

A Computational Study of the Linear and Nonlinear Optical Properties of Aminopyridines, Aminopyrimidines and Aminopyrazines

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Abstract: In this study, we investigated the linear and nonlinear optical properties of 22 heterocyclic aromatic amines including aminopyridines, aminopyrimidines and aminopyrazines. The theoretical calculations were performed with the different three hybrid density functional theories (DFT), BPV86, B3PW91 and B3LYP, and used the 6-311++G(3d, 3p) basis set. The results show that 2-amino-5-nitropyridine and 2-amino-4methyl-5-nitropyridine compounds exhibit large nonlinear optical properties.

We also consider semi-empirical polarizability and molecular volume calculations at the AM1 level of theory together with QSAR-quality empirical polarizability calculations. Least-squares correlations between the various sets of results show that these less costly procedures are reliable predictors of $\langle\alpha\rangle$ for these molecules, but less reliable for the larger molecules.

Keywords: Nonlinear optical properties, aminopyridines, hyperpolarizability, B3LYP

1 Introduction

The search for nonlinear optical (NLO) materials has been of great interest in recent years because of their potential applications in laser spectroscopy and laser processing [1], [2], optical communications, data storage and image processing [3], [4], [5], [6] and terahertz (THz) wave generation technology [7] which use in the fields of semiconductor, tomographic imaging, label free genetic analysis, cellular level imaging, biological sensing and so on [8]. Organic materials are optically more nonlinear than inorganic materials due to weak Van der Waals and hydrogen bonds which possess a high degree of delocalization. Amino acids and their complexes belong to a family of organic materials that have applications in NLO [9], [10], [11]. Aminopyridines are bioactive N-heterocyclic tertiary amines, which increase the strength of the nerve signal by blocking of the voltage-dependent K^+ channel [12]. Also, aminopyridines have been proposed as drugs for the treatment of many diseases such as antithrombotic drugs and antimicrobial agents [13]. In particular, 2-aminopyridine is one of the potential impurities in piroxicam and tereoxicam which are non-steroidal anti-inflammatory drugs that used in musculo-skeletal and joint disorders [14]. Moreover, aminopyridines are commonly present in synthetic and natural products [15]. They form repeated moiety in many large molecules with interesting photophysical, electrochemical and catalytic applications [16].

Amino acids are interesting materials for NLO applications as they contain a proton donor carboxyl acid (COO^-) group and the proton acceptor amine (NH_2) group with them [8], [17]. 2-Aminopyridines are promising substituted pyridines which have been shown to be biologically active molecules [18]. Additionally, because of their chelating abilities, 2-aminopyridines are commonly used as ligands in inorganic and organometallic chemistry [19]. If substituted with optically active groups, they could potentially serve as chiral auxiliaries or chiral ligands in asymmetric reactions. For these reasons, 2-aminopyridines are valuable synthetic targets. 4-aminopyridine is a voltage-gated K^+ (K_v) channel blocker that is useful clinically in the treatment of spinal cord injuries [20] and multiple sclerosis [21]. In addition to its therapeutic applications, 4-aminopyridine is routinely used to isolate different types of K_v channels expressed in native tissues based on their affinities for the drug [22].

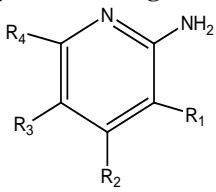
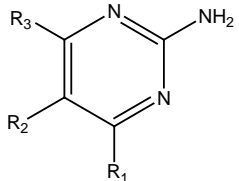
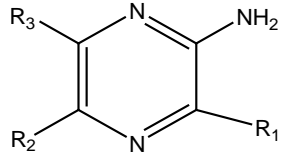
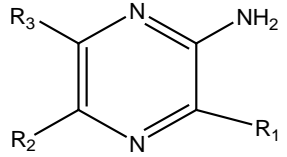
Aminopyridine analogues					Aminopyrimidine analogues					
										
