

Computational Study of Solvation Free Energy, Dipole Moment, Polarizability, Hyperpolarizability and Molecular Properties of Betulin, a Constituent of *Corypha taliera* (Roxb.)

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ABSTRACT: Ab initio calculations were carried out to study solvation free energy, dipole moment, molecular electrostatic potential (MESP), Mulliken charge distribution, polarizability, hyperpolarizability and different molecular properties like global reactivity descriptors (chemical hardness, softness, chemical potential, electronegativity, electrophilicity index) of betulin. B3LYP/6-31G(d,p) level of theory was used to optimize the structure both in gas phase and in solution. The solvation free energy, dipole moment and molecular properties were calculated by applying the Solvation Model on Density (SMD) in six solvent systems namely water, dimethyl sulfoxide (DMSO), acetonitrile, *n*-octanol, chloroform and carbontetrachloride. The solvation free energy of betulin increases with decreasing polarity of the solvent. No systematic trend of hyperpolarizability with solvent polarity is found. Molecular electrostatic potential (MESP) and Mulliken population analysis (MPA) reveal that the most possible sites for nucleophilic attack are C30, H76 and H77 and electrophilic attack are O1 and O2 among the atoms in betulin. However, the dipole moment, polarizability, chemical potential, electronegativity and electrophilicity index of betulin increase on going from non-polar to polar solvents. Chemical hardness was also increased with decreasing polarity of the solvent and opposite relation was found in the case of softness. These results provide better understanding of the stability and reactivity of betulin in different solvent systems.

Key words: Betulin, Solvation free energy, Dipole moment, Polarizability, Solvation model.

INTRODUCTION

Corypha taliera Roxb. (Bengali name-tali palm; Family: Palmae) is a giant monocarpic palm that grows very slowly upto 10 m in height and 70 cm in diameter near the base. It is thought to be distributed in Bangladesh, India and throughout the tropical Asia and takes nearly a century for the flowers to blossom, which will eventually lead to its gradual death. Some species of *Corypha* are traditionally used for bowel complaints, diarrhoea and cough.¹ Previous biological investigations have demonstrated antimicrobial, cytotoxic and antioxidant activities of a methanol

extract of the unripe fruits of this palm.² Phytochemical investigations of *C. taliera* revealed that the plant contains stigmasterol, β -sitosterol, β -amyrin, lupeol and betulinic acid (reduced form of betulin).³

Betulin [$\text{lup-20(29)-ene-3}\beta$, 28-diol] is an abundant, naturally occurring triterpene. It is converted to betulinic acid upon oxidation. Betulin inhibits the maturation of sterol regulatory element-binding protein (SREBPs) which in turn reduces the biosynthesis of cholesterol and fatty acid, improves hyperlipidemia and insulin resistance and reduces atherosclerotic plaques.⁴

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Few computational and theoretical studies of betulin have been reported. In 2012, Pospíšil and colleagues reported the theoretical study of interactions between betulin and variable amounts of water.⁵The variation in solvent polarity and the type of solute-solvent interaction(s) can affect the calculated geometry, dipole moment, polarizability, hyperpolarizability and other molecular properties^{6,7} due to variable interactions with the frontier molecular orbitals^{6,8} and hence, can influence the stability and reactivity of the molecule. Density Functional Theory (DFT) calculations provide a greater detail of molecular characteristics and

interactions which lead to a good understanding of molecular properties.⁹

In the present investigation, computational studies have been carried out to evaluate the solvation free energy, dipole moment, molecular electrostatic potential (MESP), charge distribution, polarizability, hyperpolarizability and global reactivity descriptor properties such as the chemical hardness, softness, chemical potential, electronegativity, electrophilicity index of betulin in different solvent system which would aid the development of pharmaceutical and biochemical products.

