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Solute–Solvent Dielectric Effects on PAM 120

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ABSTRACT

Quantum-chemical solvent effect theories describe the electronic structure of a molecular subsystem embedded in a solvent or other molecular environment. The solvation of biomolecules is important in molecular biology .In this theoretical study, we focus on a kind of dammarane sapogenins (PAM120). This molecule optimized in various solvent media such as heptan, carbontetrachloride, toluene, tetrahydrofurane, dichloroethane, ethanol, methanol, dimethylsulfoxide and water using the self-consistent reaction field model. This process depends on either the reaction potential function of the solvent or charge transfer operators that appear in solute-solvent interaction. We performed nonempirical quantum-mechanical calculations at the HF/3-21G, 6-31G , 6-31G,6-31G** and B3LYP/6-31G** levels of theory in the gas phase and some solvents at 298K.We studied energy ,dipole moment ,charge and so on.*

Key words: Dammarane sapogenins, anti cancer, self-consistent reaction field (SCRF), solvent.

INTRODUCTION

Sapogenin (Aglycone) is a nonsugar portion of a saponin that is typically obtained by hydrolysis, has either a complex terpenoid or a steroid structure and in the latter case forms a practicable starting point in the synthesis of steroid hormones. Sapogenin can be simply defined as the following equation:

Saponin = Sugar (glycone) + Sapogenin

Ginseng, the root of Panax Ginseng, has been considered as an important component of traditional prescription in Korea and China. It exhibits central nervous system-depressant and antipsychotic activity, protection of stress ulcer, increase of gastrointestinal motility and weak anti-inflammatory action [1-6].

Recently, sapogenin has attracted a great deal of attention to its potential efficacies, and has been widely used in many countries. Dammarane sapogenins are a group of compounds found in plants, especially in araliaceous plants. The chemical structure of dammarane sapogenins is like a tetracyclic terpene of the dammarane series. While plants (such as ginseng) containing those compounds have been extensively used for medical purpose in China and other Asian countries for thousands of years [7].

Sapogenin glycosides, a type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions.

First marketed in 2001, Careseng contains the concentrated extract of a number of anti-cancer compounds found in ginseng, a herb with a long history of use in traditional Chinese medicine. Cell culture studies on breast, liver, colon, prostate, lung, pancreatic, and brain cancer cells have shown that the extract induces apoptosis (cell death) in cancer cells. Two preliminary clinical studies also show significant inhibition of cancer growth. No adverse side effects have been reported.

The two main active anti-cancer agents in Careseng are Rh2 and a class of plant compounds known as dammarane sapogenins, found especially in the araliaceae (a large family of mostly tropical shrubs and trees, of which ginseng is one). Cell culture studies of dammarane sapogenins demonstrate that in addition to inducing apoptosis, they can also inhibit cancer cell proliferation, induce differentiation of cancer cells into a benign form, and block the function a protein (P-glycoprotein) found in cancer cells which is responsible for multi-drug resistance, thus enhancing the efficacy of chemotherapy drugs. There are also other possible anti-cancer effects. Rh2 is chemically related to dammarane sapogenins.

Ginseng saponins (dammarane saponins, also called “ginsenosides”, which are effective ingredients that organically exist in panax ginseng, panax quinguefol, panax notoginseng and other species in the ginseng family) and sapogenins (those that do not naturally exist in the ginseng plant or other species in the ginseng family and can be derived only through chemical structure modification by cleavage and/or semi-synthesis of dammarane saponins), as natural-source root compounds, have been broadly researched for their anti-cancer characteristics. Some of them have been reported to have anti-cancer effects, of which, for example, ginsenoside Rh2 [3-O-β-D-glucopyranosyl-20(s)-protopanaxadiol] has been reported for its anti-cancer activities , including induction of differentiation and apoptosis in cancer cells , inhibition of the growth of human ovarian cancer in nude mice after oral administration , and the ability to inhibit the multiplication of multi-drug resistance (MDR) cancer cells while used with other chemotherapy drugs in vitro .

Ginsenoside Rg3 [3-O-[β-D-glucopyranosyl(1,2)-β-D-glucopyranosyl]-20(s)- protopanaxadiol] has been reported to inhibit the invasion by various cancer cells and suppress the proliferation of human prostate cancer cells in vitro, and to inhibit lung metastasis in mice and peritoneal metastasis in rats[8,9].

