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CALCULATION OF HOMA AND BIRD AROMATICITY INDICES, NLO AND NBO PROPERTIES OF BENIDIPINE*

BENİDİPİNİN HOMA VE BIRD AROMATİKLİK ENDEKSLERİ, NLO VE NBO ÖZELLİKLERİNİN HESAPLANMASI

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Abstract

Benidipine hydrochloride, being the derivate of 1,4-dihydropyridine is a calcium channel blocker antihypertensive drug. The aromaticity, natural bond orbital (NBO) and Nonlinear Optical (NLO) parameters properties of Benidipine (BEN) and BENHCl compounds were theoretically investigated using density functional theory (DFT) electronic structure method. Among the values of common aromaticity indices, the Harmonic Oscillator Aromaticity Model (HOMA) and BIRD's (Aromaticity Index) for electronic delocalization show that the aromaticity of the nitrophenyl group is higher in BEN and BENHCl compounds, and also the aromaticity in the gas phase is higher than that in water, octanol and DMF phase. In compound BEN, it was observed that as the dielectric constant of the medium increased, the aromaticity difference increased slightly. In the compound BEN, the correlation coefficient between HOMA values and aromatic fluctuation index (FLU), para delocalization index (PDI) and para-linear response (PLR) for the nitrophenyl group is higher than that the phenyl group. Donor-acceptor transitions, stabilization energies, intramolecular charge transfer were determined by natural population analyses. NLO parameters such as dipole moment, polarisibility and first order hyperpolarizability values of the BEN and BENHCl compound were also studied.

Keywords: Benidipidine, HOMA, BIRD, natural bond orbital, NLO.

Öz

1,4-dihidropiridin'in türevi olan benidipin hidroklorür, bir kalsiyum kanal bloker antihipertansif ilaçtır. Benidipin (BEN) ve BENHCl bileşiklerinin aromatiklik, doğal bağ orbital (NBO) ve Doğrusal Olmayan Optik (NLO) parametrelerinin özellikleri, yoğunluk fonksiyonel teorisi (DFT) elektronik yapı yöntemi kullanılarak teorik olarak araştırıldı. Ortak aromatiklik indeksi değerlerinden Harmonik Osilatör Aromatiklik Modeli (HOMA) ve elektronik delokalizasyon için BIRD's (Aromatiklik İndeksi), BEN ve BENHCl bileşiklerinde nitrofenil grubunun aromatikliğinin daha yüksek olduğunu, ayrıca gaz fazındaki aromatik de su, oktanol ve DMF fazındakinden daha yüksektir. BEN bileşiğinde ortamın dielektrik sabiti arttıkça aromatiklik farkının bir miktar arttığı gözlendi. BEN bileşiğinde nitrofenil grubu için HOMA değerleri ile aromatik dalgalanma indeksi (FLU), para delokalizasyon indeksi (PDI) ve para-lineer yanıt (PLR) arasındaki korelasyon katsayısı fenil grubuna göre daha yüksektir. Donör-alıcı geçişleri, stabilizasyon enerjileri, molekül içi yük transferi ve doğal popülasyon analizleri ile belirlendi. BEN ve BENHCl bileşiğinin dipol momenti, polarizasyon ve birinci dereceden hiperpolarizasyon değerleri gibi NLO parametreleri de incelenmiştir.

Anahtar Kelimeler: Benidipin, HOMA, BIRD, doğal bağ orbital, NLO.

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1. INTRODUCTION

Aromatics are encounter in our daily lives. The chemistry of our body would be distorted in the absence of aromatic molecules in our system, also, we would be lacking many materials needs. Many industrial raw materials are aromatics based, ranging from polymer, medicine and various other industries (Edim et al., 2021).

Aromaticity, one of the most important concepts in chemistry, still does not have a unified definition (Krygowski et al., 2000). Since aromaticity is a collective phenomenon, various criteria must be used to discuss this term in any particular research topic (Matito et al., 2005).

Benidipine, also known as Benidipinum or Benidipine hydrochloride, a Long-acting T-type Calcium Channel Blocker, is commonly used to treat hypertension and angina pectoris (Seino et al., 2007; Tuncel & Kandemirli, 2024).

Benidipine is a triple calcium channel blocker that inhibits T type as well as L and N type calcium channels. The vasodilator effect of Benidipine, whose molecular formula is $C_{28}H_{32}ClN_3O_6$, is due to its affinity for dihydropyridine binding sites in calcium channels. Since Benidipine binds to calcium channels, it blocks calcium flow. The onset of action is slow, resulting in minimal tachycardia or palpitations (Gopika & Remi, 2018).

In this article, we introduced HOMA, BIRD, PDI, PLR, NLO and FLU indices for BEN and BENHCl compoud in gas, n-octanol, DMF and water phases. Furthermore, we were led to NBO studies on BEN and BENHCl due to their pharmacological importance, but for which there are limited reports on their structural properties. Observations from NBO analysis will shed further light on understanding the stability of the molecule.

2. MATERIAL AND METHOD

2.1. Computational Methods

The structures of BEN and BENHCl molecules in gas, n-octanol, DMF and water phases were realized with Density Functional Theory (DFT) calculations using the Gaussian09 program, with the B3LYP hybrid functional and 6–311G(d,p) basis set and is displayed in Figure 1. n-octanol, DMF and water modeled by the conductor-like polar continuum model (CPCM).