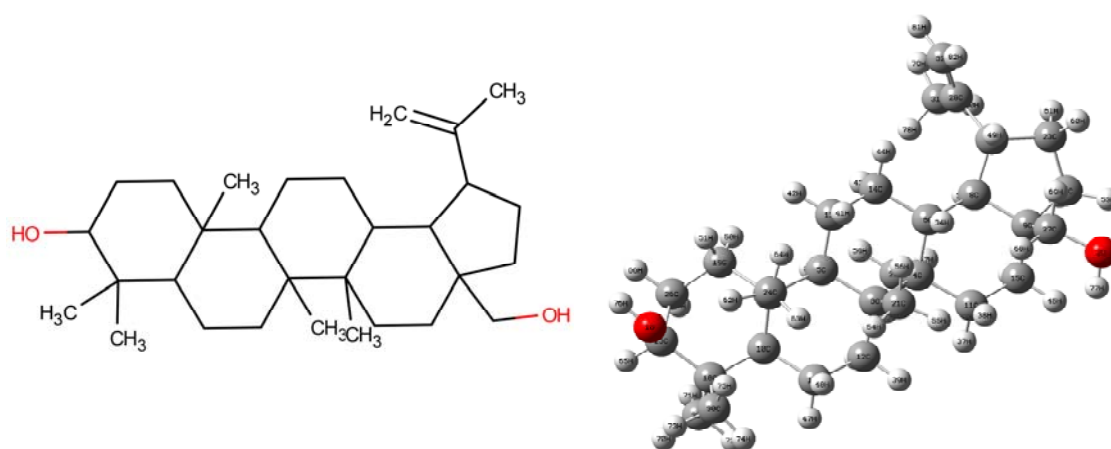


Figure 1. Structure of betulin.

METHODOLOGY

Computational methods. All calculations were conducted with the Gaussian 09 software package.¹⁰The geometries of betulin were optimized at the B3LYP electronic structure method¹¹⁻¹³ using the 6-31G(d,p) basis set. Frequencies were calculated to ensure the absence of imaginary frequencies in the lowest energy state. The Solvation Model on Density (SMD),¹⁴ as implemented in Gaussian 09, was used for all calculations involving the solvents, water, dimethyl sulfoxide (DMSO), acetonitrile, *n*-octanol, chloroform and carbontetrachloride. All calculations involving solvation were performed using the optimized solution-phase structures.

RESULTS AND DISCUSSION

Solvation free energy. The most important properties of a chemical system (solute) with surrounding solvent can best be described by means of free energy variation.¹⁵The solvation free energies of betulin calculated with the B3LYP/6-31G(d,p) and with the SMD model¹⁶ are summarized in Table 1. The solvation energies in water, DMSO, acetonitrile, *n*-octanol, chloroform and carbontetrachloride were -30.14 kJ/mol, -46.44 kJ/mol, -64.76 kJ/mol, -66.01 kJ/mol, -66.99 kJ/mol and -56.84 kJ/mol, respectively. Generally solvation free energy of betulin increases with decreasing

polarity of the solvent, however carbontetrachloride, being the most nonpolar solvent, demonstrated lower solvation free energy than acetonitrile, *n*-octanol and chloroform but higher than that of water and DMSO.

Table 1. Solvation free energy of betulin in different solvents.

Medium (dielectric constant)	Solvation free energy (kJ/mol)
Water (78.3)	-30.14
DMSO (46.8)	-46.44
Acetonitrile (35.7)	-64.76
<i>n</i> -Octanol (9.9)	-66.01
Chloroform (4.7)	-66.99
Carbontetrachloride (2.2)	-56.84

Dipole moment. The dipole moment of betulin was found to be higher in different solvents than that of the gas phase. Table 2 presents the dipole moments computed in the gas phase and different solvents (water, DMSO, acetonitrile, *n*-octanol, chloroform and carbontetrachloride) at the B3LYP/6-31G (d,p) using SMD solvation model. The dipole moments were 2.90D, 3.19D, 3.44D, 3.75D, 3.71D, 3.72D and 4.08D in the gas phase, carbontetrachloride, chloroform, *n*-octanol, DMSO and water, respectively. Therefore, the dipole moment increases with the increasing polarity of the solvent (Figure 2).

Table 2. Dipole moment in gas phase and in different solvents.