This study relates to a type of sapogenins, its use in anti-cancer applications, PAM-120 (the dammarane sapogenin structure in this sapogenin is specifically clean of any sugar moieties (glycons) at any position) (Figure 1) with molecular formula $C_{30}H_{50}O_2$ and molecular weight 442.723gmol^{-1}.

In this paper, we use non empirical calculations in one of the first detailed studies of sapogenines, geometries, energies, atomic charges, dipole moments, and other thermochemical properties with special emphasis on solvent effects on them.

Computational methods and details

Most of the current investigations in theoretical chemistry are based on the molecules immersed in a solvent phase. There are also a series of indications that various characteristics of solutions in which processes are performed, such as the dielectric constant, are determining factors.

The ability to accurately calculate solvation energies of molecules using molecular simulation methods is an important development in computational chemistry. These methods have wide applicability in studies of free energies of solvation [10].

The solvent effect is taken into account using the self-consistent reaction field (SCRF) method [11]. This method is based on the Onsager reaction field theory of electrostatic solvation [12]. In this model, a solvent is treated as a uniform dielectric with a given dielectric constant. A solute is placed into a cavity within the solvent. Various SCRF approaches differ in how they treat the cavity and reaction field [13, 14].

We optimized the geometries of the PAM120 in various solvents using the Onsager model at the Hartree–Fock and B3LYP levels of theory and compared our results with those obtained for the gas phase. A theoretical analysis at the HF and B3LYP/3-21, 6-31G, 6-31G* and 6-31G** levels of theory was performed to characterize all the stationary points of the potential energy surface as minima and obtain thermodynamic corrections. Solvation effects were modeled by the Onsager method as implemented in the GAUSSIAN 98 program [15].

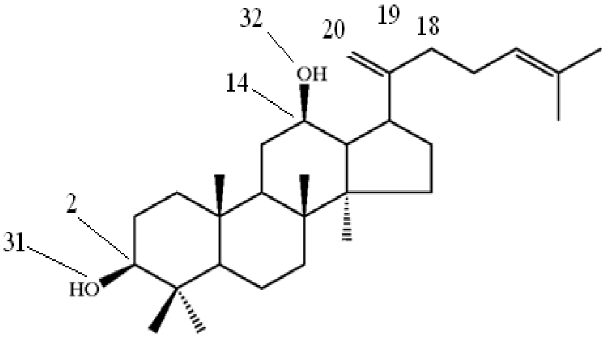


Figure 1. The structure of PAM 120.

It can be concluded from the results of model calculations that the simple model assuming a spherical or an ellipsoidal shape of the cavity for the solute molecule is likely satisfactory for comparatively small and rigid molecules. Therefore, this method was selected in our calculations [16, 17].

The Onsager-SCRF code elaborated by Wiberg and co-workers [18, 19] for the Gaussian computational code has been fairly popular in the past years. The Onsager model is an attractive alternative when PCM calculations fail [20].

RESULTS AND DISCUSSION

Quantum-chemical solvent effect theories give a self-consistent description of the electronic structure of solutes, which is closely related to the polarizable environment. Such calculations are indispensable for getting insight into the molecular properties and reactivity of condensed phases. This goal is usually achieved by means of a solute–solvent Schrödinger equation corresponding to some simplified representation of the solvent. In particular, the electronic structure of solute molecules can be closely related to the solvent structure and vice versa. This effect can be of key importance, for example, for the understanding of the microscopic mechanism of certain reactions in solutions.

We should note that there is interaction energy between solutes and solvents. Because of this, solute properties that depend on energy and several other factors, such as geometry, vibrational frequencies, total energy, and electronic spectrum, also depend on the solvent. The presence of a solvent, particularly a polar solvent can also stabilize charge separation within a molecule. This not only changes energy, but also causes electron density shifts and influences associated properties.