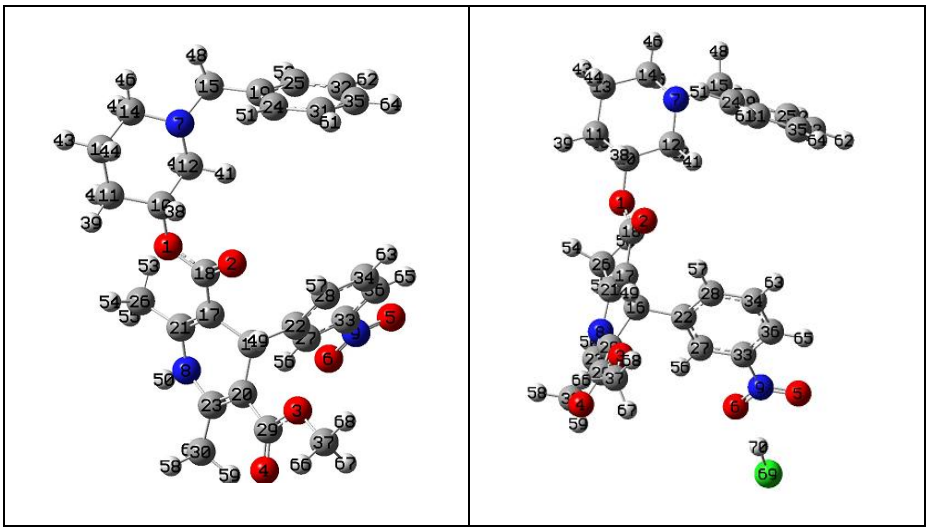

Figure 1. Optimized Molecular Structure with The Atomic Number

HOMA, BIRD, PDI, PLR indices were used to describe the aromaticity of these systems. HOMA index is known as displacement in cyclic structures and was defined by Kruszewski and Krygowski (Krygowski, 1993). PDI and FLU are both based on electron delocalization indices. A detailed NBO (Read et al., 1988) analysis was performed to understand the hyper conjugation interaction, which chiefy contributes for stabilization of BEN and BENHCl compound. With NBO analysis, the role of intermolecular orbital interactions or exchange transfer within a molecule is understood. It is calculated by taking into account all possible interactions between occupied donor and empty acceptor NBOs. Additionally, their energetic importance is predicted by second-order perturbation theory.

2.2. Result and Discussion

When the length of each bond is the same as the optimal value R_{Ref}, HOMA is equal to 1 and the ring is completely aromatic. If HOMA is equal to 0, the ring is not aromatic; if it is negative, the ring is anti-aromatic.

A decrease in the aromatic character of the π-electron system can be recognized by the increase in bond length change and the observed increase in the average bond length of the respective system.

In the DFT method, HOMA and BIRD indices in gas, n-octanol, DMF and water phases are calculated with B3LYP functionals and 6-311G(d,p) basis set and are given in Table 1 and Table S2-S4. The HOMA indices of the phenyl group of the BEN compound in the gas, n-octanol, DMF and water phases were found to be 0,986921, 0,982769, 0,982299 and 0,9822, respectively. The difference between the HOMA value of the phenyl group of the BEN compound in the gas phase and the HOMA values in n-octanol, DMF and water environments is very small and is, found to be as 0,004152, 0,004622 and 0,004721.

The HOMA indices of the nitrophenyl group of the compound BEN in the gas, n-octanol, DMF and water phases were found to be 0,988998, 0,987661, 0,987495, 0,987461, respectively. The difference between the HOMA value of the nitrophenyl group of the BEN compound in the gas phase and the HOMA values in n-octanol, DMF and water environments is very small and is found to be as 0,001337, 0,001503 and 0,001537, respectively.

As the dielectric constant of the medium increased, a slight decrease was observed in the aromaticity of the phenyl group and nitrophenyl group in the BEN compound. However, a slightly irregular change was observed in the BENHCl compound (Gajda et al., 2018). Since the aromaticity values of the phenyl and nitrophenyl groups of BEN and BENHCl compounds are close to 1, HOMA analysis shows that they have relatively strong aromaticity. In BEN and BENHCl compounds, the HOMA values of the nitrophenyl group are higher than the HOMA values of the phenyl group. This excess was found as 0,002077, 0,004892, 0,005196, 0,005261 for the BEN compound and 0,001083, 0,004274, 0,004892, 0,004543 for the BENHCl compound in gas, n-octanol, DMF and water environments.

In compound BEN, it was observed that as the dielectric constant of the medium increased, the aromaticity difference increased slightly in Table 1 and Table S.2-S.4.

Table 1. HOMA and BIRD Values of BEN and BENHCl Compounds in Gaseous Phase

Comp	Group	Atoms	Contribution	Bond Lengths	N-term	Bond Lengths
BEN	Phenyl	C32-C25	-0,00176	1,394405	1,787283	1,394405
		C25-C19	-0,00297	1,39631	1,777747	1,39631
		C19-C24	-0,00515	1,398955	1,764574	1,398955
		C24-C31	-0,00049	1,391371	1,802555	1,391371
		C31-C35	-0,00199	1,394801	1,7853	1,394801
		C35-C32	-0,00072	1,392099	1,798884	1,392099
		Aromaticity	HOMA	0,986921	BIRD	97,85646
	Nitrophenyl	C36-C33	-0,00025	1,390401	1,807459	1,390401
		C33-C27	-0,00016	1,389932	1,809832	1,389932
		C27-C22	-0,00212	1,395022	1,78419	1,395022
		C22-C28	-0,00672	1,400506	1,75688	1,400506
		C28-C34	-0,00157	1,394036	1,789136	1,394036
		C34-C36	-0,00019	1,390125	1,808855	1,390125
		Aromaticity	HOMA	0,988998	BIRD	96,82656
BENHCl	Phenyl	C32-C25	-0,00169	1,394273	1,787946	1,394273
		C25-C19	-0,00307	1,396449	1,777057	1,396449
		C19-C24	-0,00506	1,398851	1,76509	1,398851
		24C-C31	-0,00053	1,391516	1,801822	1,391516
		C31-C35	-0,00194	1,394726	1,785678	1,394726
		C35-C32	-0,00077	1,392235	1,798198	1,392235
		Aromaticity	HOMA	0,986943	BIRD	97,9114
	Nitrophenyl	C36-C33	-0,00054	1,391534	1,80173	1,391534
		C33-C27	-0,00047	1,391323	1,802797	1,391323
		C27-C22	-0,00158	1,394058	1,789027	1,394058
		C22-C28	-0,00753	1,401244	1,75323	1,401244
		C28-C34	-0,00178	1,394438	1,78712	1,394438
		C34-C36	-0,00073	1,389302	1,813023	1,389302
		Aromaticity	HOMA	0,988026	Bird	96,79117

The calculated BIRD indices of the phenyl group of the compound BEN in the gas, n-octanol, DMF and water phases were found to be 97,85646, 97,7685, 97,75407 and 97,74762, respectively. The difference between the BIRD value of the phenyl group of the BEN compound in the gas phase and the BIRD values in n-octanol, DMF and water environments is very small and was found to be 0,08796, 0,10239 and 0,10884, respectively.

