulin.

![Figure 1. SEM micrographs of betulin particles (a,b).](image-url)
crystals form agglomerates, the size of which already exceeds hundreds of micrometers. As the size of agglomerates increases, their form factor decreases.

It is known that the chemical composition of betulin can be described using IR spectroscopy [21–24]. The IR spectrum of betulin is displayed in Figure 2.

![IR spectrum of betulin powder](image)

**Figure 2.** IR spectrum of betulin powder.

In the spectrum of betulin, one can distinguish a band at 1645 cm\(^{-1}\), corresponding to the stretching vibration of C=CH\(_2\) in the isopropenyl group. The 1450 cm\(^{-1}\) appears because of bending vibrations of the methyl and CH\(_2\) groups in the rings, while the 1370 cm\(^{-1}\) band can be assigned to bending vibrations of the CH\(_3\) groups. The intense band in the region of 2930–2932 cm\(^{-1}\) can be attributed to CH\(_3\), CH\(_2\), and CH symmetric and asymmetric stretching vibrations. The hydrogen-bonded hydroxyls are represented by a wide band in the spectral area of 3650 to 3200 cm\(^{-1}\), similar to cellulose.

Unfortunately, betulin is practically insoluble in water at room temperature, and alcohols, ethers, etc. are used to extract it and obtain solutions. To achieve the maximum solubility of betulin, the temperature of the system is increased. From the data in Table 1, it can be seen that when using DMSO, it is possible to obtain only low-concentration solutions with a betulin content of not more than 0.0045%. For systems based on ethanol, the content of betulin increases to 5.44%. Mixing these two polar solvents in various ratios from 0:100 to 50:50 (DMSO:ethanol, wt.%) made it possible to increase the concentration of betulin in the solution. So, a mixed solvent of 25 wt.% DMSO and 75 wt.% ethanol solutions with a betulin content of up to 7% were obtained. With an increase in the proportion of DMSO to 50 wt.%, the concentration of betulin in the solution increased to 10%.

Figure 3 shows photographs of the original betulin and its solutions in the mixed solvent of 50 wt.% DMSO/50 wt.% ethanol. Solutions with different concentrations have been obtained on a heated magnetic stirrer, and dissolution temperatures have been detected. The morphology of the solutions and betulin particles was studied by optical methods (Figure 3c–e).

As the concentration of betulin in the system increases, the color of the solution darkens from yellow to dark brown (Figure 3b). Upon cooling the solutions, crystals are formed. When the system is reheated, the crystals dissolve, forming a homogeneous solution. All solutions obtained are characterized by uniform homogeneity. In Figure 3c,d, betulin particles (initial average size up to 15 μm (Figure 3e)) are not observed. With an increase in the concentration of betulin in the system, the temperature of complete dissolution increases (Figure 4).
Figure 2. IR spectrum of betulin powder. In the spectrum of ... The morphology of the solutions and betulin particles was studied by optical methods (Figure 3c–e).

Figure 3. Betulin powder (a), solutions of betulin in the mixed solvent of 50 wt.% DMSO/50 wt.% ethanol (concentration of betulin 1–10%) (b), morphology of 7% (c) and 10% (d) solutions of betulin in the mixed solvent, and morphology of the betulin particles (e).

Figure 4. Solubility curve of betulin in the mixed solvent of 50 wt.% DMSO/50 wt.% ethanol.

The obtained solubility curve shows the room temperature is sufficient to obtain low-concentration solutions, but for systems containing 10% betulin, it is necessary to heat the system up to 85 °C. In other words, to obtain more concentrated solutions, the temperature of the system must be increased. In contrast to the previously given results of the solubility of betulin (Table 1), where it was shown that the use of DMSO and ethanol separately does not allow obtaining solutions with a concentration of more than 5.5% (T = 78 °C), when using a mixed system of 50 wt.% DMSO/50 wt.% ethanol, dissolution up to 10% betulin at T = 85 °C. It is worth paying attention to the fact that the solubility has doubled compared to pure ethanol at high temperatures. The solution preparation time increases with an increase in the concentration of betulin, and the temperature of the system changes slightly.
Since the increase in betulin in the system will affect the viscosity properties of the solutions, the rheological characteristics of the resulting solutions were studied. To evaluate the reproducibility of rheological tests for betulin solutions and to avoid the influence of solvent evaporation, particularly alcohol, time dependences of viscosity were obtained at 80 °C (Figure 5). To slow down the evaporation of ethanol, a solvent trap was used, in which an atmosphere saturated with a solvent (alcohol) was created.