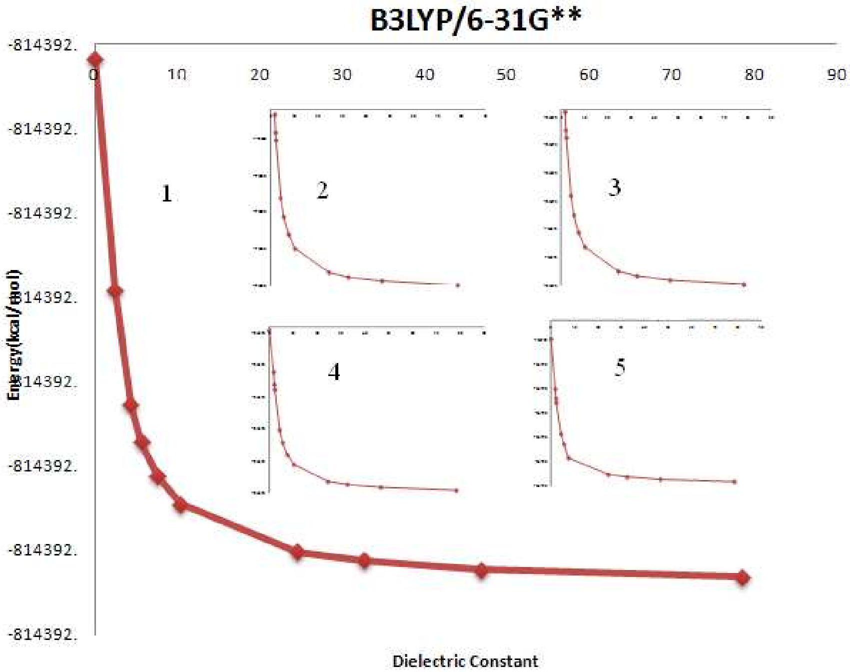


Figure2. Energies (kcal/mol) of PAM120 versus dielectric constants 1)B3LYP/6-31G 2)HF/3-21G 3)HF/6-31G 4)HF/6-31G* 5)HF/6-31G**.**

PAM 120 was studied in the gas phase (ε= 1) and various solvent media with dielectric constants of water (ε= 78.39), dimethylsulfoxide (ε= 46.7), methanol (ε=32.63), ethanol (ε=24.55),dichloroethane(ε=10.36),tetrahydrofurane(ε=8.93),toluene(ε=2.379),carbontetrachloride (ε=2.225) and heptan (ε=1.92) at 298K.

First, the molecule was fully optimized by the HF and DFT (B3LYP) methods using the 3-21G, 6-31G,6-31G* and 6-31G** basis sets to obtain minima of the potential energy surface.

The influence of the solvent on the relative stability of PAM 120 was studied by means of the Onsager approach. The results listed in Table 1.Table1 and figure 2 reveal that, as the dielectric constant increases in passing from the vacuum to heptan, carbontetrachloride , toluene , tetrahydrofurane , dichloroethane , ethanol , methanol , dimethylsulfoxide and water , the dipole moment of each solvent increases when different quantum-mechanical levels are used.

Table 1.Energy (kcal/mol) and dipole moment (Debye) of PAM 120 obtained in various solvent media

Solvent (dielectric constant)	Method	Basis set	Energy (kcal/mol)	Dipole moment (Debye)
Water (78.39)	HF	3-21G	-772009.21	3.9258
		6-31G	-753373.0613	4.5158
		6-31G*	-753679.3859	3.6322
		6-31G**	-753729.3297	3.6269
	DFT (B3LYP)	6-31g**	-814392.5158	3.6995
DiMethilSolfoxide (46.8)	HF	3-21g	-772009.2041	3.9169
		6-31g	-753373.0538	4.5046
		6-31g*	-753679.3813	3.6239
		6-31g**	-753729.3251	3.6181
	DFT (B3LYP)	6-31g**	-814392.3251	3.6906
Methanol (32.63)	HF	3-21g	-772009.1989	3.9075
		6-31g	-753373.0464	4.4929
		6-31g*	-753679.3767	3.6152
		6-31g**	-753729.3205	3.6089
	DFT (B3LYP)	6-31g**	-814392.5059	3.6814
Ethanol (24.55)	HF	3-21g	-772009.1924	3.8974
		6-31g	-753373.0378	4.4802
		6-31g*	-753679.3721	3.6058
		6-31g**	-753729.3153	3.5990
	DFT (B3LYP)	6-31g**	-814392.501	3.6714
DiChloroEthan (10.36)	HF	3-21g	-772009.1599	3.8440
		6-31g	-753372.9948	4.4135
		6-31g*	-753679.3457	3.5562
		6-31g**	-753729.2425	3.4575
	DFT (B3LYP)	6-31g**	-814392.4727	3.6187
TetraHydroFurane (7.58)	HF	3-21g	-772009.1404	3.8124
		6-31g	-753372.969	4.3740
		6-31g*	-753679.3303	3.5268
		6-31g**	-753729.2815	3.5332
	DFT (B3LYP)	6-31g**	-814392.4561	3.5875
ChloroBenzene (5.621)	HF	3-21g	-772009.1168	3.7735
		6-31g	-753372.9374	4.3255
		6-31g*	-753679.3114	3.4907
		6-31g**	-753729.2529	3.4781
	DFT (B3LYP)	6-31g**	-814392.4358	3.5492
Ether (4.335)	HF	3-21g	-772009.0908	3.7318
		6-31g	-753372.9036	4.2736