Aromaticity was assessed at the same level of theory as: geometry-based HOMA of aromaticity, PDIs, FLU (Matito et al., 2005; Krygowski, 1993; Kruszewski & Krygowski, 1972; Poater et al., 2003).

In the DFT method, FLU, PDI, PLR indices of BEN and BENHCl compounds in gas, n-octanol, DMF and water phase with B3LYP functionals and 6-311G(d,p) basis set are calculated and given in Table 2-Table 4.

Table 2. FLU Values of BEN and BENHCl Compounds in Gas, n-octanol, DMF and Water Environment

Phase	**BEN**		**BENHCl**	
	Phenyl	**Nitrophenyl**	**Phenyl**	**Nitrophenyl**
Gas	0,000908	0,002913	0,000901	0,003198
n-octanol	0,000909	0,00306832	0,000916	0,003422
DMF	0,000910	0,003084	0,000916	0,003446
Water	0,000910	0,003087	0,000915	0,003451

Table 3. PDI Values of BEN and BENHCl Compounds in Gas, n-octanol, DMF and Water Environment

PD1	**BEN**		**BENHCl**	
	Phenyl	**Nitrophenyl**	**Phenyl**	**Nitrophenyl**
Gas	0,101226	0,091941	0,101181	0,090456
n-octanol	0,101343	0,091098	0,101256	0,089383
DMF	0,101352	0,091015	0,101267	0,089274
Water	0,101353	0,091000	0,101269	0,089253

Table 4. PLR Values of BEN and BENHCl Compounds in Gas, n-octanol, DMF and Water Environment

PLR	**BEN**		**BENHCl**	
	Phenyl	**Nitrophenyl**	**Phenyl**	**Nitrophenyl**
Gas	0,609000	0,549424	0,609012	0,537577
n-octanol	0,608863	0,542532	0,608711	0,528510
DMF	0,608828	0,541857	0,608694	0,527615
Water	0,608819	0,541732	0,608689	0,527444

The correlation between the HOMA values of the phenyl and nitrophenyl groups of BEN and BENHCl compounds and the FLU, PDI and LPR values were examined and given in Figure 2-Figure 4.

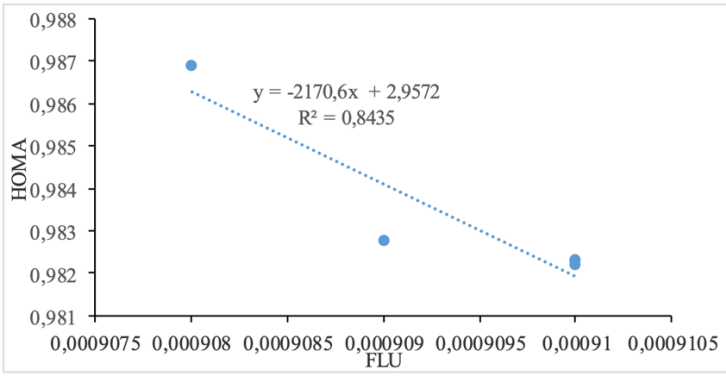

Figure 2. HOMA-FLU Relationship of The Phenyl Group in The BEN Compound in Gas, n-octanol, DMF and Water Phases

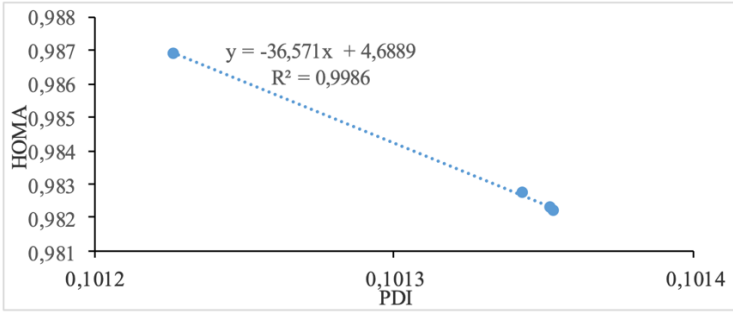

Figure 3. HOMA-PDI Relationship of The Phenyl Group in The BEN Compound in Gas, n-octanol, DMF and Water Phases

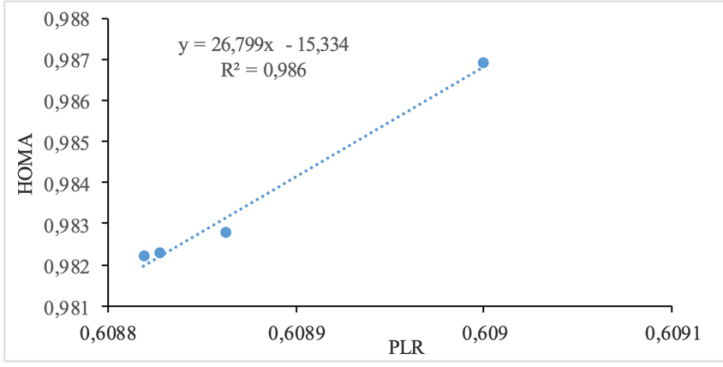

Figure 4. HOMA-PLR Relationship of The Phenyl Group in The BEN Compound in Gas, n-octanol, DMF and Water Phases