Medium (dielectric constant)	Dipole Moment (Debye, D)
Gas	2.90
Carbontetrachloride (2.2)	3.19
Chloroform (4.7)	3.44
<i>n</i> -Octanol (9.9)	3.75
Acetonitrile (35.7)	3.71
DMSO (46.8)	3.72
Water (78.3)	4.08

Molecular electrostatic potential (MESP). The Molecular electrostatic potential (MESP) represents the net electrostatic effect of a molecule which is generated from the total charge distribution in the molecule. The MESP correlates very well with the partial charges, electronegativity, dipole moments and chemical reactivity of the molecule.¹⁷⁻¹⁹ In the case of chemical reactivity, the region of the molecule susceptible to electrophilic or nucleophilic attack can be identified by the total electron density surface mapped with the electrostatic potential. The MESP contour map of betulin, calculated at the B3LYP/6-31G(d,p), is shown in Figure 3. The red (negative) and blue (positive) color regions in the MESP surface represent the regions susceptible to the attack of electrophiles and nucleophiles, respectively. The map reveals that the most possible sites for nucleophilic attack are C30, H76 and H77 and electrophilic attack are O1 and O2.

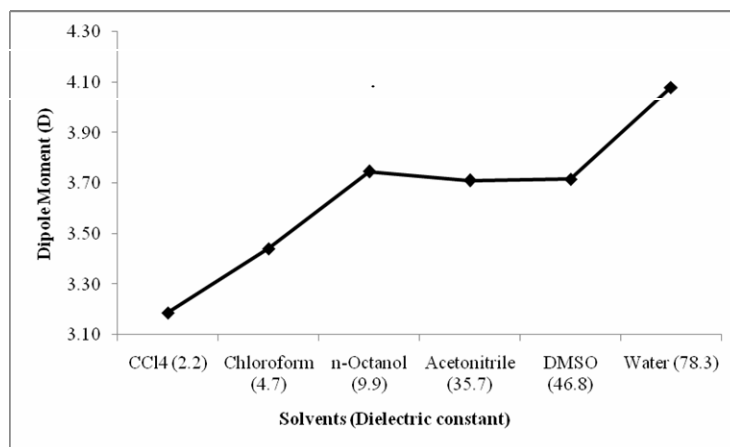


Figure 2. Effect of solvent polarity on dipole moment (D) of betulin.

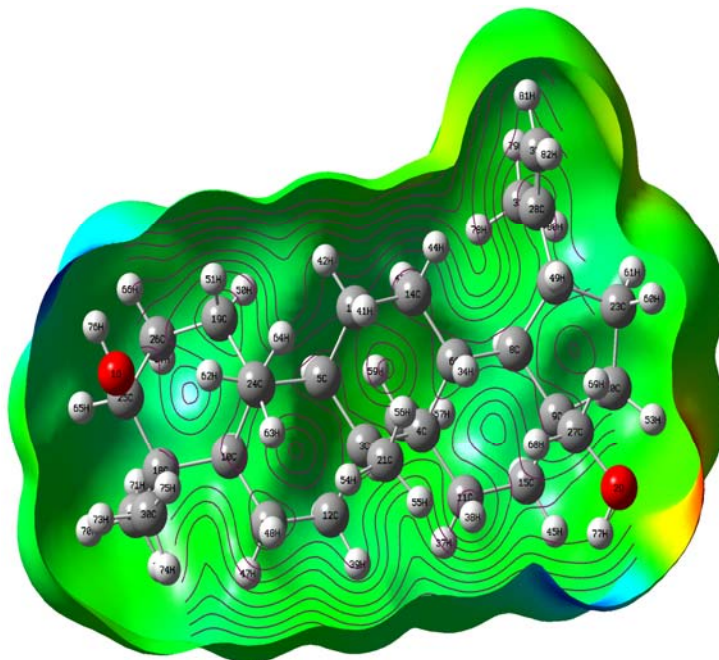


Figure 3. Electrostatic potential contour of betulin.

Mulliken population analysis. The Mulliken charges present net atomic charges in the molecule; while electrostatic potentials are generated by the electric field of internal charge distribution. Thus, in the reactivity studies, population analysis and MESP are complementary tools, and correlation between the schemes is expected.²⁰ In this study, Mulliken population Analysis (MPA) has been carried out to clearly understand the charge distribution among the atoms in betulin. Atomic charges obtained from MPA are presented in Table 3. According to MPA, among all the carbon atoms C31 has the highest (-0.374) negative charge. The presence of two nitrogen atoms N(1) and N(3) imposes large positive charges on C(2) atom. The MPA shows that all the hydrogen and oxygen atoms have positive and negative charges, respectively. Among all the H atoms, the H76 and H77 possess highest positive charge (0.302 and 0.306, respectively). This shows that the charge distribution and the MESP information are concordant.

