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The Study of Solvation Effects on an Anticancer Drug: Dammarane sapogenins

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ABSTRACT

In this theoretical study, we focus on a kind of dammarane sapogenins. 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 about energy ,dipole moment ,charge and so on.

Keywords: Dammarane sapogenins; Anti cancer; Self-consistent reactioa field (SCRF); Solvent

INTRODUCTION

Dammarane sapogenins are a group of compouads fouad ia plants, especially in araliaceous plants. The dammarane sapogenins backbone is a tetracyclic terpene of the dammarane series. While plants (such as ginseng) coataining those compounds have been extensively used for medicinal use ia China and other Asian countries for thousands of years, extracts do not shown significant cancer killing activity. Dammarane sapogenins are series of compounds derived from natural plants including ginseng, and produced through aa advanced chemical technology. Ginseng, the root of Panax Ginseng, has been considered as aa important componeat of traditional prescription in Korea and China. It exhibits central oervous system-depressant and antipsychotic activity, protection of stress ulcer, increase of gastrointestinal motility and weak anti-inflammatory action [1-4].

Ginseng saponins (dammarane saponins, also called "ginsenosides", which are effective ingredients that organically exist in panax ginseng, panax quinquefol, panax notoginseng and other species in the ginseng family) and sapogenins (those that do aot naturally exist in the ginseng plant or other species in the ginseag 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 [3-O-β-D-glucopyranosy 1-20(s)-protopanaxadiol] has been reported for its anti-cancer activities, including induction of differentiation aad apoptosis in cancer cells,

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inhibition of the growth of human ovarian cancer in nude mice after oral administration, and the ohility 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[5,6].

Some kinds of dammarane sapogenins are: PAM-20, PBM-110 and PBM-100 (the dammarane sapogenin structure in these three sapogenins is specifically clean of any sugar moieties (glycons) at any position and a hydroxyl at C-20) and PAN-20 and PAN-30 (the dammarane sapogenin structure has sugar moieties (glycons) but is free of hydroxyl at C-20), obtained by chemical cleavage of dammarane saponins.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 positiaa) with molecular formula $C_{30}H_{50}O_2$ and molecular weight 442.723gmol^{-1}.

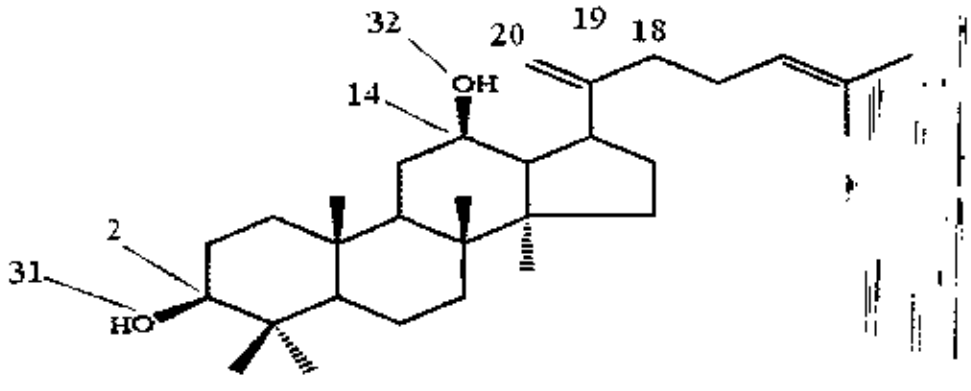


Fig.1. The structure formula of PAM 120.

COMPUTATIONAL METHOD

The calculations were carried out at the different levels of theory using the methods, namely, the Hartree-Fock (HF) [7] as an electron uncorrelated method, and the Becke's three-parameter hybrid functional combined with gradient corrected functional of Lee, Yang and Parr (B3LYP) [8].

A theoretical analysis at the HF /3-21, 6-31G,6-31G* , 6-31G** and B3LYP/6-31G** levels of theory was performed to characterize all the stationary points of the potential energy surface as minima and obtain thermodynamic corrections. The mentioned basis sets have been chosen based on the difference between the number of primitives in minimal ones, splitting in valence layer and the number of primitives in core and valence layer. Solvent effects were modeled by the Onsager method as implemented in the GAUSSIAN 98 program [9]. 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. PAM 120 was studied in the gas phase (ε= 1) and various solvent media and dielectric constants: 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.

THEORETICAL BACKGROUNDS

The use of the SCRF model in quantum-chemical theory requires that the shape and

volume of the solute molecule be defined uniquely fnr any set of compounds.

A number of approaches to calculating these characteristics are known, hut no annempirical methods for their estimation have been developed. However, 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 [10, 11].

The Onsager-SCRF code elahorated by Wiberg and co-workers [12, 13] for the Gaussian computational code has been fairly popolar in the past yeara.