In compound BEN, the correlation coefficient between HOMA values and FLU, PDI and LPR for the phenyl group was found to be 0,8435, 0,9986 and 0,986, respectively, and for the nitrophenyl group, 0,9996, 0,9994 and 0,9994, respectively. The close similarity between them can be partially attributed to the fact that FLU was created to some extent follow the HOMA philosophy, that is, to measure aromaticity by comparing it with the values of an aromatic substance (Pasban et al., 2016). NBO analysis is an effective method used to study intra- and intermolecular bonding, conjugate interactions and charge transfer. The larger the E_2 value, the stronger the interaction between the electron donor and electron acceptor. Delocalization of electron density between electron-filled Lewis-type NBO orbitals and electron-empty non-Lewis orbitals corresponds to a stable acceptor-donor interaction (Foster & Weinhold, 1980). NBO analysis has proven to be an effective tool for the chemical interpretation of hyperconjugative interaction and electron density transfer from the unpaired electron. These changes in electron density are called "delocalization" corrections to the zero-order native Lewis structure, a stabilizing donor-acceptor interaction. It has been used to consider the different quadratic perturbation energies (E_2) between occupied orbitals of one subsystem and unoccupied orbitals of another subsystem, predicting delocalization or hyperconjugation. The stabilization energy associated with delocalization for each donor (i) and acceptor (j) can be calculated from the equation given below:

$$\mathrm{E}_2 = \Delta E_{ij} = q_i \frac{F_{ij}^2}{(E_j - E_i)} \quad (1)$$

q_i, E_i F_{ij} indicate donor orbital occupancy, diagonal NBO Fock matrix elements, and non-diagonal NBO Fock matrix elements, respectively. Interactions greater than or close to 5 kcal.mol^{-1} in gas, n-octanol and water environments for molecules of BEN and BENHCl compounds are given in Table 5 and Table S.4. The occupancy rate and hybritization of unshared electron pairs are given in Table 6. The strong intramolecular hyperconjugative interaction of the C33−C36 bond of the compound BEN is formed by the overlap of the πC33−C36 bonding orbital with the π*O5−N9 antibonding orbital, the π*C22−C27 antibonding orbital and the π*C28−C34 antibonding orbital in the gas phase, and the electron density increases by 0,61996, 0,31343, and 0,30309, leading to stabilization energy of 25,06, 20,27, and 16,81 kcal.mol^{-1}, resulting in intramolecular charge transfer leading to stabilization of the molecule. This stabilization energy is 28,53, 28,91 and 28,13 kcal.mol^{-1} in the interaction of the πC33−C36 bonding orbital and the π*O5−N9 antibonding orbital in the n-octanol, DMF and water phases, respectively. The overlap of the πC33−C36 bonding orbital and the π*C22−C27 antibonding orbital is 20,12, 20,11 and 19,95, and the overlap of the πC33−C36 bonding orbital and the π*C28−C34 antibonding orbital is 16,53, 16,51 and 16,29 (Table 5).

Table 5. Second Order Perturbation Theory Analysis of Fock Matrix in BEN Compound Based on NBO

Bonds	Bonding	Bonds	Anti bonding	Occupancy	Gas	n-octanol	DMF	Water
O2-C18	π	C17-C21	π*	0,22837	4,94	4,69	4,66	4,66
O5-N9	π	LP(3)O6		1,45495	12,37	12,11	12,09	12,09
O5-N9	π	O5-N9	π*	0,61996	7,52	7,56	7,56	7,57
C16-C17	σ	C21-C26	σ*	0,01851	5,41	5,21	5,18	5,39
C16-C20	σ	C23-C30	σ*	0,01804	5,25	5,06	5,05	4,32
C17-C21	π	O2-C18	π*	0,10065	22,28	23,86	24,07	24,11
C19-C25	π	C24-C31	π*	0,31444	19,41	19,41	19,41	19,41
C19-C25	π	C32-C35	π*	0,32677	20,62	20,6	20,60	20,6
C20-C23	π	O4-C29	π*	0,02368	21,44	23,27	23,47	23,51
C22-C27	π	C28-C34	π*	0,30309	20,48	20,39	20,38	20,38
C22-C27	π	C33-C36	π*	0,38927	21,86	21,71	21,69	21,69
C24-C31	π	C19-C25	π*	0,35134	21,48	21,32	21,30	21,41
C24-C31	π	C32-C35	π*	0,32677	20,36	20,14	20,11	20,29
C27-C33	σ	C33-C36	σ*	0,02368	5,43	5,47	5,47	5,53
C28-C34	π	C22-C27	π*	0,31343	19,58	19,61	19,61	19,21
C28-C34	π	C33-C36	π*	0,38927	24,29	24,74	24,78	25,09
C30-H58	σ	C20-C23	π*	0,21836	5,63	5,73	5,74	5,69
C32-C35	π	C19-C25	π*	0,35134	20,08	20,03	20,02	20,11
C32-C35	π	C24-C31	π*	0,31444	20,19	20,29	20,31	20,3
C33-C36	σ	C27-C33	σ*	0,02371	5,55	5,6	5,60	5,63
C33-C36	π	O5-N9	π*	0,61996	25,06	28,53	28,91	28,13
C33-C36	π	C22-C27	π*	0,31343	20,27	20,12	20,11	19,95
C33-C36	π	C28-C34	π*	0,30309	16,81	16,53	16,51	16,29
C34-C36	σ	N9-C33	σ*	0,10829	4,87	4,92	4,92	4,87
C36-H65	σ	C27-C33	σ*	0,02371	4,95	4,95	4,95	4,94
LP(2)O1		O2-C18	π*	0,10065	42,5	44,28	44,49	42,95
LP(2)O2		O1-C18	σ*	0,10019	31,42	30,22	30,07	31,16
LP(2)O2		C17-C18	σ*	0,05911	16,22	15,66	15,59	16,22
LP(1)O3		O4-C29	σ*	0,01805	6,14	6,24	6,24	6,15
LP(2)O3		O4-C29	π*	0,29315	44,59	45,33	45,38	44,5
LP(2)O4		O3-C29	σ*	0,10065	31,85	31,02	30,95	31,92
LP(2)O4		C20-C29	σ*	0,06150	16,67	16,1	16,03	16,73
LP(2)O5		O6-N9	σ*	0,05591	18,86	18,75	18,74	19,56
LP(2)O5		N9-C33	σ*	0,10829	13,13	12,53	12,48	13,42
LP(2)O6		O5-N9	σ*	0,05480	18,67	18,65	18,66	13,48
LP(2)O6		N9-C33	σ*	0,10829	13,02	12,45	12,40	14,4
LP(3)O6		O5-N9	π*	0,61996	161,07	157,9	157,66	137,41
LP(1)N7		C12-H42	σ*	0,03746	7,95	7,81	7,79	7,96
LP(1)N7		C14-H45	σ*	0,03871	7,98	7,65	7,60	7,95
LP(1)N7		C15-H47	σ*	0,03339	7,64	7,40	7,37	7,61
LP(1)N8		C17-C21	π*	0,22837	36,84	38,36	38,55	7,95
LP(1)N8		C20-C23	π*	0,21836	35,94	38,04	38,29	36,85

