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Theoterical study of benidipine and benidipine hydrochloride

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Abstract
Ground state geometry, molecular properties and electronic structure for Benidipine and Benidipine Hydrochloride in gas, octanol, DMF and water phase were reported at B3LYPl evel. 6-311G (d,p), 6-311++G (d,p) and, 6-311++G (2d,2p) basis sets were used for Benipidine and only 6-311G (d,p) basis set was used for Benidipine Hydrochloride. The NBO analysis were performed to understand the intra-molecular delocalization along with the inter-molecular interaction. The effects of solvents such as DMF, octanol, and water on the optimized geometry and intra-molecular delocalization of Benidipine and Benidipine Hydrochloride molecules were evaluated. Electronic properties of the title compound such as frontier orbitals and their corresponding energy gap were calculated by DFT approach. Solvation free energy values in different solvents decrease in the order water > DMF > n-octanol, and HOMO-LUMO energy gap values follow the order of gas > octanol > DMF > water for BEN and BENHCl molecule.
Thermodynamic parameters such as SEZPE,:SETE,: SETEmt and SETFE values, Rotational constants, Entropy, Thermal Energy and Thermal Capacity, as well as the change of thermodynamic properties such as the heat capacity, entropy, enthalpy, Gibba free energy in the temperature range of 200-1000 K were calculated from the data obtained by DFT.

Keywords: Benidipine hydrochloride, DFT

Introduction

Benidipine (BEN), a 1,4-dihydropyridine calcium channel blocker that has clinical advantages and has been used successfully in the treatment of hypertension and angina pectoris, has an improved pharmacodynamic profile [1].

The electro oxidative behavior of Benidipine was examined using glassy carbon and boron-doped diamond electrodes. The oxidation mechanism of Benipidine, BEN, was elucidated using cyclic voltammetry depending on pH values and working electrodes. They also reported using phase-liquid chromatography that Benipidine is a weak monoprotic base [2].

This study has three-folds: first, carrying out a detailed investigation of electrochemical behavior of BEN; second, its quantitative determination at carbon-based electrodes by using cyclic (CV), linear sweep (LSV), and pulse voltammetric techniques and by using RP-LC with stability tests performing based on ICH standards; and third, determining the pKa value of BEN by using RP-LC.

It has been reported that Benidipine hydrochloride may play a certain protective role in cerebral I/R injury, and this effect may be related to the improvement in the antioxidant capacity of brain tissue and the inhibition of excessive production of inflammatory cytokines [3].

Much effort has been spent over the years to develop solvent effects theoretically and to incorporate them practically into quantum mechanical calculations. Quantum mechanical investigation of solvent effects can be done in two main areas. The first are simulation methods such as molecular dynamics, Monte Carlo, which use a classical force field and explicit manipulation of solvent molecules [4]. The second focuses on the use of self-consistent reaction field (SCRF) continuum models, where the explicit solvent structure is not taken into account [5]. However, the main advantage of the second over the first is that the electronic distribution of the solute can be handled quantitatively and the polarization effects can be evaluated at low cost, and there are many developed SCRF methods [6, 7].

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They reported that Benidipine reduces the formation of Reactive oxygen species by polymorphonuclear cells of hypertensive patients, partly by reducing blood pressure, and the formation of Reactive oxygen species by polymorphonuclear cells may be a marker of long-term antihypertensive treatment and intravascular oxidative stress in humans [8].They reported that Benidipine tilts the balance between ERK1/2 and p38 MAPK towards an antiapoptotic state, reduces mitochondrial cytochrome c release, reduces caspase-9 activation, and attenuates subsequent caspase-3 activation and postischemic myocardial apoptosis [9].

In this study, the highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LOMO) energy, geometry, solvation free energy, molecular electrostatic potential (MESP), charge for BEN and BENHCl were analyzed in different solvents such as octanol, DMF and water. We carried out a comprehensive study on its effects on molecular properties such as distribution. The chemical reactivity of Bu BEN and BENHCl in various solvents using DFT can provide a better understanding of these systems and may also be potentially useful in the development of pharmaceutical and (bio) chemical products.

Materials and Methods
In this study, theoretical calculations of BEN compound were made using the Density Functional Theory (DFT) method, and B3LYP functionals including Becke's three-parameter exchange functional [10] and Lee, Yang, and Parr's correlation functional, which are among the most widely used exchange-correlation functionals and basis sets 6-311G (d,p), 6-311++G(d,p), 6-311++G (2d,2p), in gas, n-octanol, DMF and, water environment were performed and for BENHCl compound B3LYP functional and 6-311G (d,p) basis set were used.

Parameters such as the energy of the lowest electron-empty molecular orbital (ELUMO) and the energy of the highest electron-occupied molecular orbital (EHOMO) reflect the molecular orbital energies, which play an important role in activating many chemical reactions and determining the molecular electronic transition [11] [12] and EHOMO and ELUMO, which characterize the susceptibility of molecules to attack by electrophiles and nucleophiles, respectively, are directly related to ionization potential and electron affinity and can be calculated from Equations 1 and 2.described here with their proper references. The details of the study area should also be provided.

$$I = -E_{HOMO} \tag{1}$$

$$A = -E_{LUMO} \tag{2}$$

Parameters such as hardness (η), softness (S), electronegativity (χ),chemical potential (μ), electrophilicity index (ω), nucleofugality (ΔE_n), electrofugality (ΔE_e), electron donating power (ω^-) and electron accepting power (ω^+), respectively are calculated from EHOMO and ELUMO value as following.

$$\eta_s = \frac{1}{2}(I_s - A_s) \tag{3}$$

$$\eta = \frac{1}{2}(E_{LUMO} - E_{HOMO}) = \frac{1}{2}(I - A) \tag{4}$$

$$\Delta E = E_{LUMO} - E_{HOMO} \tag{5}$$

$$S = \frac{1}{2\eta} \tag{6}$$

$$\chi = -\frac{1}{2}(E_{HOMO} + E_{LUMO}) \tag{7}$$

$$\mu = -\chi = \frac{1}{2}(E_{HOMO} + E_{LUMO}) \tag{8}$$

$$\omega = \frac{\mu^2}{2\eta} \tag{9}$$

$$\Delta E_n = \frac{(\mu + \eta)^2}{2\eta} \tag{10}$$

$$\Delta E_e = \frac{(\mu - \eta)^2}{2\eta} \tag{11}$$

$$\omega - = (3I + A)^2 / (16(I - A)) \tag{12}$$

$$\omega + = (I + 3A)^2 / (16(I - A)) \tag{13}$$

Thermodynamic parameters such as SEZPE,: SETE,: SETEmt and SETFE values, Rotation constants, Entropy, Thermal Energy and Thermal Capacity were calculated. Additionally, its change in the temperature range of 100-1000 K was calculated from the data obtained by DFT.