The Onsager model describes the system as a molecule with a multipnle moment inside a spherical cavity surrounded by a continuous dielectric. In some programs, only the dipole moment is used, and calculations therefore fail for molecules with zero dipole moment. Tbe results obtained using the Onsager model and HF calculations are as a rule qualitatively correct.

Accuracy increases significantly with the use of MP2 or hybrid DFT functions. This is not the most accurate method available, but it is stable and fast. This makes the Onsager model an attractive altemative when PCM calculations fail [14]. The Onsager-SCRF code elahorated by Wiberg and co-workers [12, 13] for the Gaussian computational code has hcen fairly popular in the past years. The Onsager model is an attractive altemativc whcn PCM calculations fail [14].

RESULTS AND DISCUSSION

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), methannl (e = 32.63), ethanol (ε=24.55), dichlnroethane (e = 10.36), tetrahydrofurane (ε=8.93), toluene (ε=2.379), carbontetrachloride (e = 2.225) and heptan (ε=1.92) at 298K.

First, the molecule was fully optimized by tbe 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 hy means of the Onsager approach. The results listed in Table 1.Tahle1 and figure2 reveal that, as the dielectric constant increases in passing from the vacuum to heptan, carbontetrachlnride, toluene, tetrahydrofurane, dichloroethanc, ethanol, methanol, dimethylsulfoxide and water, the dipole moment of each solvent increases when different quantum-mechanical levels are used.

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.

The effect of solvents on the stabilization of the PAM120 is of interest; it plays a major role in its activities. Thc standard Oosager approach (the SCRF method) to PAM120 with different basis scts, as is used here, appears to be a good first step in theoretical investigations of solvent cffects.

Table 1. Energy (kcal/mal) 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
Dimethylsulfoxide (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	3-21 G	-772009.1989	3.9875
		6-31 G	-753373.0464	4.4929
		6-31 G *	-753679.3767	3.6152
		6-31 G **	-753729.3205	3 6889
	DFT (B3LYP)	6-31 G **	-814392.5059	3.6814
Ethanol (24.55)	HF	3-21 G	-772009 1924	3.8974
		6-31 G	-753373.0378	4.4802
		6-31 G *	-753679.3721	3.6058
		6-31 G **	-753729.3153	3.5990
	DFT (B3LYP)	6-31 G **	-814392.581	3.6714
DiChloroEthan (18.36)	HF	3-21 G	-772009.1599	3.8440
		6-31 G	-753372.9948	4.4135
		6-31 G *	-753679.3457	3 5562
		6-31 G **	-753729.2425	3 4575
	DFT (B3LYP)	6-31 G **	-814392.4727	3.6187
TetraHydroFurane (7 58)	HF	3-21 G	-772889.1404	3.8124
		6-31 G	-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