Table 6. Hybridization of Unshared Electron Pairs in The BEN Compound

	Occupancy	**Hybridisation**	
LP(2)O1	1,80995	p	p(99,96%)
LP(2)O2	1,85116	p	p(99,93%)
LP(1)O3	1,96559	$sp^{1,56}$	s(39,12%), p(60,85%)
LP(2)O3	1,79534	p	p(99,95%)
LP(2)O4	1,84767	p	p(99,92%)
LP(2)O5	1,89923	p	p(99,90%)
LP(2)O6	1,90029	p	p(99,90%)
LP(3)O6	1,45495	p	p(99,88%)
LP(1)N7	1,87087	$sp^{5,94}$	s(14,40%), p(85,57%)
LP(1)N8	1,66339	$sp^{99,99}$	s(0,88%), p(99,12%)

The strong intramolecular hyperconjugative interaction of the C33−C36 bond of the compound BENHCl is formed by the overlap of the πC33−C36 bonding orbital with the π*O5−N9 antibonding orbital, the π*C22−C27 antibonding orbital, and the π*C28−C34 antibonding orbital. This leads to stabilization energy of 28,13, 19,95 and 16,29 kcal.mol^{-1} in the gas environment, which results in intramolecular charge transfer that causes stabilization of the molecule.

This results in intramolecular charge transfer resulting in stabilization of the molecule. This stabilization energy is 31,96, 32,39, and 32,47 kcal.mol^{-1} in the interaction of the πC33−C36 bonding orbital and the π*O5−N9 antibonding orbital in the octanol, DMF and water phases, respectively, and The overlap of the the πC33−C36 bonding orbital and π*C22−C27 antibonding orbital was found to be 19,95, 19,95, 19,94 and 19,94, and the overlap of the C33−C36 bonding orbital and the π*C28−C34 antibonding orbital is found to be 16,07, 16,05 and 16,05 kcal.mol^{-1}, respectively. The overlap of πC28−C34 bonding orbitals with π*C22−C27 and π*C33−C36 antibonding orbitals led to 19,21 and 25,09 kcal.mol^{-1} stabilization in the gas environment, 19,24 and 25,59 kcal.mol^{-1} in the octanol environment, 19,23 and 25,62 kcal.mol^{-1} in DMF medium and 19,23 and 25,63 kcal.mol^{-1} in water (Table S.4).

According to the NBO analysis of the BEN compound in the gas phase, the second of the unshared electron pairs of the O atoms has a p character. The unshared first electron pair of the O3 atom has $sp^{1,56}$ character. The third unshared electron pair of the O6 atom has p character. The hybridization of the first unshared electrons of N7 and N8 atoms is $sp^{5,94}$ and $sp^{99,99}$, respectively, and their occupancy is 1,87087 and 1,66339. Unshared electron pairs cause strong stabilization (Table 6). Therefore, p orbitals, which are unshared electron pairs, interact by donating electrons to the orbitals opposite the bond. The strongest stabilization energy was seen in the LP(3)O6→ π*O5-N9 interaction, where the electron density increased by 0,61996 and the stabilization energy was found to be 161,07 kcal.mol^{-1}. The stabilization energy calculated in n-octanol, DMF and water phases were 157,9, 157,66 and 137,41 kcal.mol^{-1}, respectively, and as the dielectric coefficient of the medium increased, the stabilization energy decreased.

In the interaction of LP(2)O6→σ*O5-N9 and σ*N9-C33, the electron density increased by 0,05480 and 0,10829 and the stabilization energy became 18,67 and 13,02 kcal.mol^{-1}. Calculated stabilization energies in the n-octanol, DMF and water phase in the LP(2)O6→σ*O5-N9 interaction are 18,65, 18,66 and 13,48 kcal.mol^{-1}, respectively. In the LP(2)O6→σ*N9-C33 interaction, the stabilization energies calculated in n-octanol, DMF and gas phase are 12,45, 12,40, 14,4 kcal.mol^{-1}, respectively.

NLO effects arise from the interactions of electromagnetic fields in various environments (Sun et al., 2009). NLO is at the forefront of current research due to its importance in providing essential functions such as frequency shifting, optical modulation, optical switching, optical logic, and optical memory for emerging technologies in areas such as telecommunications, signal processing, and optical interconnects (Andraud et al., 1994; Geskin et al., 2003; Dege et al., 2013).

In order to investigate the relationships between molecular structures and NLO properties, the dipole moment, polarizability and first-order hyperpolarizability of the BEN compound, in gas, n-octanol, DMF and water media was calculated with B3LYP functional and 6-311G(d,p), 6-311++G(d,p) and 6-311++G(2d,2p) and for BENHCl only 6-311G(d,p) was used.