Results
Benidipine has the formula 1, 4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine-dicarboxylic acid methyl 1-(phenylmethyl)-3-piperidinyl ester hydrochloride. It is a synthetic dihydropyridine derivative with anti-hypertensive and anti-anginal effects. It is manufactured by Kyowa Hakko in Japan, has been submitted for FDA approval, and is now available in some Asian countries such as India and Japan (https://go.drugbank.com/drugs/DB09231).

Benidipine HCl (BENCl), (±)-(R')-3- [(R')-1-benzyl-3-piperidyl] methyl 1,4 dihydro-2,6-dimethyl-4-(m-nitrophenyl) 3,5-pyridene carboxylate hydrochloride is a dihydropyridine-derived calcium channel blocker with general properties similar to those of nifedipine. Optimization of 1,4 Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid. methyl 1-(phenylmethyl)-3-piperidinyl ester (BEN) was performed with B3LYP functional and 6-311G(d), p), 6-311++G(d,p), 6-311++G (2d,2p) basis sets in gas, octanol, DMF, and water media, and optimization of 1,4 Dihydro-2,6-dimethyl-4-(3-nitrophenyl) 3,5-pyridine dicarboxylic acid methyl 1-(phenylmethyl)-3-piperidinyl ester HCl (BENCl) was calculated with B3LYP functional and 6-311G (d,p) basis set in gas, octanol, DMF, and water media. The geometries of BEN and BENCl molecules were optimized without any symmetry restrictions.

The optimization form, HOMO, LUMO, and electron density graphs of BEN and BENHCl compounds calculated with the 6-311G (d, p) basis set at the B3LYP level in the gas phase are given in Figure 1, and 2. In the calculation performed with the 6-311G (d, p) basis set at the B3LYP level and gas phase, the 133rd orbital of the BEN compound shows HOMO, and the 134th orbital shows LUMO. The 143rd orbital of the BENCl compound shows HOMO, and the 144th orbital shows LUMO. As seen in Figures 1 and 2, there are two phenyl rings in BEN and BENCl compounds,

one of which has a nitro group and the other has a methyl group. The difference between the BEN compound and the BENHCl compound is that in the BENHCl compound, there is the HCl compound on the side where the nitro group is attached. Changes in the electronic properties of the BEN molecule of this compound in the article were examined.
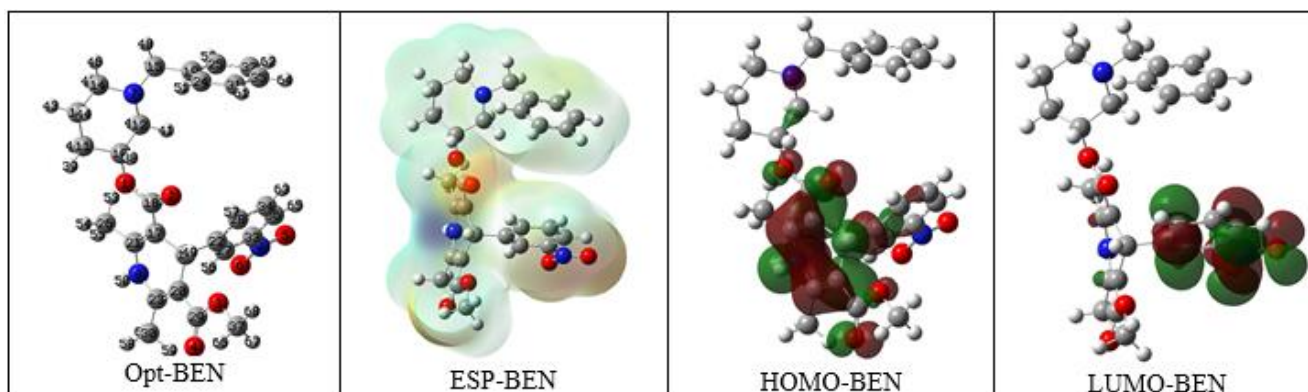

Fig 1: Optimized structure of compound I with B3LYP functional and 6-311G (d,p) basis set, ESP, HOMO and LUMO images
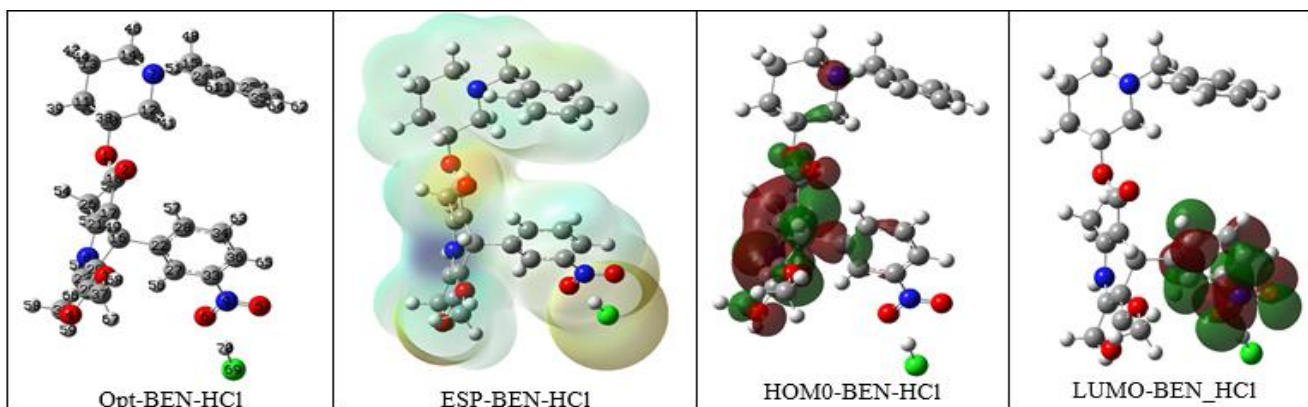