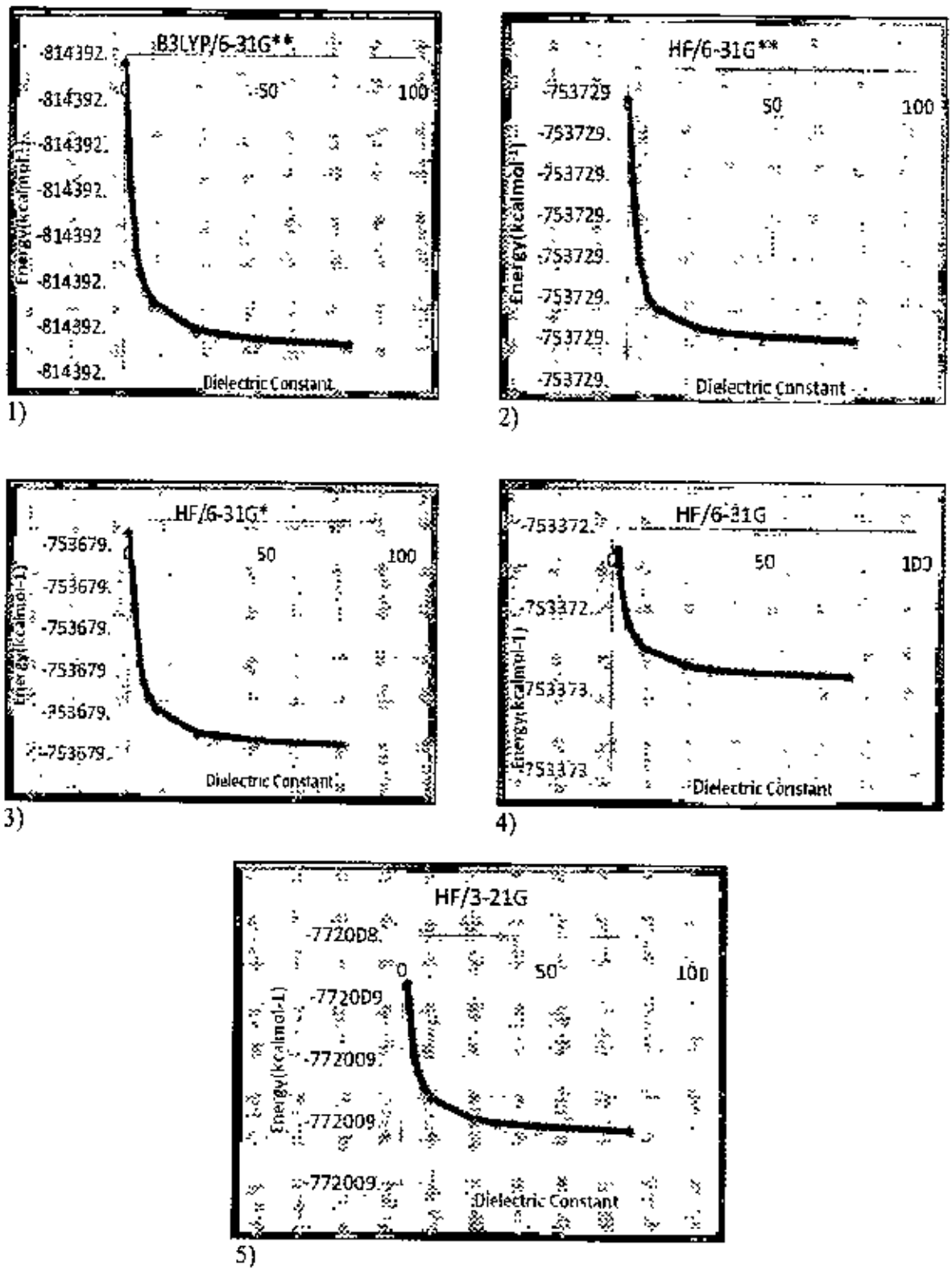


Fig.2. Energies (kcal/mol) of PAM12D versus dielectric constants 1)B3LYP/6-31G**, 2) HF/6-31G**, 3) HF/6-31G*, 4) HF/6-31G, 5)HF/3-21G.

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 table2 wc have listed angel of atoms 18-19-20 (see figure1) versus dielectric coastant.

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. We have listed these values in table 3 .In figure 3 the charge of O32 was plotted versus dielectric constants.

CONCLUSION

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

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

The influence of the dielectric constant on the standard geometry of PAM120 in solution are smaller than in the gas phase, because interactinns 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 nxygen became more nucleophyl and carbons became more electrophyle.

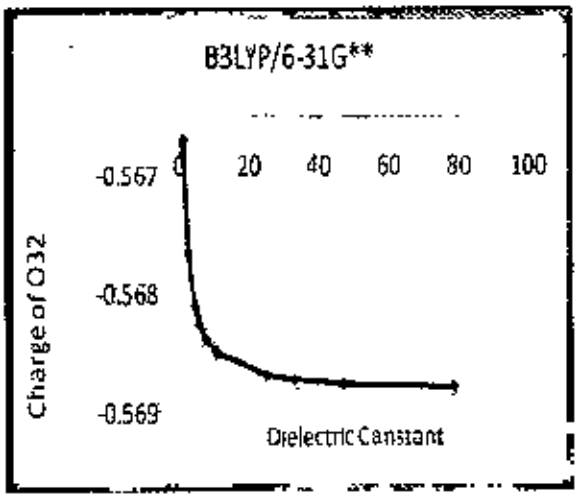
The dipole of a molecule induces a dipole in the medium, and the electric field of the solvent dipole in turn interacts with the molecular dipole, leading to overall stabilization.

Table2. Angle of atoms18-19-20 versus dielectric constant

Basis set / Dielectric constant	HF/3-21G	HF/6-31G	HF/6-31G**	HF/6-31G**	B3LYP/6-31G**
1	117.314	117.314	117.314	117.314	119.18
1.92	117.314	117.314	117.314	117.314	119.18
2.228	117.314	117.314	117.314	117.314	119.18
2.379	117.314	117.314	117.314	117.314	119.18
4.335	117.314	117.314	117.314	117.314	119.18
5.621	117.314	117.314	117.314	117.314	119.18
7.58	117.314	117.314	117.314	117.314	119.18
10.36	117.314	117.314	117.314	117.314	119.18
24.55	117.314	117.314	117.314	117.314	119.18
32.63	117.314	117.314	117.314	117.314	119.18
46.8	117.314	117.314	117.314	117.314	119.18
78.39	117.314	117.314	117.314	117.314	119.18