The electric dipole moment, a vector quantity significantly affected by molecular symmetry and flexibility, characterizes both the magnitude and direction of electric charge separation within the molecule and is equal to the vector sum of the electric dipole moments of the individual bonds. If there is perfect symmetry in a molecule's structure and charge distribution, individual bond moments will cancel each other, causing the overall dipole moment to disappear. However, if the molecule is not symmetrical, the dipole moment increases, reflecting the increased charge separation within the molecule.

The dipol moment of the compound BEN, in the gas, n-octanol, DMF, and water phase calculated with B3LYP functional and basis sets 6-311G(d,p), 6-311++G(d,p), 6-311++G(2d,2p), and the dipol moment of the compound of the BENHCl compound calculated in the gas, n-octanol, DMF, and water phases with the B3LYP functional and 6-311G(d,p) basis set are given in Figure 5.

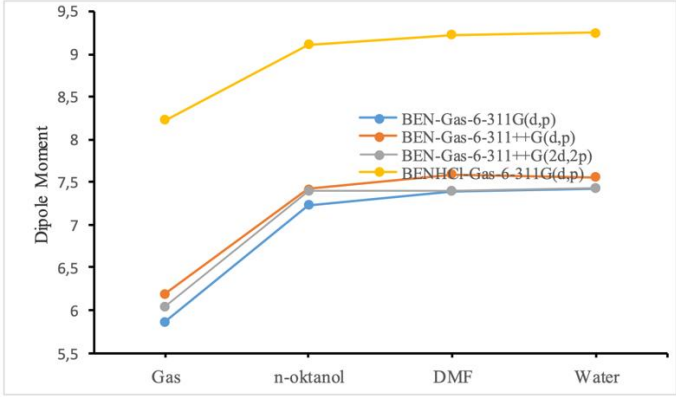

Figure 5. Dipole Moment Values of The Compound BEN and BENHCl in Debye Units

As seen in Figure 5 the dipole moment (μ) of the BEN compound varies depending on the basis set used (Alhanzal et al., 2023). The fact that the dipole moment value of the BENHCl compound is higher than the dipole moment value of the BEN compound shows that it affects the charge distribution of the HCl group.

The dipole moment values of the BEN molecule when we pass from gas to n-octanol, from gas to DMF and from gas to water, increases 1,37 (23,29%) respectively; 1,53 (20,72%), 1,57 (26,70%), respectively, while that of the BENHCl molecule increases to 0,89 (10,79%), 1,00 (10,86%) 1,03 (12,47%), respectively.

The polarizability, kappa and anisotropic polarizability of the compound BEN, in the gas, n-octanol, DMF, and water phase calculated with B3LYP functional and basis sets 6-311G(d,p), 6-311++G(d,p), 6-311++G(2d,2p), and the dipol moment, the polarizability, kappa and anisotropic polarizability of the compound of the BENHCl compound calculated in the gas, n-octanol, DMF, and water phases with the B3LYP functional and 6-311G(d,p) basis set are given in Figure 6-Figure 8.

The response of a system to an applied electric field is called polarizability. They determine not only the strength of molecular interactions (long-range intermolecular induction, dispersion forces, etc.) and the cross-sections of different scattering and collision processes, but also the nonlinear optical properties of the system (Safronova et al., 2015).

From Figure 6, it was found that the polarizability of BEN and BENHCl compounds changed with the addition of the solvent phase. Additionally, there is a visible change in the polarization values of both molecules from the gas phase to the solvent phase.

The polarizability of atoms and molecules and the concepts of hardness and softness are closely linked. It is assumed that softness and polarizability are related. Soft molecules can be polarizable more easily. The fact that the polarizability value of the BENHCl compound is higher than the polarizability value of the BEN compound means that the BENHCl compound is softer.

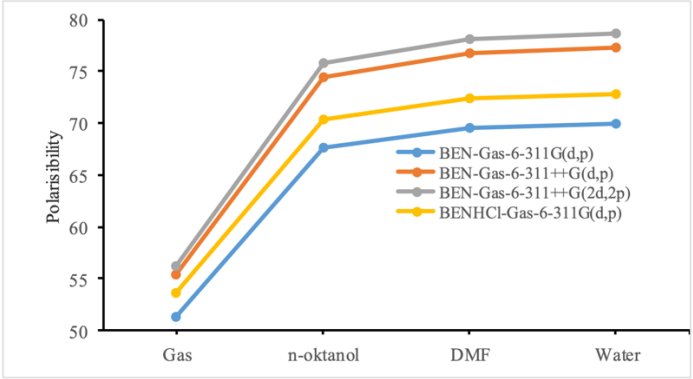

Figure 6. Polarisibility Values of The Compound BEN and BENHCl (10^{-24} esu)

Calculated polarizability for BEN and BENHCl in different basis sets shows that the polarizability gradually increases as we go from lower dielectric constant to higher dielectric constant that supports that as the polarity of the solution increases, the reactivity of the molecule increases, and this is due to the fact that HOMO and LUMO orbitals are affected differently in solvents with different dielectric coefficients (Khan et al., 2017).

Both isotropic polarization and anisotropy are used to understand how functional groups act as sources of linear optical responses. It is used to determine how they interact with each other in a way that strengthens the macroscopic optical behavior within the material and how non-covalent interactions such as covalent bonds and hydrogen bonds determine refractive indices and birefringence (Liu & Ueda, 2009; Jose et al., 2023).

The anisotropy of BEN and BENHCl molecules increased in the transition from the gas phase to the solvent phase. In the calculations made with the 6-311G(d,p) basis set, this increase was found to be 31,98% in the BEN molecule and 31,35% in the BENHCl molecule.