Fig 2: Optimized structure of compound I with B3LYP functional and 6-311G (d,p) basis set, ESP, HOMO and LUMO images

The HOMO of the BENHCl compound consists of O1, O2, O4, N7, N8, C16, C17, C20, C21, C22, C23, and H49 atoms, and the percentage contributions of these atoms to HOMO are 1.38, 3.84, 4.74, 1.38, 20.40, 1.81, 23.26, 21.98, 4.65, 4.26, and 4.21, respectively. Its LUMO consists of O5, O6, N9, C27, C28, C33, and C36 atoms, and the contributions of these atoms to HOMO as a percentage are 22.33%, 19.52, 27, 29, 7.85, 9.86, 2.94, and 8.18, respectively, The dielectric coefficients of water, DMF, and n-octanol are 80.1, 36.7, and 10.3, respectively. As the medium's dielectric coefficient changes, the atoms' contributions to HOMO and LUMO also change. In the BEN compound, it was observed that the contributions of O1, C17, C18, C20, H49 atoms to HOMO increased with the increase of the dielectric coefficient of the medium, while the coefficients of O2, O4, N8, C16, C22 atoms decreased with the increase of the dielectric coefficient. Again, in the same compound, it was observed that the contributions of O5, O6, N9, and C27 atoms to LUMO increased with the increase of the dielectric coefficient of the medium, while the coefficients of C28, C33, and C36 atoms decreased with the increase of the dielectric coefficient.

Table 1: The percentage contribution of the atoms of these compounds BENCl and BEN compounds to HOMO and LUMO in the gas, ethanol, DMF, and water phases in B3LYP level and 6-311G (d,p) basis set.

Atoms	Gas	Octanol	DMF	Water	Gaz	Octanol	DMF	Water
	HOMO-BEN				**HOMO-BENHCl**			
O1	1.24	1.54	1.57	1.57	1.38	1.53	1.56	1.56
O2	3.89	3.83	3.83	3.84	3.84	3.81	3.82	3.82
O4	4.72	4.60	4.58	4.58	4.74	4.59	4.58	4.58
N7					1.38			
N8	20.64	20.58	20.57	20.57	20.40	20.59	20.60	20.60
C16	1.90	1.79	1.77	1.77	1.81	1.76	1.75	1.75
C17	23.50	24.10	24.21	24.22	23.26	24.06	24.19	24.21
C18		1.05	1.07	1.07		1.04	1.06	1.07
C20	22.16	22.44	22.43	22.43	21.98	22.47	22.47	22.47
C21	4.78	4.29	4.25	4.24	4.65	4.26	4.23	4.22
C22	4.39	4.28	4.26	4.26	4.26	4.19	4.19	4.19
C23	4.30	3.65	3.56	3.55	4.21	3.64	3.56	3.54
H49	1.91	1.93	1.93	1.93	1.86	1.99	1.99	1.99

	LUMO-BEN				LUMO-BENHCl			
O5	20.10	20.81	20.85	20.85	22.33	22.69	22.72	22.72
O6	17.97	20.75	20.80	20.81	19.52	19.53	19.52	19.51
N9	24.65	26.86	27.03	27.06	27.29	28.83	28.96	28.99
C27	7.66	7.89	7.90	7.90	7.85	7.88	7.88	7.88
C28	10.91	10.01	9.94	9.93	9.86	9.37	9.33	9.33
C33	4.53	3.34	3.25	3.23	2.94	2.11	2.04	2.02
C36	8.52	8.09	8.06	8.06	8.18	7.95	7.94	7.93

Mulliken atomic charges of the compound BEN, B3LYP functional and basis sets 6-311G (d,p), 6-311++G(d,p), 6-311++G (2d,2p), in the gas, ethanol, DMF, and water phase were calculated, and the Mulliken atomic charges of the BENHCl compound were calculated in the gas, ethanol, DMF, and water phases with the B3LYP functional and 6-311G (d,p) basis set and are given in Table 2 and S1-S4.

Mulliken population analysis [13], based on wave function partitioning and for orbital-based population methods, uses orbital partitioning schemes that take into account atomic orbital overlap and overlapping population. The Mulliken charge for atom k is calculated as follows, using the difference between the atomic number (Zk) of atom k and the sum of basis functions centered on atom k plus the overlap contribution from basis set functions centered on other atoms [14].

$$\left(\sum_{i \varepsilon k} P_{i,i} + \sum_{i \varepsilon k} \sum_{i \varepsilon k} S_{i,j} P_{i,i} \right)$$

In the calculation performed with the B3LYP functional and 6-311G (d,p) basis set in the BEN compound, the charge densities on the O1, O2, O3, O4, O5 and O6 atoms are -0.385, -0.372; -0.343; -0.377; -0.273; -0.278 ē, respectively; in the calculation performed with B3LYP functional and 6-311++g(d,p) basis set, they were found to be 0.225; -0.168; -0.033; -0.256; 0.012; 0.002 ē, and in the calculation made with the 6-311++g(2d,2p) basis set; -0.294; -0.389; -0.380; -0.483; -0.140; -0.146 ē, and in the calculation performed with B3LYP functional and 6-311G (d,p) basis set in the BENCl compound; -0.384 -0.373; -0.344; -0.374; -0.250; -0.302 ē.

While there is no significant change in the Mulliken atomic charges of O1, O2, O3, and O4 atoms of BEN and BENHCl compounds, there are significant changes in the Mulliken atomic charge densities of O5 and O6 atoms.

While the charge densities of the N7, N8, and N9 atoms of the BEN compound are -0.397, -0.438 and 0.174 ē, respectively, the charge densities of the N7, N8 and N9 atoms of the BENHCl compound are -0.438 0.188, and -0.399 ē, respectively; While the Mulliken atomic charge densities of the C22, C27, C28, C33, C34, and C35 atoms in the phenyl ring of the BEN compound to which the nitro group is attached are -0.048, -0.015, -0.021, 0.114, -0.098, and -0.092 ē, respectively, in the BENHCl are 0.050, -0.007, -0.018, 0.122, -0.097, and -0.093 ē, respectively. As can be seen, slight changes of the phenyl ring to which the nitro group is attached in the BENHCl compound and the BEN compound.