No	R ₁	R ₂	R ₃	R ₄	Name	No	R ₁	R ₂	R ₃	Name
1	H	H	H	H	2-Aminopyridine	14	H	H	H	2-Aminopyrimidine
2	CH ₃	H	H	H	2-Amino-3-methylpyridine	15	OH	H	OH	2-Amino-4,6-dihydropyrimidine
3	H	CH ₃	H	H	2-Amino-4-methylpyridine	16	CH ₃	H	CH ₃	2-Amino-4,6-dimethylpyrimidine
4	H	H	CH ₃	H	2-Amino-5-methylpyridine	17	CH ₃	CH ₃	H	2-Amino-4-methyl-6-hydroxypyrimidine
5	NO ₂	H	H	H	2-Amino-3-nitropyridine	18	CH ₃	H	OCH ₃	2-Amino-4-methyl-6-methoxypyrimidine
6	H	H	NO ₂	H	2-Amino-5-nitropyridine					
7	CO ₂ H	H	H	H	2-Aminonicotinic acid					
8	H	H	CO ₂ H	H	6-Aminonicotinic acid					
9	H	H	CO ₂ NH ₂	H	6-Aminonicotinamide					
10	OH	H	H	H	2-Amino-3-hydroxypyridine					
11	Cl	H	H	H	2-Amino-3-chloropyridine					
12	H	CH ₃	H	CH ₃	2-Amino-4,6-dimethylpyridine					
13	H	CH ₃	NO ₂	H	2-Amino-4-methyl-5-nitropyridine					
Aminopyrazine analogues					Aminopyrazine analogues					
										
No	R ₁	R ₂	R ₃	Name	No	R ₁	R ₂	R ₃	Name	
19	H	H	H	Aminopyrazine	19	H	H	H	Aminopyrazine	
20	CO ₂ H	H	H	3-Aminopyrazine-2-carboxylic acid	20	CO ₂ H	H	H	3-Aminopyrazine-2-carboxylic acid	
21	C ₆ H ₅	H	H	2-Amino-3-phenylpyrazine	21	C ₆ H ₅	H	H	2-Amino-3-phenylpyrazine	
22	H	C ₆ H ₅	H	2-Amino-5-phenylpyrazine	22	H	C ₆ H ₅	H	2-Amino-5-phenylpyrazine	

Fig.1. Structures of the aminopyridine, aminopyrimidine and aminopyrazine analogues.

The polarizability and hyperpolarizability of 4-aminopyridine have been studied by Z. Latajka et al. with semi-empirical PM3 and time-dependent Hartree Fock(TDHF) methods [23]. Although the fluorescence properties of 22 heterocyclic aromatic amines including aminopyridines, aminopyrimidines aminopyrazines were studied by K. Yamamoto et al. [24], there do not appear to be any corresponding experimental data in the literature, neither are there any other ab initio calculations for title molecules except for 4-aminopyridine. In earlier studies, we calculated the torsional barrier and nonlinear optical properties of phenylpyridines, phenyltriazines and thalidomide. In this paper, we study the nonlinear optical properties of aminopyridines, aminopyrimidines and aminopyrazines. Studied molecules are presented at the **Fig.1.**

This study is extended to the determination of AM1 [25] semi-empirical polarizability together with QSAR-quality empirical polarizability and molecular volume calculations from optimized geometries using HyperChem v7 [26]

2 Computational details

The geometries were fully optimized without any constraint with the help of analytical gradient procedure implemented within Gaussian 03W program [27]. All the parameters were allowed to relax and all the calculations converged to an optimized geometry which corresponds to a true energy minimum revealed by the lack of imaginary values in the frequency calculations.

The performance of various DFT functionals and of basis sets in hyperpolarizability calculations have been extensively studied for organic NLO materials [28], [29]. Accurate calculation of nonlinear optical properties requires the use of extended basis sets and high level of theory. In particular, these basis sets have to include d and p polarization functions

together with s and p diffuse functions. In the present study, we utilized three hybrid density functionals (B3LYP, BPV86, B3PW91) methods [30], [31], [32], [33] with 6-311++G(3d,3p) basis set [34], [35] to estimate molecular static polarizability, anisotropy of polarizability and first static hyperpolarizability (β) of 22 heterocyclic aromatic amines including aminopyridines, aminopyrimidines aminopyrazines. The first static polarizability (α) calculated analytically, whereas first static hyperpolarizability (β) has been computed by using a finite-field procedure based on the numerical differentiation twice with respect to electric field.