Polarizability and first order hyperpolarizability. Polarizability is the measure of distortion of a molecule in an electric field. It is a tensor and can

be represented in a 3×3 real symmetric matrix i.e. the off-diagonal elements are equal. The polarizability (α) was calculated according to the following equation:

$$\alpha = \frac{1}{3} (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

The quantities α_{xx} , α_{yy} and α_{zz} are known as principal values of polarizability tensor.

This property measures the strength of molecular interactions (e.g., long-range intermolecular induction, dispersion forces, etc.), the cross sections of different scattering, and collision processes, and the optical properties of a system.⁸ The calculated polarizability of betulin in different solvents is presented in Table 4, which shows that polarizability (α_{tot}) of betulin in these solvents ranged from 356.35 to 455.06 a.u. The plot of polarizability vs. solvent is shown in Figure 4. It is clear from the Figure 4 that the polarizability gradually increases when going from lower to higher dielectric constant.

The first order hyperpolarizability (β) is the measure of the nonlinear optical activity which can be of different types such as β_{vec} (β vector), $\beta_{||}$ (β parallel) and β_{tot} (β total). It is a third rank tensor that

can be described by a $3 \times 3 \times 3$ matrix. The Kleinman symmetry enables us to reduce the 27 components of 3D matrix into 10 components²¹. GAUSSIAN provides 10 components of this matrix as β_{xxx} , β_{yxx} , β_{xyy} , β_{yyy} , β_{xxz} , β_{xyz} , β_{yyz} , β_{xzz} , β_{yzz} , β_{zzz} , respectively, from which all x, y and z components of β can be calculated. The hyperpolarizability (β_{tot}) can be calculated using the following equation:

$$\beta_{tot} = (\beta_x^2 + \beta_y^2 + \beta_z^2)^{1/2}$$

Where,

$$\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}$$

$$\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yzz}$$

$$\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz}$$

The β_{tot} for different solvents have been listed in Table 6, which shows that the hyperpolarizability in different solvents ranges from 202.24 to 238.02 a.u. No systematic trend of hyperpolarizability with solvent polarity was observed (Figure 5).

Table 3. Atomic charges of betulin obtained from Mulliken population Analysis (MPA).

Atom	Mulliken population analysis	Atom	Mulliken population analysis	Atom	Mulliken population analysis
O1	-0.549	C29	-0.316	H56	0.101
O2	-0.551	C30	-0.292	H57	0.096
C3	0.052	C31	-0.374	H58	0.098
C4	0.050	C32	-0.295	H59	0.101
C5	-0.065	H33	0.072	H60	0.105
C6	-0.052	H34	0.076	H61	0.096
C7	0.064	H35	0.077	H62	0.136
C8	-0.064	H36	0.066	H63	0.087
C9	0.022	H37	0.090	H64	0.088
C10	-0.043	H38	0.080	H65	0.067
C11	-0.187	H39	0.082	H66	0.077
C12	-0.189	H40	0.084	H67	0.096
C13	-0.193	H41	0.092	H68	0.085
C14	-0.194	H42	0.086	H69	0.104
C15	-0.204	H43	0.084	H70	0.098
C16	-0.194	H44	0.100	H71	0.094
C17	-0.122	H45	0.069	H72	0.100
C18	0.020	H46	0.091	H73	0.096
C19	-0.177	H47	0.084	H74	0.089
C20	-0.184	H48	0.095	H75	0.117
C21	-0.319	H49	0.080	H76	0.302
C22	-0.325	H50	0.088	H77	0.306
C23	-0.202	H51	0.092	H78	0.118
C24	-0.339	H52	0.081	H79	0.107
C25	0.191	H53	0.109	H80	0.110
C26	-0.222	H54	0.099	H81	0.084
C27	0.059	H55	0.091	H82	0.086
C28	0.184				

Table 4. Effect of solvent polarity on polarizability (a.u.) and first order hyperpolarizability (a.u.)