		6-31g*	-753679.2913	3.4519
		6-31g**	-753729.2323	3.4374
	DFT (B3LYP)	6-31g**	-814392.4136	3.5081
Toluene (2.379)	HF	3-21g	-772009.0117	3.6029
		6-31g	-753372.7999	4.1140
		6-31g*	-753679.2282	3.3323
		6-31g**	-753729.1681	3.3123
	DFT (B3LYP)	6-31g**	-814392.346	3.3815
CarbonTetrachloride (2.228)	HF	3-21g	-772009.0016	3.5860
		6-31g	-753372.7867	4.0931
		6-31g*	-753679.2202	3.3166
		6-31g**	-753729.1595	3.2959
	DFT (B3LYP)	6-31g**		
Heptan (1.92)	HF	3-21g	-772008.9769	3.5455
		6-31g	-753372.754	4.0433
		6-31g*	-753679.2002	3.2791
		6-31g**	-753729.14	3.2567
	DFT (B3LYP)	6-31g**		
Gas phase (1)	HF	3-21g	-772012.5371	3.3101
		6-31g	-753374.2519	3.7553
		6-31g*	-753679.1353	3.1312
		6-31g**	-753729.0379	3.0593
	DFT (B3LYP)	6-31g**	-814392.2088	3.1253

As the dielectric constant increases in passing from the vacuum to water there is not any changes in different angels of PAM 120. For example in figure 3 we have drown angel of atoms 18-19-20 (see figure 1) versus dielectric constant.