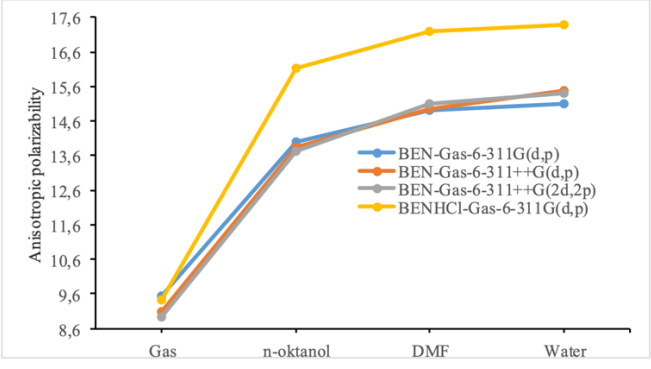

Figure 7. Anisotropic Polarizability Values of The Compound BEN and BENHCl

Kappa values give a measure of deviations from spherical symmetry. In a spherically symmetric charge distribution, the Kappa value will be zero (Hinchliffe et al., 2004). Kappa values calculated in gas, n-octanol, DMF and water phases are given in Figure 7.

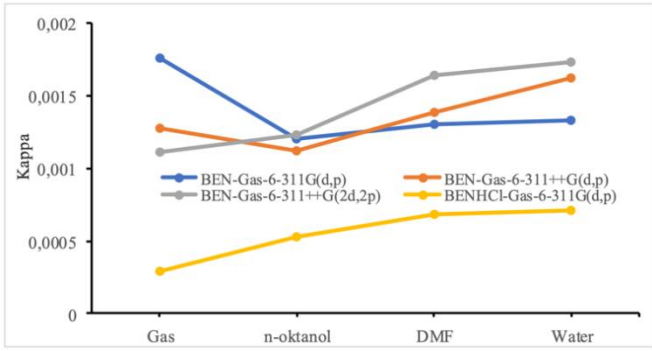

Figure 8. Kappa Values of The Compound BEN and BENHCl

Calculation results showed that both BEN and BENHCl compounds had high hyperpolarization values. The hyperpolarizability value of the carbamide molecule was found to be 0,1944x10^{-30}esu and in the calculation made with the 6-311G(d,p) basis set for those of BEN and BENHCl compound were found as 1,146 and 6,341x10^{-30}esu, respectively, (Figure 9).

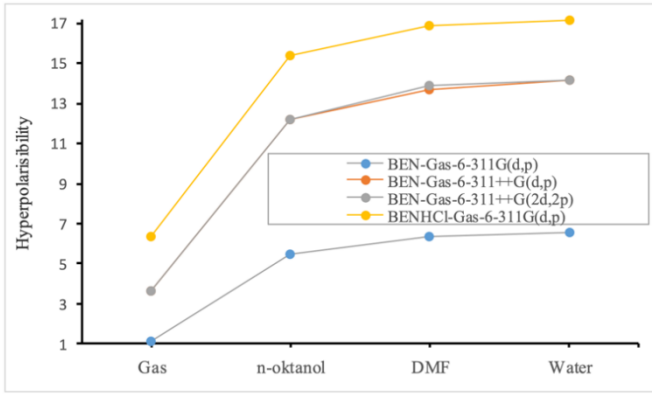

Figure 9. Hyperpolarisibility Values of The Compound BEN and BENHCl

These values are 10 times higher than the hyperpolarizability values of carbamide. Therefore, it has a good NLO feature. The hyperpolarizability values of the BENHCl compound are greater than the hyperpolarizability values of the BEN compound. The magnitude of hyperpolarizations depends on the chemical reactivity and structural properties of the molecule. The large value of the first hyperpolarizability (β), a measure of nonlinear optical activity, is attributed to the intramolecular charge transfer that occurs due to the movement of the electron cloud from the electron donor to the

acceptor groups through a π-conjugated framework (Chen et al., 2014; Varghese et al., 2019).

3. CONCLUSION

The aromaticity of BEN and BENHCl compounds were evaluated indices of aromaticity such as HOMA, BIRD, PDI, PLR, NLO and FLU. NBO calculations reveals that BEN and BENHCl compounds have types of interactions like σ→σ*, π→π*, σ→π* and lone pair of O and N atoms → π*. Dipole moment, polarizability, anisotropic polarizability, and hyperpolarisibility values of the BENHCl compound is found higher than the polarizability value of the BEN compound. Dipole moment, polarizability, anisotropic polarizability, and hyperpolarisibility values vary depending on the basis set used.

Authorship Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by FK and DHT. The first draft of the manuscript was written by FK, DHT and FG and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All authors reviewed the manuscript.

Conflict of Interest
The authors declare that there is no conflict of interest.

Statement of Research and Publication Ethics
Research and publication ethics were observed in the study.

REFERENCES

Alhanzal, F., Joudieh, N., Hussein, K., & Chamoun, N. (2023). Comparison between pbe-d3, b3lyp, b3lyp-d3 and MP2 methods for quantum mechanical calculations of polarizability and ir-nmr spectra in C24 isomers, including a novel isomer with D2d symmetry. *Nano-Structures & Nano-Objects,* 36, 101036. https://doi.org/10.1016/j.nanoso.2023.101036

Andraud, C., Brotin, T., Garcia, C., Pelle, F., Goldner, P., Bigot, B., & Collet, A. (1994). Theoretical and experimental investigations of the nonlinear optical properties of vanillin, polyenovanillin, and bisvanillin derivatives. *Journal of the American Chemical Society*, 116(5), 2094-2102. https://doi.org/10.1021/ja00084a055.

Chen, X., Jia, C., Wan, Z., Zhang, J., & Yao, X. (2014). Theoretical investigation of phenothiazine–triphenylamine-based organic dyes with different π spacers for dye-sensitized solar cells. Spectrochimica *Acta Part A: Molecular and Biomolecular Spectroscopy*, 123, 282-289. https://doi.org/10.1016/j.saa.2013.12.072

Dege, N., Şenyüz, N., Batı, H., Günay, N., Avcı, D., Tamer, Ö., & Atalay, Y. (2014). The synthesis, characterization and theoretical study on nicotinic acid [1-(2,3-dihydroxyphenyl)methylidene]hydrazide. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy,* 120, 323-331. https://doi.org/10.1016/j.saa.2013.10.030

Edim, M. M., Enudi, O. C., Asuquo, B. B., Louis, H., Bisong, E. A., Agwupuye, J. A., Chioma, A. G., Odey, J. O., Joseph, I., & Bassey, F. I. (2021). Aromaticity indices, electronic structural properties, and fuzzy atomic space investigations of naphthalene and its aza-derivatives. *Heliyon*, 7(2), e06138. https://doi.org/10.1016/j.heliyon.2021.e06138.