Table 2: Mulliken atomic charges calculated in the gas phase of the compound BEN and BenHCl for B3LYP functional

GAZ Atoms	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p	6-311G (d,p)	GAZ Atoms	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p	6-311G (d,p)
		BEN		BenHCl			BEN		BenHCl
O1	-0.385	0.225	-0.294	-0.384	C21	0.235	-0.211	0.090	0.238
O2	-0.372	-0.168	-0.389	-0.373	C22	-0.048	0.818	0.569	-0.050
O3	-0.343	-0.033	-0.380	-0.344	C23	0.226	0.279	0.346	0.224
O4	-0.377	-0.256	-0.483	-0.374	C24	-0.037	-0.062	0.043	-0.037
O5	-0.273	0.012	-0.140	-0.250	C25	-0.061	-0.174	-0.265	-0.061
O6	-0.278	0.002	-0.146	-0.302	C26	-0.220	-0.671	-0.493	-0.224
N7	-0.397	0.378	0.027	-0.399	C27	-0.015	-0.415	-0.382	-0.007
N8	-0.438	-0.003	-0.057	-0.438	C28	-0.021	-0.507	-0.339	-0.018
N9	0.174	-0.220	0.019	0.188	C29	0.439	0.201	0.610	0.439
C10	0.035	-0.624	-0.201	0.036	C30	-0.251	-0.718	-0.530	-0.249
C11	-0.206	0.021	0.053	-0.206	C31	-0.090	-0.169	-0.160	-0.090
C12	-0.045	-0.468	-0.370	-0.047	C32	-0.092	-0.332	-0.234	-0.093
C13	-0.201	-0.529	-0.321	-0.201	C33	0.114	-0.221	0.135	0.122
C14	-0.071	-0.171	-0.063	-0.071	C34	-0.098	-0.617	-0.419	-0.097
C15	-0.010	-0.779	-0.435	-0.008	C35	-0.092	-0.376	-0.307	-0.093
C16	-0.123	-0.118	-0.228	-0.122	C36	-0.043	0.196	-0.068	-0.040
C17	-0.250	0.097	-0.087	-0.251	C37	-0.107	-0.236	0.028	-0.108
C18	0.460	-0.479	0.241	0.459					-0.265
C19	-0.164	0.807	0.630	-0.165					0.193
C20	-0.283	-0.397	-0.222	-0.288					

In the calculation made in the BEN compound with B3LYP functional and 6-311G (d,p) basis set in gas, n-propanol, DMF and water environments, as the dielectric coefficient of the medium increased, the negative charges on O1 and N8 atoms decreased, but The negative charges on O2, O3, O4, O5, O6 and N7 atoms have increased. There was an increase in the positive charge density of the N9 atom. The N9 atom belongs to the nitro group and is bonded to the more electronegative O atom. The Mulliken charge value of the N9 atom in the BENHCl compound is 0.188, which is higher than the Mulliken charge value of the N9 atom of the BEN compound. As the dielectic coefficient of the medium increased, the Mulliken charge value of the N9 atom in the BENHCl compound increased. (n-octanol was found to be

0.199; 0.201 and 0.201 in DMF and water phases, respectively.

Mulliken atomic charges obtained for the gas phase in BEN and BENHCl compounds are consistent with those calculated for n-octanol, DMF, and water environments. The mean square deviation (R2) was calculated to demonstrate the consistency of the results obtained for gas, n-octanol, DMF and water environments. The correlation coefficients (R2) between the Mulliken atomic charges calculated in the gas phase in the BEN molecule and the Mulliken atomic charges calculated in DMF, n-octanol, and water are 0.9972, 0.9975 and, 0.9968, respectively; The correlation coefficients (R2) between the Mulliken atomic charges calculated in the gas phase in the BENHCl molecule and the Mulliken atomic charges calculated in DMF, n-octanol and water were found to be 0.9969, 0.9975 and 0.9969, respectively [15].

Some selected bond lengths of the compound BEN, B3LYP functional and basis sets like 6-311G (d,p), 6-311++G(d,p),

6-311++G (2d,2p), in the gas, ethanol, DMF and, water phase, and some selected bond lengths of the BENHCl compound calculated with the B3LYP functional and 6-311G (d,p) basis set were in the gas, ethanol, DMF, and water phases are given in Table 4.3 and Table S.4-S7. The C18-O2 bond length of the Corboxyl group in the BEN compound was determined using the B3LYP functional and 6-311G (d,p), 6-311++G(d,p), and 6-311++G (2d,2p) basis sets and It was found as 1.216, 1.216 and 1.215 Å, respectively.

The C18-O2 bond length belonging to the carboxylic group of the BENHCl compound was found to be 1.216 Å in the calculation made with the B3LYP functional and 6-311G (d,p) basis sets. The C29-O4 bond length of the other carboxylic group is calculated using the B3LYP functional and 6-311G (d,p), 6-311++G(d,p), and 6-311++G (2d,2p) basis sets is found as 1.215; be 1.216 and 1.215 Å, respectively.

Table 3: Some selected bond lengths (Å) of BEN and BENHCl compound optimized in gas environment with B3LYP functional

GAZ	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p)	6-311G (d,p)	GAZ	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p	6-311G (d,p)
		Gas		HCl-gas			Gas		HCl-gas
N7-C15	1.463	1.464	1.463	1.463	C29-C20	1.475	1.472	1.470	1.475
N7-C12	1.463	1.463	1.462	1.462	C29-O4	1.215	1.216	1.215	1.214
N7-C114	1.463	1.464	1.463	1.463	C37-O3	1.436	1.437	1.436	1.436
C10-O1	1.452	1.453	1.451	1.453	N9-C33	1.479	1.478	1.474	1.471
C18-01	1.360	1.360	1.358	1.359	N9-O5	1.224	1.226	1.226	1.219
C18-O2	1.216	1.216	1.215	1.216	N9-O6	1.225	1.227	1.227	1.236
C21-N8	1.386	1.388	1.385	1.387	O6-H70				1.907
N8-H50	1.008	1.008	1.005	1.008	O5-H70				2.867
C23-N8	1.388	1.387	1.385	1.388	H70-Cl				1.307

The C18-O2 bond length belonging to the Corboxyl group of the BENHCl compound in the calculation made with the B3LYP functional and 6-311G (d,p) basis sets was found to be 1.214 Å. As can be seen, the C18-O2 bond length in the BENHCL compound is larger than the C18-012 bond length in the BEN compound, but the opposite is true for the C29-O4 bond length,

The distance between the N atom of the nitro group and the C atom of the phenyl group (N9-C33), calculated with the B3LYP functional and 6-311G (d,p) basis set in the gas phase, was found to be 1.479 Å in the BEN compound and 1.471 Å in the BENHCl compound. In the calculations made in n-octanol, DMF and, water environment, the N9-C33 bond length in the BEN compound is 1.474, 1.473 and, 1.473 Å While it was found as 1.465, 1.464 and, 1.464 Å in the BENHCl compound. As can be seen, in both compounds, the N9-C33 bond length increases as the dielectric coefficient of the medium increases.