Medium (dielectric constant)	α_{xx}	α_{yy}	α_{zz}	α_{tot}	β_x	β_y	β_z	β_{tot}
Gas Phase	360.13	306.29	259.17	308.53	164.23	81.92	53.35	191.13
Water (78.3)	457.35	468.34	439.50	455.06	190.49	99.85	101.99	238.02
DMSO (46.8)	452.42	461.84	431.18	448.48	174.95	88.60	86.40	214.29
Acetonitrile (35.7)	452.39	460.20	427.76	446.78	182.96	90.25	84.03	220.63
<i>n</i> -Octanol (9.9)	442.756	436.527	393.93	424.40	193.54	94.93	86.45	232.26
Chloroform (4.7)	426.541	405.235	355.58	395.78	182.02	90.31	72.91	215.88
Carbontetrachloride (2.2)	400.085	360.59	308.37	356.35	171.20	85.99	64.80	202.24

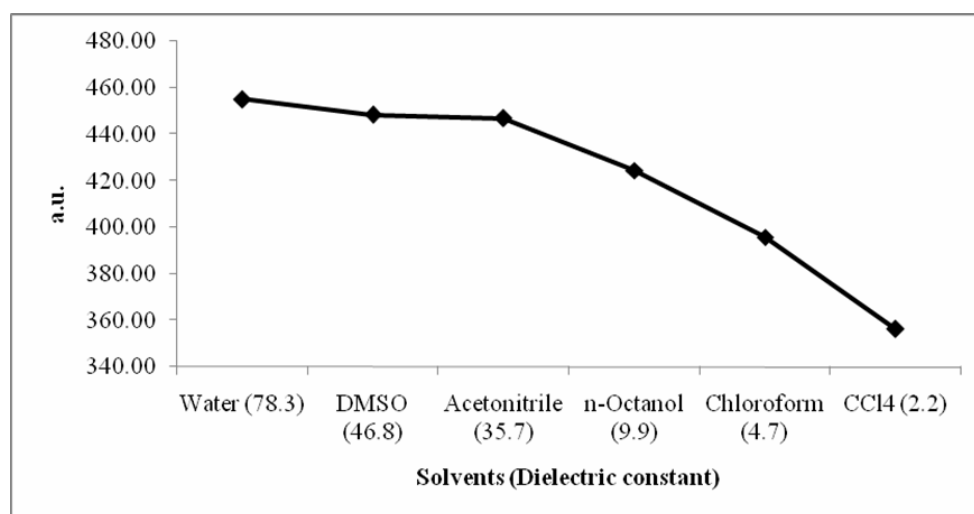


Figure 4. Effect of solvent polarity on polarizability of betulin.

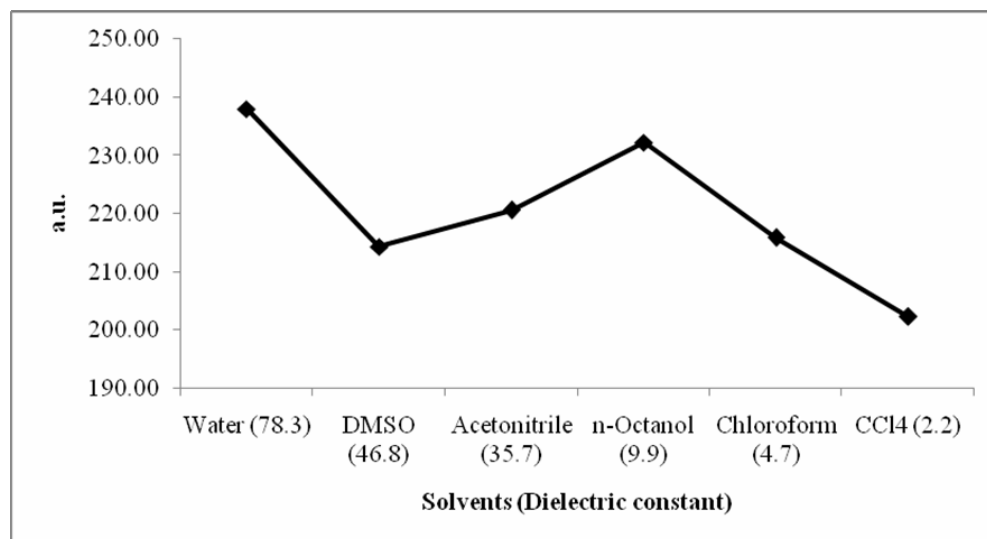


Figure 5. Effect of solvent polarity on first order hyperpolarizability of betulin.