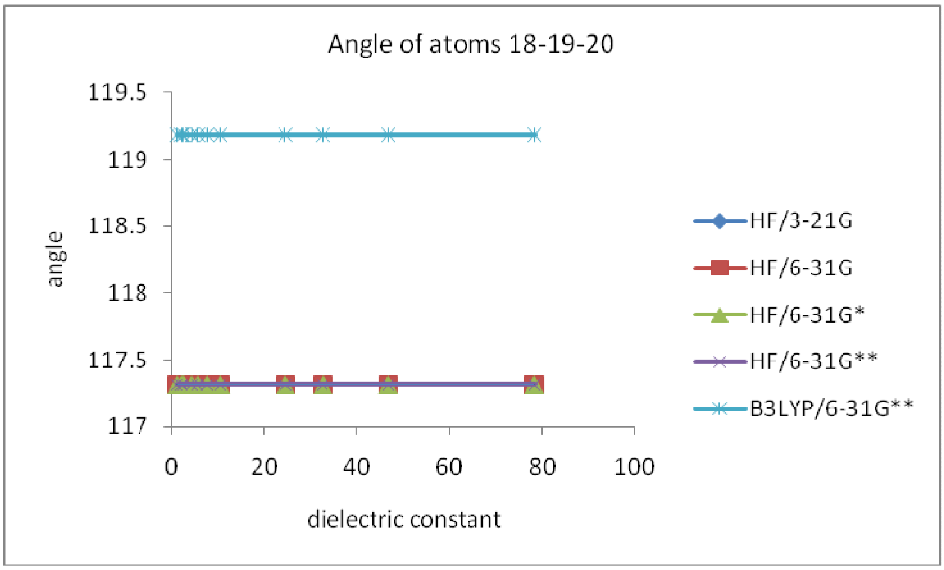
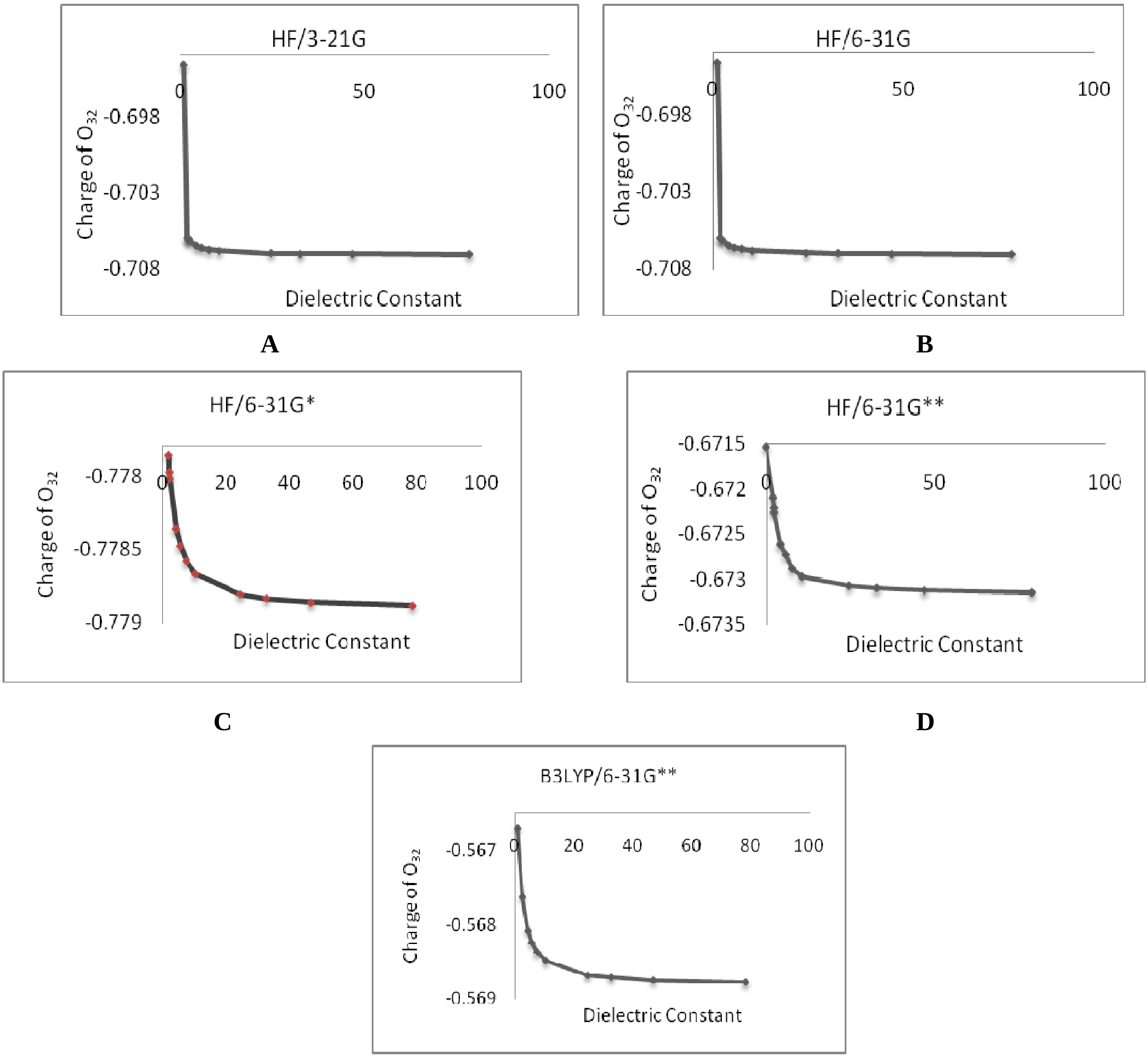


Figure3. Angle between atoms18-19-20 versus dielectric constant.

Also we study the effects of solvents and basis sets on charge of some important atoms like O31, O32, C2 and C14 (see figure 1). Table 2 and figure 4(for example about O32) are shown these relationships.



A **B**

b

C **D**

E

Figure4.Charge of atom O32 versus dielectric constants, a)HF/3-21G b)HF/6-31G c) HF/6-31G* d) HF/6-31G e)B3LYP/6-31G**.**

Table2. The effects of dielectric constants and basis sets on charges of some atoms