Foster, J. P., & Weinhold, F. (1980). Natural hybrid orbitals. *Journal of the American Chemical Society*, 102(24), 7211-7218. https://doi.org/10.1021/ja00544a007 1

Gajda, Ł., Kupka, T., & Broda, M. A. (2018). Solvent impact on the planarity and aromaticity of free and monohydrated zinc phthalocyanine: *A theoretical study. Structural Chemistry*, 29(3), 667-679. https://doi.org/10.1007/s11224-017-1063-3

Geskin, V. M., Lambert, C., & Brédas, J. (2003). Origin of high second- and third-order nonlinear optical response in Ammonio/Borato Diphenylpolyene Zwitterions: the remarkable role of polarized aromatic groups. *Journal of the American Chemical Society*, 125(50), 15651-15658. https://doi.org/10.1021/ja035862p.

Gopika, V.C., Remi, S.L (2018). Validated UV spectrophotometric method for simultaneous estimation of metoprolol succinate and benidipine hydrochloride in their combined tablet dosage form, *Asian Journal of Pharmaceutical and Health Sciences* (8), 1968-1975.

Hinchliffe, A., Nikolaidi, B., & Soscún Machado, H. (2004). Density functional studies of the dipole Polarizabilities of substituted stilbene, Azoarene and related push-pull molecules. *International Journal of Molecular Sciences*, 5(8), 224-238. https://doi.org/10.3390/i5050224

Khan, M. F., Rashid, R. B., Rahman, M. M., Faruk, M. A., Rahman, M. M., & Rashid, M. A. (2017). Effects of solvent polarity on solvation free energy, dipole moment, polarizability, hyperpolarizability and molecular reactivity of aspirin. *International Journal of Pharmacy and Pharmaceutical Sciences,* 9(2), 217. https://doi.org/10.22159/ijpps.2017v9i2.15853.

Kruszewski, J., & Krygowski, T. (1972). Definition of aromaticity basing on the harmonic oscillator model. *Tetrahedron Letters*, 13(36), 3839-3842. https://doi.org/10.1016/s0040-4039(01)94175-9

Krygowski, T. M. J. Chem. Inf. Comput. Sci. 1993, 33, 70-78.

Krygowski, T., Cyrañski, M., Czarnocki, Z., Häfelinger, G., & Katritzky, A. R. (2000). Aromaticity: A theoretical concept of immense practical importance. *Tetrahedron*, 56(13), 1783-1796. https://doi.org/10.1016/s0040-4020(99)00979-5.

Liu, J., & Ueda, M. (2009). High refractive index polymers: Fundamental research and practical applications. *Journal of Materials Chemistry*, 19(47), 8907. https://doi.org/10.1039/b909690f

Matito, E., Duran, M., & Solà, M. (2004). The aromatic fluctuation index (FLU): A new aromaticity index based on electron delocalization. *The Journal of Chemical Physics*, 122(1). https://doi.org/10.1063/1.1824895

Pasban, S., Raissi, H., & Mollania, F. (2016). Solvent effects on the structural, electronic properties and intramolecular N–H O hydrogen bond strength of 5-aminomethylene-pyrimidine-2,4,6 trion with DFT calculations. *Journal of Molecular Liquids*, 215, 77-87. https://doi.org/10.1016/j.molliq.2015.11.038

Poater, J., Fradera, X., Duran, M., & Solà, M. (2003). An insight into the local Aromaticities of polycyclic aromatic hydrocarbons and fullerenes. *Chemistry – A European Journal*, 9(5), 1113-1122. https://doi.org/10.1002/chem.200390128.

Reed, A. E., Curtiss, L. A., & Weinhold, F. (1988). Intermolecular interactions from a natural bond orbital, donor-acceptor viewpoint. *Chemical Reviews*, 88(6), 899-926. https://doi.org/10.1021/cr00088a005

Rodrigues, J. L., Ligorio, R. F., Krawczuk, A., Diniz, R., & Dos Santos, L. H. (2023). Distributed functional-group polarizabilities in polypeptides and peptide clusters toward accurate prediction of electro-optical properties of biomacromolecules. *Journal of Molecular Modeling*, 29(2). https://doi.org/10.1007/s00894-023-05451-5.

Safronova, M. S., Mitroy, J., Clark, Charles W., Kozlov, M. G., (2015). AIP Conference Proceedings [AIP Publishing LLC Proceedings of The International Conference of Computational Methods in Sciences And Engineering 2010 (ICCMSE-2010) - Kos, Greece (3–8 October 2010)] - *Atomic polarizabilities*. 1642, 81–89. doi:10.1063/1.4906633.

Seino, H., Miyaguchi, S., Yamazaki, T., Ota, S., Yabe, R., & Suzuki, S. (2007). Effect of Benidipine hydrochloride, a long-acting T-type calcium channel blocker, on blood pressure and renal function in hypertensive patients with diabetes mellitus. *Arzneimittelforschung,* 57(08), 526-531. https://doi.org/10.1055/s-0031-1296643

Tuncel, D. H., & Kandemirli, F. (2024). Theoterical study of benidipine and benidipine hydrochloride. *International Journal of Pharmacology and Pharmaceutical Research*, 6(1), 47-56. https://doi.org/10.33545/26647184.2024.v6.i1a.31

Varghese, A. L., Abraham, I., & George, M. (2019). Structural dependence of non-linear optical properties of molecules containing naphthalene linked to Nitrophenyl Group–A DFT study. *Asian Journal of Chemistry*, 31(3), 505-509. https://doi.org/10.14233/ajchem.2019.21557