![Figure 5](image_url)

**Figure 5.** Time dependence of viscosity for the 7% solution of betulin in the mixed solvent of 50 wt.% DMSO/50 wt.% ethanol at 80 °C and a shear rate of 10 s⁻¹.

All the obtained time dependencies reveal that the system viscosity remains stable for 20 min, implying that the solution composition varies slightly. This time, the interval is sufficient to obtain traditional flow curves for solutions with different contents of betulin (Figure 6).

![Figure 6](image_url)

**Figure 6.** The flow curves (viscosity versus shear rate) for solutions of betulin in the mixed solvent of 50 wt.% DMSO/50 wt.% ethanol (the concentration of betulin in the system and the temperature are indicated on the graph).

All the obtained flow curves have a similar character. The Newtonian behavior dominates at low and high shear rates, where the viscosity is independent of the shear rate. An increase in the content of betulin in the system leads to a proportional growth in viscosity values. It is important to notice that the viscosity of the initial complex solvent at ambient temperature differs slightly from that of betulin solutions at temperatures where it is completely dissolved. The contact angle for surface water wetting was determined...
using the drop’s profile. To compare, we utilized a glass plate and the same plate with a thin layer of betulin (Figure 7).

![Photographs of a drop of water on the surface of glass (a) and betulin (b).](image)

**Figure 7.** Photographs of a drop of water on the surface of glass (a) and betulin (b).

A comparison of images reveals that when a drop is placed on the glass surface, it spreads over the surface; the contact angle is significantly less than 90°, which means we can talk about wetting the glass surface with water. When a thin layer of betulin was placed on glass, the surface contact angle changed and the surface exhibited more hydrophobic properties. The contact angle increases significantly, although the drop preserves its appearance. The contact angles range from 85 to 95°. The shift in contact angle values may be associated with different morphologies formed on the glass surface by betulin. SEM revealed that betulin particles can collect into diverse morphologies when the solvent is removed.

When drops of linseed oil were applied to the surface of glass and betulin, the result is depicted in Figure 8.

![Photographs of a drop of linseed oil on the surface of glass (a) and betulin (b).](image)

**Figure 8.** Photographs of a drop of linseed oil on the surface of glass (a) and betulin (b).

A drop of oil behaves differently on glass than on a glass surface coated with betulin. A drop of oil placed on glass is spread after a few seconds, and the observed contact angle is similar to that of water. When a drop of linseed oil was put on the surface of betulin, it quickly spread and was absorbed into the volume of the functional layer.

The hydrophilicity (hydrophobicity) of paper can be changed by applying betulin to its surface (Figures 9 and 10).
Regardless of the chemical composition, betulin changes the color of white liner cardboard from white to light brown and kraftliner to cream. Based on this, we can conclude that the hydrophilic qualities of the surfaces, which is useful for creating biodegradable packaging. The modest variance in contact angle can be explained by the philicity of the surface will alter for cardboard and kraftliner.

Because of its properties, betulin is becoming increasingly popular. SEM revealed that betulin particles are needle-shaped crystals that can aggregate into particles of large effect size. This is the first study to suggest the use of a complex (multicomponent) betulin solvent based on ethanol and DMSO for extracting and producing highly concentrated solutions. The solubility of betulin increases when the amount of DMSO in the system does not exceed 5.5%, it is planned in the future to study the effect of DMSO concentration on betulin solubility.