Since thermodynamic parameters contribute to obtaining information about whether a chemical reaction takes place or not, thermodynamic data are used to examine the reaction mechanisms of organic compounds. In the DFT method, with B3LYP) functional and 6-311G (d,p), 6-311++G(d,p), 6-311++G (2d,2p) basis sets, at 298.150 K and 1 atm pressure, Thermodynamic parameters such as Sum of Electronic and Zero Point Energies (SEZPE), Sum of Electronic and Thermal Energies (SETE), Sum of Electronic and Thermal Enthalpies (SETEmt) and Sum of Electronic and Thermal Free Energy (SETFE), Rotational constants, Entropy, Thermal Energy, Thermal Capacity of the compound BEN were calculated in gas, n-octanol, DMF and

water phase, and the thermodynamic parameters of the BENHCl compound with the 6-311G (d,p) basis set were calculated and are given in Table 4 and Table S7-S9.

SEZPE, SETE, SETEmt and, SETFE values Rotational constants Entropy: Thermal Energy Thermal Capacity are given in au, GHz, cal/molK, Kcal/mol Cal/Mol-Kelvin units, respectively. The thermodynamic parameters of the BENHCl compound were calculated with the 6-311G (d,p) basis set in the gas, n-octanol, DMF, and water phases and are given in Table 4.10-Table 4.15. SEZPE, SETE, SETEmt and SETFE values calculated with 6-311G (d,p) in the gas phase of the compound BEN were calculated as -1701.057999; -1701.023184; -1701.022240 and -1701.130822 au, respectively. In the BENHCl compound, it was calculated as -2161.894125, -2161.856448, -2161.855504 and, -2161.972638 au, respectively. It is seen that as the dielectric constant of the medium increases, the SEZPE, SETE, SETEmt and, SETFE values of both BEN and BENHCl compounds decrease.

The compound BEN has been studied with different basis sets. The same situation was observed in other basis sets studied. Thermal energy increased as the dielectric coefficient of the medium increased, but thermal capacity decreased as the dielectric coefficient of the medium increased.

Thermodynamic parameters are helpful in understanding chemical processes. DFT is a well-established and effective tool for estimating these parameters [16].

Correlations between statistical thermodynamics versus the temperature were obtained using the B3LYP level. Since the intensity of molecular vibrations increases with temperature,

it is seen that heat capacities, entropies, and enthalpies increase with increasing temperature. The correlation graphs between the heat capacity, entropy, enthalpy, Gibbs free energy versus the temperature of BEN BENHCL compounds calculated in gas phase with 311G(d,p) basis set are given in Figure 3, 4.

Table 4: SEZPE, SETE, SETEmt and SETFE, Rotational constants, Entropy, Thermal Energy and Thermal capacities of BEN and BENHCl compounds optimized in gas phase with B3LYP functional

|	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p)	6-311G (d,p)
	BEN			BENHCl
SEZPE	-1701.057999	-1701.086013	-1701.141752	-2161.894125
SETE	-1701.023184	-1701.051258	-1701.107114	-2161.856448
SETEmt	-1701.022240	-1701.050314	-1701.106170	-2161.855504
SETFE	-1701.130822	-1701.158916	-1701.214083	-2161.972638
Dönme sabitleri				
A	0.13056	0.13068	0.13064	0.10493
B	0.06338	0.06336	0.06383	0.04997
C	0.05317	0.05273	0.05293	0.04422
Entropi				
Ötelenme	44.546	44.546	44.546	44.751
Dönme	37.833	37.84	37.83	38.469
Titreşim	146.151	146.185	144.746	163.309
Toplam	228.53	228.572	227.122	246.529
Termal Enerji				
Ötelenme	0.889	0.889	0.889	0.889
Dönme	0.889	0.889	0.889	0.889
Titreşim	367.922	367.603	368.29	375.339
Toplam	369.699	369.38	370.068	377.116
Termal Kapasite				
Ötelenme	2.981	2.981	2.981	2.981
Dönme	2.981	2.981	2.981	2.981
Titreşim	125.026	125.111	124.786	133.311
Toplam	130.988	131.073	130.748	139.272
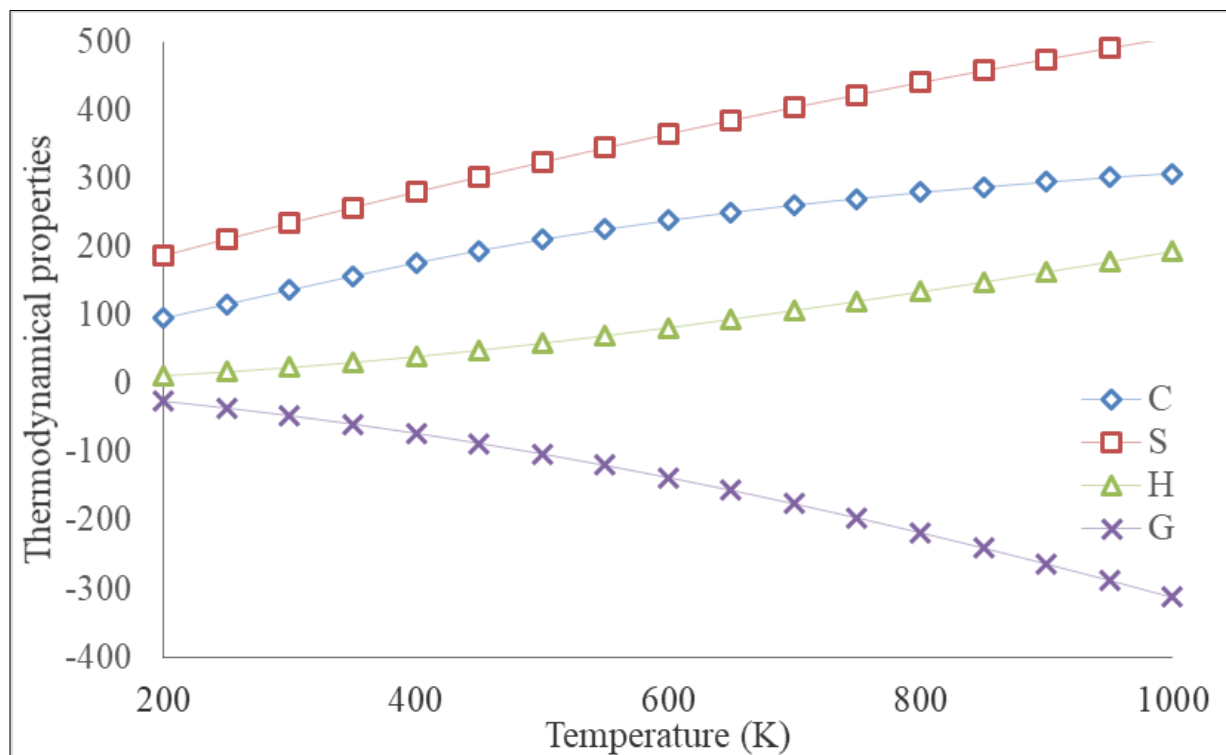
Fig 3: Correlation graphs between heat capacity, entropy and, enthalpy and, Gibbs free energy versus temperature for BEN calculated in the gas phase and with the 6-311G (d,p) basis set