Solvent (dielectric constant)	Method	Basis set	Charge of O31	Charge of O32	Charge of C2	Charge of O14
Water (78.39)	HF	3-21g	-0.701855	-0.707065	0.186229	0.118506
		6-31g	-0.761176	-0.766076	0.194780	0.150316
		6-31g*	-0.767376	-0.778887	0.199831	0.171528
		6-31g**	-0.669556	-0.673144	0.258576	0.222385
	DFT(b3lyp)	6-31g**	-0.561619	-0.568778	0.192762	0.182188
DiMethilSolfoxid (46.8)	HF	3-21g	-0.701820	-0.707039	0.186231	0.118506
		6-31g	-0.761125	-0.766038	0.194782	0.150313
		6-31g*	-0.767344	-0.778863	0.199835	0.171530
		6-31g**	-0.669522	-0.673120	0.258579	0.222386
	DFT(b3lyp)	6-31g**	-0.561588	-0.568746	0.192768	0.182190
Metanol (32.63)	HF	3-21g	-0.701783	-0.707011	0.186233	0.118506
		6-31g	-0.761071	-0.765999	0.194784	0.150311
		6-31g*	-0.767309	-0.778838	0.199839	0.171531
		6-31g**	-0.669486	-0.673093	0.258583	0.222387
	DFT(b3lyp)	6-31g**	-0.561555	-0.568712	0.192774	0.182191
Etanol (24.55)	HF	3-21g	-0.701744	-0.706981	0.186236	0.118507
		6-31g	-0.761013	-0.765956	0.194786	0.150308
		6-31g*	-0.767272	-0.778811	0.199844	0.171533
		6-31g**	-0.669447	-0.673065	0.258587	0.222388
	DFT(b3lyp)	6-31g**	-0.561520	-0.568676	0.192781	0.182192
DiChloroEthan (10.36)	HF	3-21g	-0.701535	-0.706825	0.186249	0.118508
		6-31g	-0.760710	-0.765731	0.194798	0.150294
		6-31g*	-0.767076	-0.778666	0.199868	0.171541
		6-31g**	-0.668895	-0.672664	0.258645	0.222404
	DFT(b3lyp)	6-31g**	-0.561333	-0.568486	0.192818	0.182200
TetraHydroFuran (7.58)	HF	3-21g	-0.701411	-0.706732	0.186257	0.118509
		6-31g	-0.760530	-0.765598	0.194805	0.150286
		6-31g*	-0.766960	-0.778581	0.199882	0.171546
		6-31g**	-0.669190	-0.672878	0.258614	0.222395
	DFT(b3lyp)	6-31g**	-0.561223	-0.568373	0.192840	0.182204
ChloroBenzen (5.621)	HF	3-21g	-0.701259	-0.706618	0.186266	0.118510
		6-31g	-0.760310	-0.765435	0.194813	0.150276
		6-31g*	-0.766818	-0.778476	0.199899	0.171553
		6-31g**	-0.668975	-0.672722	0.258637	0.222402
	DFT(b3lyp)	6-31g**	-0.561087	-0.568234	0.192866	0.182209
Ether (4.335)	HF	3-21g	-0.701096	-0.706496	0.186276	0.118512
		6-31g	-0.760074	-0.765260	0.194822	0.150265
		6-31g*	-0.766665	-0.778363	0.199918	0.171559
		6-31g**	-0.668817	-0.672607	0.258653	0.222406
	DFT(b3lyp)	6-31g**	-0.258096	-0.264522	0.192894	0.182215
Toluene (2.379)	HF	3-21g	-0.700592	-0.706118	0.186306	0.118517
		6-31g	-0.759348	-0.764721	0.194848	0.150234
		6-31g*	-0.766193	-0.778015	0.199975	0.171581
		6-31g**	-0.668329	-0.672251	0.258704	0.222421
	DFT(b3lyp)	6-31g**	-0.560491	-0.567626	0.192982	0.182234
CarbonTetrachlorid (2.228)	HF	3-21g	-0.700526	-0.706069	0.18631	0.118518
		6-31g	-0.759253	-0.764651	0.194851	0.150229
		6-31g*	-0.766131	-0.777969	0.199982	0.171584
		6-31g**	-0.668265	-0.672205	0.258710	0.222423
	DFT(b3lyp)	6-316**				
Heptan	HF	3-21g	-0.700368	-0.705950	0.18632	0.118519

(1.92)		6-31g	-0.759026	-0.764483	0.194859	0.150220
		6-31g*	-0.765983	-0.777860	0.200000	0.171590
		6-31g**	-0.668112	-0.672094	0.258726	0.222427
	DFT(b3lyp)	6-31g**				
Gas phase (1)	HF	3-21g	-0.686486	-0.694656	0.164165	0.103043
		6-31g	-0.773223	-0.779500	0.199135	0.157077
		6-31g*	-0.765591	-0.778324	0.200802	0.172162
		6-31g**	-0.667343	-0.671533	0.258804	0.222451
	DFT(b3lyp)	6-31g**	-0.559579	-0.566696	0.193157	0.182271

CONCLUSION

The results of the quantum-chemical modeling of PAM120 with Onsager reaction field calculations were obtained using the polarizable dielectric model.