The rheological behavior of the resulting systems. Applying a layer of betulin to various concentrated solutions. The solubility of betulin increases when the amount of DMSO in traditional solvents improves its solubility, but not in component organic solvents. Such solvents do not necessarily allow for large betulin yields during extraction or the formation of concentrated betulin solutions. Increasing the dissolving temperature of betulin in traditional solvents improves its solubility, but not in component organic solvents. These results are consistent with other studies that showed betulin to be highly soluble in organic solvents such as ethanol and DMSO. However, betulin is sparingly soluble in water, which limits its use in aqueous systems.

**Figure 9.** Photographs of cardboard (white liner) (a,c) and kraftliner (single-layer, 2 K-90) (b,d) before (a,b) and after (c,d) application of betulin.

**Figure 10.** Photographs of water droplets on the surface of cardboard (white liner) (a,c) and kraftliner (single-layer, 2 K-90) (b,d) before (a,b) and after (c,d) application of betulin.
Regardless of the chemical composition, betulin changes the color of white liner cardboard and light brown kraftliner to cream. Based on this, we can conclude that the hydrophilicity of the surface will alter for cardboard and kraftliner. The images show that drops of water applied to the surface of the original cardboard and kraftliner look comparable. The modest variance in contact angle can be explained by the samples’ differing chemical compositions and preparation histories. The observed contact angle values of untreated materials suggest that they are hydrophilic ones. However, when betulin is given to the samples, their hydrophilic properties transform into hydrophobic. The contact angle increases for cardboard and kraftliner. Thus, betulin, a natural hydrophobic birch coating, can be employed to minimize hydrophilicity on a variety of surfaces.

4. Conclusions

Because of its properties, betulin is becoming increasingly popular. SEM revealed that betulin particles are needle-shaped crystals that can aggregate into particles of large diameter. It is extracted from birch bark and then processed in solutions using typical one-component organic solvents. Such solvents do not necessarily allow for large betulin yields during extraction or the formation of concentrated betulin solutions. Increasing the dissolving temperature of betulin in traditional solvents improves its solubility, but not in sufficient amounts. This is the first study to suggest the use of a complex (multicomponent) betulin solvent based on ethanol and DMSO for extracting and producing highly concentrated solutions. The solubility of betulin increases when the amount of DMSO increases to 50 wt.%. It has been shown that using an equally concentrated mixture of ethanol and DMSO solvents allows for the transfer of up to 10% betulin into solution at temperatures as high as 85 °C. In contrast to the use of monosolvents, where the concentration of betulin in the system does not exceed 5.5%, it is planned in the future to study the effect of the mixed solvent’s component ratio on the extractability (solubility) of betulin as well as the rheological behavior of the resulting systems. Applying a layer of betulin to various surfaces, including cellulose (cardboard or paper), increases the hydrophobic and water-repellent qualities of the surfaces, which is useful for creating biodegradable packaging.

Author Contributions: Conceptualization: I.S.M.; methodology, S.A.Y.; software, E.M.N., S.A.Y. and A.V.K.; validation, A.I.A. and D.Z.K.; formal analysis, G.K.S.; investigation, G.I.M. and A.S.B.; data curation, M.I.V.; writing—original draft preparation, I.S.M.; writing—review and editing, I.S.M.; visualization, G.I.M. and A.S.B.; project administration, M.I.V.; funding acquisition, G.K.S. All authors have read and agreed to the published version of the manuscript.

Funding: This work was carried out within the State Program of TIPS RAS.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: NSF (grant No. DMR-2122108 (PREM)).

Conflicts of Interest: Authors Sergey A. Yakimov and Alexander V. Koksharov were employed by the company Ilim Group. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References


11. Moodley, K.; Rarey, J.; Ramjugernath, D. Experimental solubility for betulin and estrone in various solvents within the temperature range T=(293.2 to 328.2)K. *J. Chem. Thermodyn.* **2016**, *98*, 42–50. [CrossRef]


Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.