As shown from Figure 3 and Figure 4, standard heat capacities, entropies and enthalpies and, Gibbs free energy values vary at any temperature from 200 K to 1000 K. temperature causes the intensity of molecular vibration to increase.
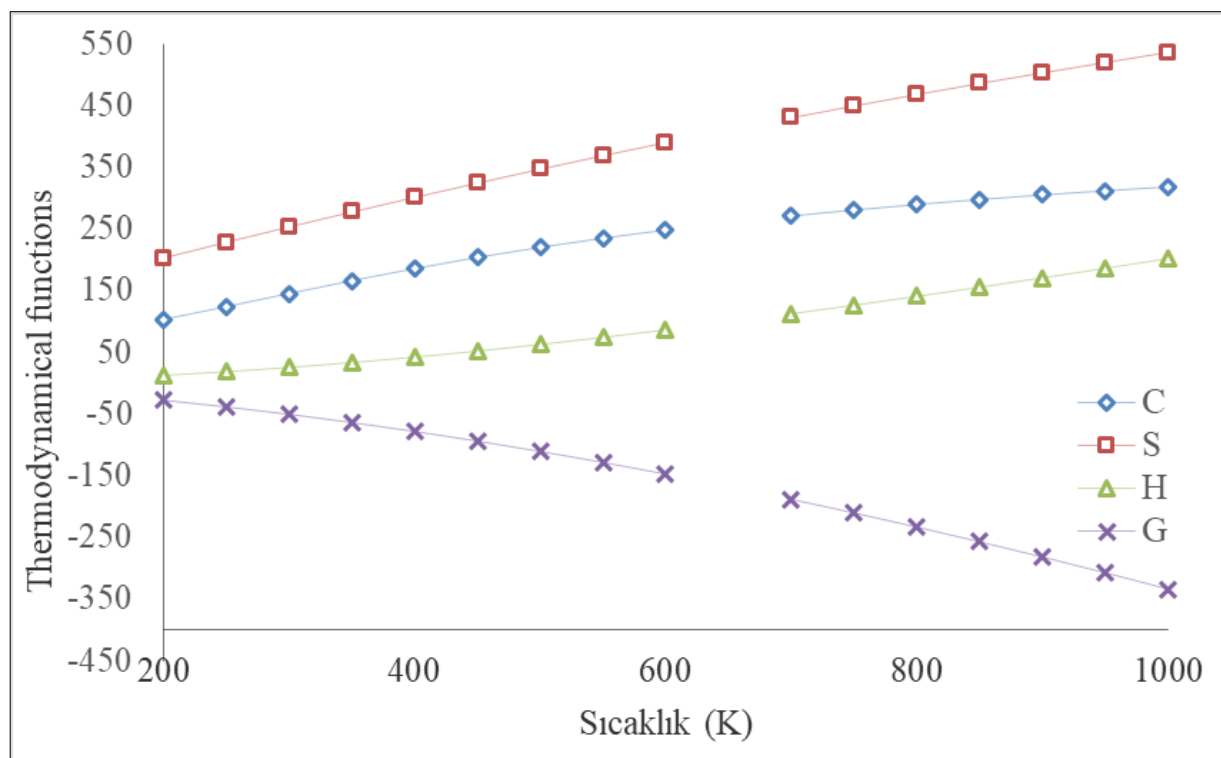
Fig 4: Correlation graphs between heat capacity, entropy and, enthalpy and, Gibba free energy versus temperature for BENHCl calculated in the gas phase in the 6-311G (d,p) basis set

The correlation equations between entropy, heat capacity, enthalpy, Gibbs free energy changes and temperatures were created by quadratic formulas, and the corresponding correlation factors (R2) for these thermodynamic properties were 1.00, 0.9997, 0.9997 and, 1.00, respectively, in the BEN molecule in the gas environment has been found (Table 5).