All systems were optimized by the Hartree–Fock, and B3LYP methods. In all cases, the steadystate nature (minimum of the potential energy surface) of the optimized complexes has been confirmed through the investigation of theoretical levels. We can conclude that, for the system studied in this work, the density functional calculation gives similar or even better results than ab initio method.

The influence of the dielectric constant on the standard geometry of PAM120 in solution are smaller than in the gas phase, because interactions in solution are stronger than in the gas phase. More dielectric constant, more negative charge in O31 and O32 and positive charge in C2 and C14. So with increase dielectric constant oxygens became more nucleophyl and carbons became more electrophyle.

The dipole of a molecule induces a dipole in the medium, and the electric field of the solvent dipole in turn interacts with the molecular dipole, leading to overall stabilization.

REFERENCES

[1] S.Cinta Pinzaru , N. Leopold, N. Peica, W. Kiefer, Monitoring the sweetner content in leaves of Stevia Rebaudiana plant using Raman and SERS spectroscopy, Proc. XIXth Intern.Conf. Raman Spectroscopy, P. M. Fredericks, R.L. Frost and L. Rintoul, eds. CSIRO Publishing, Australia, Sidney, **(2004)**pp. 419–420.
[2] V.Kren, L. Martinkova, *Current Medicinal Chemistry,* **(2001)** ,8, 1313–1338.
[3] H.Kohda, O. Tanaka, *Yakugaku Zasshi,* **(1975)** ,95 , 246–249.
[4] Li, Y.M., S.Q. Sun, Q. Zhou, Z. Qin, J.X. Tao, J. Wang, X. Fang, *Vibrational Spectroscopy* , 36, 227–232 (**2004**),.
[5] Nabata, H., H. Saito, K. Takagi, *Japan J.Pharmacol*., 23, 122–127 (**1973**).
[6] Woo, Y.A., H.J. Kim, H. Chung, *Analyst*, 124, 1223–1226 (**1999**).
[7] http://www.bioportfolio.com/biocorporate/27846.html.
[8] D.Huang, , D.F. Qi, Dammarane sapogenins, their use as anti-cancer agents, and a process for producing same US**(2005)**6888014.
[9] D.Huang, , D.F. Qi, Aglycon dammarane sapogenins,their use as anti-cancer agents, and a process for producing same US**(2005)**6949523.
[10] V. I. Vanloads, , A. S. Spirm, , R.Brimaeomb, , et al., *Nucleic Acids Res*. **(1992)** 20, 2627.

[11] Y.Kyogoku, , R. C.Lord, , and Rich, *A.Biochem. Biophys.Acta* **(1969)**179, 10.
[12] Y. L. Wang , J.Bao, , Y.Sun, and J.Yang, ,*J. Theor. Biol.* **(2006)**238, 85.
[13] Z. G.Kudritskaya and V. I.Danilov , *J. Theor. Biol.* **(1976)**59,303 .
[14] J.Langlet, , P.Claverie, , F.Caron, and J. C.Boeuve, ,*Int. J. Quantum Chem.* **(1981)**19, 299.
[15] M. J. Frisch, , G. W.Trucks, , H. B. Schlegel, et al., *Gaussian 98, Revision A.7* (Gaussian, Inc., Pittsburgh, PA,(1998).
[16] J. G. Kirkwood, *J. Chem. Phys.* **(1939)** 7, 911.
[17] L.Onsager, *J. Am. Chem. Soc.* **(1936)**58, 1486.
[18] M. A. Wong, , M. J. Frisch, and K. B.Wiberg, *J. Am.Chem. Soc.* **(1991)**113, 4776.
[19] M. A.Wong, , M. J. Frisch, and K. B.Wiberg , *J. Am.Chem. Soc.* **(1992)** 114, 523.
[20] J.Tomasi, B.Mennucci, and R. Cammi, *Chem. Rev.* **(2005)** 105,2999.