Table 3. 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	-0.307065	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
	OFT(b3lyp)	6-31G**	-0.561619	-0.568778	0.192762	0.182188
Dimethylsulfoxide (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
Methanol (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
Ethanol (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
Dichlaromethane (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
TetraHydroFurane (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	-8.759348	-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
CarbonTetrachloride (2.228)	HF	3-21G	-0.788526	-0.706069	0.18631	0.118518
		6-31G	-0.759253	-0.764651	0.194851	0.150229
		6-31G*	-0.766131	-0.773969	0.199982	0.171584
		6-31G**	-0.668265	-0.672205	0.258710	0.222423
	DFT(b3lyp)	6-31G**				
Heptan (1.92)	HF	3-21G	-0.700368	-0.705950	0.18632	0.118519
		6-31G	-0.759026	-0.764483	0.194859	8.150220
		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	-8.778324	0.200802	0.172162
		6-31G**	-0.667343	-0.671533	0.258804	0.222451
	OFT(b3lyp)	6-31G**	-0.559579	-0.566696	8.193157	0.182271



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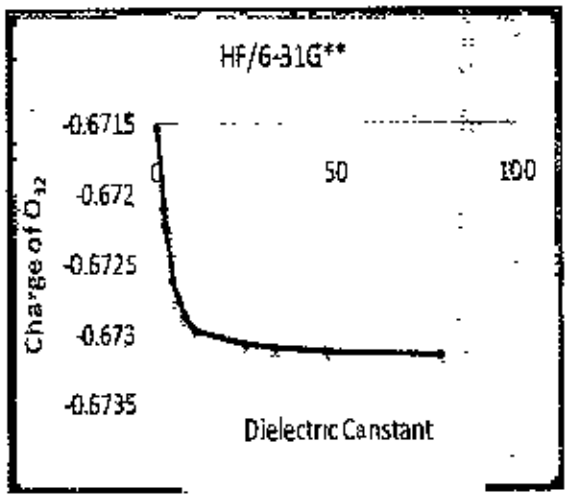

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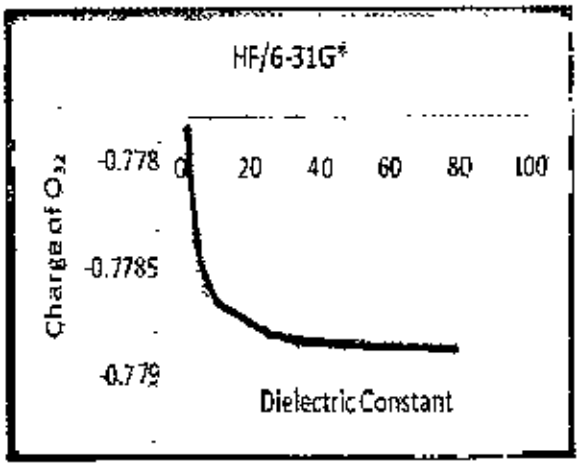

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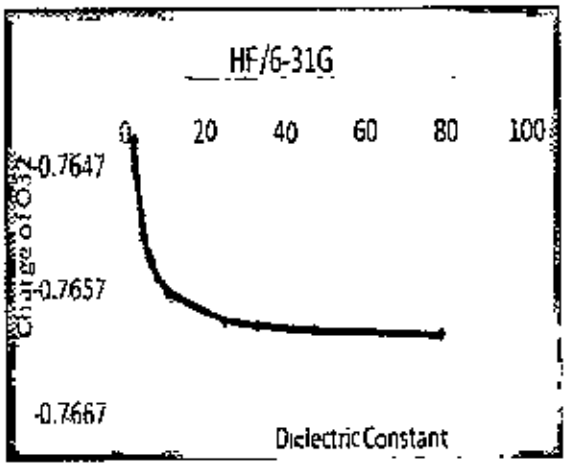

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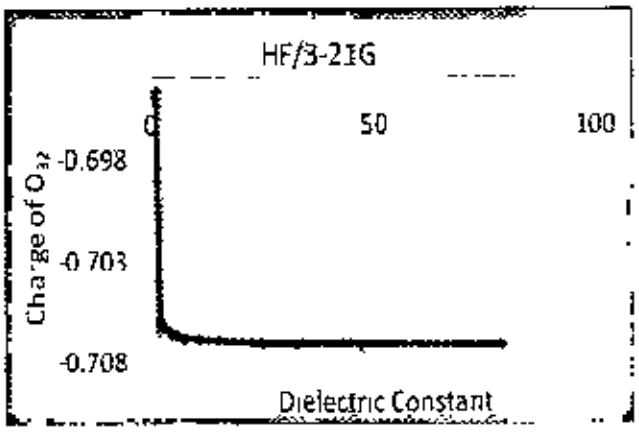

5)

Fig.3. Charge of O32 versus dielectric constant in PAM 120 1) B3LYP/6-31G**, 2) HF/6-31G**,3) HF/6-31G*, 4) HF/6-31G, 5) HF/3-21G.

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