Table 5: Correlation equations between entropy, heat capacity, enthalpy and Gibbs free energy changes of BEN and BENHCl compounds with temperature

Properties	BEN gas	R²	BEN DMF	
S	$y = -0.0001x^2 + 0.537x + 84.372$	1	$y = -0.0001x^2 + 0.537x + 84.372$	1
C	$y = -0.0002x^2 + 0.5454x - 4.338$	0.9997	$y = -0.0002x^2 + 0.5454x - 4.338$	0.9997
H	$y = 0.0001x^2 + 0.0753x - 10.453$	0.9997	$y = 0.0001x^2 + 0.0753x - 10.453$	0.9997
G	$y = -0.0002x^2 - 0.1213x + 7.0848$	1	$y = -0.0002x^2 - 0.1213x + 7.0848$	1
	BenHCl gas		**BENHCl DMF**	
S	$y = -0.0001x^2 + 0.5696x + 93.455$	1	$y = -0.0001x^2 + 0.5696x + 93.455$	1
C	$y = -0.0002x^2 + 0.5553x + 1.1804$	0.9997	$y = -0.0002x^2 + 0.5553x + 1.1804$	0.9997
H	$y = 1E-04x^2 + 0.1157x - 18.028$	0.9963	$y = 1E-04x^2 + 0.1157x - 18.028$	0.9963
G	$y = -0.0002x^2 - 0.1897x + 19.973$	0.9969	$y = -0.0002x^2 - 0.1897x + 19.973$	0.9969
	BEN n-octanol		**BEN water**	
S	$y = -0.0001x^2 + 0.537x + 84.508$	1	$y = -0.0001x^2 + 0.537x + 84.508$	1
C	$y = -0.0002x^2 + 0.5454x - 4.3457$	0.9997	$y = -0.0002x^2 + 0.5454x - 4.3457$	0.9997
H	$y = 0.0001x^2 + 0.0753x - 10.453$	0.9997	$y = 0.0001x^2 + 0.0753x - 10.453$	0.9997
G	$y = -0.0002x^2 - 0.1213x + 7.0848$	1	$y = -0.0002x^2 - 0.1213x + 7.0848$	1
	BENHCl n-octanol		**BENHCl water**	
S	$y = -0.0001x^2 + 0.5696x + 93.448$	1	$y = -0.0001x^2 + 0.5696x + 93.448$	1
C	$y = -0.0002x^2 + 0.5554x + 1.1589$	0.9997	$y = -0.0002x^2 + 0.5554x + 1.1589$	0.9997
H	$y = 0.0001x^2 + 0.0826x - 11.007$	0.9997	$y = 0.0001x^2 + 0.0826x - 11.007$	0.9997
G	$y = -0.0002x^2 - 0.1346x + 8.2861$	1	$y = -0.0002x^2 - 0.1346x + 8.2861$	1

The quadratic equations for BEN molecule are given below, respectively.

$S = -0.0001T^2 + 0.5362T + 84.19$
$C = -0.0002T^2 + 0.5429T - 3.9012$
$H = 0.0001T^2 + 0.0751T - 10.368$
$G = -0.0002T^2 - 0.121T + 7.1221$

These data help provide information for further studies on the compound BEN and BENHCl, with the aim of calculating other thermodynamic energies according to the relationships between thermodynamic functions and predicting the directions of chemical reactions according to the second law of thermodynamics.

Solvation Energy
The effect of the solvent on the chemical system is measured very accurately by the free energy of dissolution of the solute. The free energy of dissolution is one of the

fundamental thermo physical properties in the study of thermochemistry in solution, where most real-life chemistry occurs. In theoretical studies of solution chemistry, the estimation of free energies allows the evaluation of reaction rates and equilibrium constants of physical or chemical reactions of interest. CPCM is a polarizable continuum model that considers the polarization of solute and solvent molecules in the continuum, whereas PCM models the solvent as a polarizable continuum medium but assumes that the solute is nonpolarizable.

In the DFT method, solvation energy was calculated in gas, n-octanol, DMF, and water phase with B3LYP functionals and 6-311G (d,p), 6-311++G(d,p), 6-311++G basis set with cpcm model and also BENHCl solvation energy of the compound were calculated with the B3LYP functional and 6-311G (d,p) basis set in the gas, n-octanol, DMF, and water phases and are given in Table 6.

The free energy of dissolution (ΔG) is calculated according to the following equation

$$\Delta G = G(sol) - G(gas)$$

Where, G(gas) is the sum of electronic and thermal free energy in the gas phase;

G(sol) is the sum of the electronic and thermal free energy of the solvent.

Solvation free energy in different solvents decreases in the order of water > DMSO > n-octanol [17]. The solvation energies gradually increased from a high dielectric constant to a low dielectric constant; that is, as the polarity of the solvent decreases, the free energy increases [18].

Table 6: Solvation free energy in different solvents (kcal mol-1)

Solvent	6-311G (d,p)	6-311++g(d,p)	6-311++g(2d,2p)	6-311G (d,p)
	BEN			BENHCl
n-octanol	-12.2647	-13.2957	-12.7736	-13.2241
DMF	-13.6057	-14.8594	-13.9376	-14.4346
Su	-13.8849	-15.0948	-14.1936	-14.6869

In the DFT method, with B3LYP functionals and 6-311G (d,p), 6-311++G(d,p), 6-311++G (2d,2p) basis sets HOMO energy (EHOMO), LUMO energy (ELUMO), HOMO and LUMO energy difference (ΔE) Parameters such as hardness (η), softness (S), electronegativity (χ), chemical potential (μ), electrophilicity index (ω), nucleofugality (ΔE_n), electrofugality (ΔE_e), electron donating power ($\omega-$) and electron accepting power ($\omega+$) calculated from EHOMO and ELUMO of compound BEN in gas, n-octanol, DMF and water phases and those of compound BENHCl only with 6-311G (d,p) basis set are given in Table 7 and 8.