Global reactivity descriptors. The electrical transport properties of a molecule depends on the energy gap of HOMO and LUMO orbitals. The values of HOMO-LUMO energy gap in various solvents are presented in Table 5 and their trend is shown in Figure 6. Generally the HOMO-LUMO energy gap increases as the solvent shifts from polar solvent (Water) to non-polar solvent (Carbon-tetrachloride). This suggests that the molecule is stabilized with decreasing polarity of the solvent i.e. the molecule is less likely to be kinetically reactive which is in agreement with the calculations of chemical softness.

The global chemical reactivity descriptors such as softness, hardness, chemical potential and electrophilicity index can be calculated from the HOMO-LUMO energy gap of a molecule.²²⁻²⁶ Using Koopman's theorem for closed-shell molecules the hardness (η), chemical potential (μ), electronegativity (χ) and softness (S) are defined as follows.

$$\eta = \frac{I - A}{2}$$

$$\mu = -\frac{I + A}{2}$$

$$\chi = \frac{I + A}{2}$$

$$S = \frac{1}{\eta}$$

Where I and A are the ionization potential and electron affinity of the molecule, respectively. The ionization energy and electron affinity can be quantified as $I = -E_{\text{HOMO}}$ and $A = -E_{\text{LUMO}}$. Parr et al., defined and calculated the global electrophilic power

of a molecule as electrophilicity index (ω) as follows^{23,25}:

$$\omega = \frac{\mu^2}{2\eta}$$

These new reactivity descriptors can be used to understand the toxicity of various pollutants in terms of their reactivity and site selectivity.²⁷⁻²⁹ The molecular properties of betulin in different solvent medium are presented in Table 6. As the polarity of solvent increases, the chemical potential, electrophilicity index and electronegativity are increased. However, the carbontetrachloride, being the most non-polar solvent, displayed chemical potential, electrophilicity index and electronegativity value near similar to water.

Chemical hardness of betulin increases as solvent polarity decreases, while opposite relation is found in case of chemical softness.

Table 5. Molecular Orbital Energy (eV) (HOMO and LUMO) of betulin in different solvents.

Medium (dielectric constant)	Molecular Orbital Energy (eV)		
	HOMO	LUMO	ΔE
Gas Phase	-6.318	0.739	7.056
Water (78.3)	-6.218	0.800	7.018
DMSO (46.8)	-6.214	0.802	7.016
Acetonitrile (35.7)	-6.214	0.804	7.018
n-Octanol (9.9)	-6.215	0.811	7.025
Chloroform (4.7)	-6.211	0.821	7.032
Carbontetrachloride (2.2)	-6.230	0.813	7.043

Table 6. Effect of solvent polarity on molecular properties of betulin

Medium (dielectric constant)	Chemical hardness (η)	Softness (S)	Chemical potential (μ)	Electronegativity (χ)	Electrophilicity index (ω)
Gas Phase	3.528	0.2834	-2.789	2.789	1.103
Carbontetrachloride (2.2)	3.522	0.2840	-2.708	2.708	1.041
Chloroform (4.7)	3.516	0.2844	-2.695	2.695	1.033
n-Octanol (9.9)	3.513	0.2847	-2.702	2.702	1.039
Acetonitrile (35.7)	3.509	0.2850	-2.705	2.705	1.043
DMSO (46.8)	3.508	0.2851	-2.706	2.706	1.043
Water (78.3)	3.509	0.2850	-2.709	2.709	1.046

CONCLUSION

To understand the structure and reactivity of betulin and related molecules, we have carried out an extensive study of the solvation free energy, dipole moment, molecular electrostatic potential (MESP), atomic charge distribution, polarizability, hyperpolarizability, chemical potential, electrophilicity, chemical hardness and chemical softness using the B3LYP/6-31G(d,p) level of theory. The solvation free energy is highest in the nonpolar solvent (chloroform) and is lowest in the polar protic solvent (water). The dipole moment of betulin increases with the increasing polarity of the solvent. Similarly, polarizability also increases with the polarity of the solvent. However, no systematic trend of hyperpolarizability with solvent polarity is found. Molecular electrostatic potential (MESP) and Mulliken population analysis (MPA) reveal that the most possible sites for nucleophilic attack are C30, H76 and H77 and electrophilic attack are O1 and O2 among the atoms in betulin. The chemical potential, electrophilicity index and electronegativity increase with the increase of solvent polarity.

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