Table 7: HOMO energy (EHOMO), LUMO energy (ELUMO), HOMO and LUMO energy difference (ΔE) Parameters such as hardness (η), softness (S), electronegativity (χ) for BEN and BENHCl

Solvent	Basis set	E_{HOMO}	E_{LUMO}	ΔE	η	S	χ	overlap
Gaz	6-311(d,p)	-6.04	-2.29	3.75	1.87	0.27	4.16	0.1529723426
	6-311++g(d,p)	-6.16	-2.58	3.58	1.79	0.28	4.37	
	6-311++g(2d,2p)	-6.14	-2.55	3.59	1.79	0.28	4.34	
	6-311(d,p)-HCl	-6.19	-2.88	3.31	1.66	0.30	4.54	0.1119579893
Octanol	6-311(d,p)	-6.01	-2.68	3.33	1.67	0.30	4.35	0.1142953063
	6-311++g(d,p)	-6.10	-3.03	3.07	1.53	0.33	4.57	
	6-311++g(2d,2p)	-6.08	-2.99	3.09	1.54	0.32	4.53	
	6-311(d,p)-HCl	-6.03	-3.11	2.92	1.46	0.34	4.57	0.0983294096
DMF	6-311(d,p)	-6.01	-2.72	3.29	1.65	0.30	4.37	0.1121963548
	6-311++g(d,p)	-6.10	-3.03	3.07	1.53	0.33	4.57	
	6-311++g(2d,2p)	-6.08	-2.99	3.09	1.54	0.32	4.53	
	6-311(d,p)-HCl	-6.03	-3.11	2.92	1.46	0.34	4.57	0.0974712877
Water	6-311(d,p)	-6.01	-2.73	3.28	1.64	0.30	4.37	0.1118051771
	6-311++g(d,p)	-6.10	-3.04	3.06	1.53	0.33	4.57	
	6-311++g(2d,2p)	-6.08	-3.00	3.08	1.54	0.32	4.54	
	6-311(d,p)-HCl	-6.03	-3.12	2.91	1.45	0.34	4.57	0.0973156793

The reactivity of molecules depends on the frontier orbitals called HOMO and LUMO. The occupied molecular orbital with high energy is expressed as HOMO, and the empty molecular orbital with low energy is expressed as LUMO. In addition, HOMO corresponds to the expressions that donate electrons and LUMO corresponds to the expressions that accept electrons. The frontier orbital spacing determines the kinetic stability and chemical reactivity of molecules. The smaller the HOMO LUMO gap, the more easily the molecule can be polarized [19].

In the calculation performed with the B3LYP functional and the basis sets 6-311G (d,p), 6-311++g(d,p) and 6-311++g(2d,2p) in the BEN compound, the EHOMO values are -6.04, -6.16 and, -6.14 ē, respectively, ELUMO values are -2.29, -2.58 and -2.55 respectively; The fact that EHOMO and ELUMO values are affected by the basis set used. In the calculation performed with the B3LYP functional and 6-311G (d,p) basis set in the BENHCl compound, the EHOMO value is found as -.-6.19 ē, and the ELUMO value as -2.88 ē.

In the calculation performed with B3LYP functional and 6-311G (d,p) basis set in BEN compoun in gas, octanol, DMF and water environment ΔE values are 3.75, 3.33, 3.29 and 3.28 ē respectively, in the calculation made with 6-

311++g(d,p) basis set it was found to be 3.58, 3.07, 3.07 and 3.06. As the dielectric coefficient of the medium increases, the HOMO-LUMO energy gap decreases.

Table 8: Chemical potential (μ), electrophilicity index (ω), nucleofugality (ΔE_n), electrofugality (ΔE_e), electron donating power (ω^-) and electron accepting power (ω^+) for BEN and BENHCl

Solvent	Basis set	μ	ω	ΔE_n	ΔE_e	μ/η	$\omega -$	$\omega +$
Gaz	6-311(d,p)	-4.16	4.63	1.40	9.73	2.22	0.255	0.102
	6-311++g(d,p)	-4.37	5.34	1.86	10.60	2.44	0.285	0.124
	6-311++g(2d,2p)	-4.34	5.25	1.81	10.49	2.42	0.281	0.122
	6-311(d,p)-HCl	-4.54	6.21	2.50	11.58	2.74	0.319	0.153
DMF	6-311(d,p)	-4.37	5.80	2.25	10.99	2.66	0.301	0.140
	6-311++g(d,p)	-4.57	6.80	3.00	12.14	2.98	0.341	0.173
	6-311++g(2d,2p)	-4.53	6.66	2.89	11.96	2.94	0.335	0.168
	6-311(d,p)-HCl	-4.57	7.17	3.33	12.47	3.14	0.354	0.186
Octanol	6-311(d,p)	-4.35	5.68	2.16	10.86	2.61	0.296	0.136
	6-311++g(d,p)	-4.57	6.80	3.00	12.14	2.98	0.341	0.173
	6-311++g(2d,2p)	-4.53	6.66	2.89	11.96	2.94	0.335	0.168
	6-311(d,p)-HCl	-4.57	7.17	3.33	12.47	3.14	0.354	0.186
Water	6-311(d,p)	-4.37	5.82	2.27	11.02	2.66	0.302	0.141
	6-311++g(d,p)	-4.57	6.83	3.03	12.17	2.99	0.342	0.174
	6-311++g(2d,2p)	-4.54	6.69	2.92	11.99	2.95	0.336	0.169
	6-311(d,p)-HCl	-4.57	7.19	3.34	12.49	3.14	0.355	0.187

ΔE values of BENHCl compound in gas, octanol, DMF and water environment were calculated as 3.31, 2.92, 2.92 and 2.91, respectively. A low HOMO-LUMO energy gap is required for better NLO properties. The energy gap between HOMO and LUMO can be reduced by increasing conjugation. Structural change is another way to reduce the HOMO-LUMO gap or use of polar solvents is another way to reduce the HOMO-LUMO gap [20].

Conclusion
It was determined that the contributions of atoms to HOMO and LUMO for BEN and BENHCl compounds change depending on the dielectric constant of the medium.
The results of the theoretical investigation showed that the SEZPE, SETE, SETEmt and, SETFE values of both BEN and BENHCl compounds decrease with the increasing of the dielectric constant of the medium for studied basis sets. It was obtained that thermal energy increased as the dielectric coefficient of the medium increased, but thermal capacity decreased as the dielectric coefficient of the medium increased. Mulliken charge distribution of the atoms and bond lengths of atoms bonded to each other for BEN and BENHCl moecule is influenced by the dielectric constant of the medium and used basis set.
The correlation equations between thermodynamic functions and temperatures were fitted by quadratic formulas and it shows that thermodynamic parameters increase with increase in temperature. The chemical and thermal stability of the compound was computed by using DFT method for various temperatures and it shows that thermodynamic parameters increase with increase in temperature.
Solvation free energy in different solvents decreases in the order of water > DMSO > n-octanol
In this computational study, we have examined EHOMO, -ELUMO and parameters related to energy gap in different media for BEN and BENHCl and It has been observed that the parameters change with the dielectric constant of the medium.

Acknowledgments

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