3 Results and discussion

3.1. Linear and nonlinear optical properties

It is well known that the nonlinear optical response of an isolated molecule in an electric field E_i can be presented as a Taylor series expansion of the total dipole moment, μ_{tot} , induced by the field:

$$\mu_{tot} = \mu_0 + \alpha_{ij}E_j + \beta_{ijk}E_jE_k + \dots$$

Where α is the linear polarizability, μ_0 the permanent dipole moment and β is the first hyperpolarizability tensor components.

In this study are presented values of the static mean polarizability, $\langle\alpha\rangle$ as defined in the following equation [36]:

$$\langle\alpha\rangle = 1/3 (\alpha_{xx} + \alpha_{yy} + \alpha_{zz})$$

The complete equation for calculating the total static first hyperpolarizability magnitude of from Gaussian output is given as follows [37],

$$\beta_{tot} = [(\beta_{xxx} + \beta_{xyy} + \beta_{xzz})^2 + (\beta_{yyy} + \beta_{yzz} + \beta_{yxx})^2 + (\beta_{zzz} + \beta_{zxx} + \beta_{zyy})^2]^{1/2}$$

The polarizability and first static hyperpolarizability of 4-aminopyridine have been studied by Z. Latajka et al. [23]. They calculated the polarizability with the PM3 Hamiltonian and at the ab initio level with the minimal STO-3G basis set as 55.2 a.u. and 35.4 a.u., respectively. First static hyperpolarizability of 4-aminopyridine were calculated with two method as 638.1 a.u. and 142.3 a.u., respectively. In this study, polarizability of 4-aminopyridine were calculated with B3LYP and BPV86 methods and 6-311++G(3d,3p) basis set as 75.7 a.u. and 77.6 a.u., respectively. Also, first static hyperpolarizability of 4-aminopyridine were calculated with two method as 143.5 a.u. and 75.2 a.u., respectively. The B3LYP hyperpolarizability result is very compatible with the ab initio STO-3G level value for 4-aminopyridine.

In **Table 1**, the calculated theoretical values of the static mean polarizability and first static hyperpolarizability are shown. It can be seen that from Table 1,

1. When the H atom on the **2-aminopyridine** is replaced by methyl group (at the R_1 , R_2 , R_3 and R_4 position) hyperpolarizability of **2**, **3**, and **4** increased approximately four fold.
2. When the H atom on the **2-aminopyridine** is replaced by NO_2 group at the R_1 position, hyperpolarizability of **5** increased approximately 13, 16, 19 fold with B3PW91, BPV86, and B3LYP methods, respectively.
3. When the H atom on the 2-aminopyridine is replaced by NO_2 group at the R_3 position, hyperpolarizability of **6** increased dramatically. Hyperpolarizability value of 2-aminopyridine changed from 20.16, 28.18, and 22.08 a.u for **6** to 1313.65, 1242.88 and 1345.29 a.u. with BPV86, B3PW91 and B3LYP methods, respectively.
4. It can be seen from **Table 1**, the largest hyperpolarizability are obtained for **6**, **8**, **13** and **22** among the title molecules.
5. A large difference among the hyperpolarizability of aminopyrimidines has not been seen.
6. As can be seen from **Table 1**, hyperpolarizability values of aminopyrimidines and aminopyrazines are very close to each other, but for **22** the hyperpolarizability increased dramatically due to the H atom on the **aminopyrazine** is replaced by **phenyl** group at the R_2 position.

Table 1. Static polarizability, first static hyperpolarizability and molecular volume of studied molecules.

Mol.	$\langle\alpha\rangle/\text{a.u.}$				$\beta_{tot}/\text{a.u.}$			Vol.(Å ³)
	AM1	BPV86	B3PW91	B3LYP	BPV86	B3PW91	B3LYP	
1	51.74	75.55	73.17	73.90	20.16	28.18	22.08	354.8
2	61.15	89.46	86.45	87.20	94.01	102.04	98.00	404.82
3	63.15	92.76	89.37	90.16	242.06	256.24	265.35	405.08
4	64.43	93.05	89.67	90.41	229.69	244.65	244.73	405.26
5	72.23	99.74	96.41	97.24	325.68	379.50	420.40	403.83
6	74.04	103.30	98.94	99.75	1313.65	1242.88	1345.29	411.38
7	70.92	98.17	97.30	98.17	242.80	239.66	258.61	420.26
8	72.32	104.21	99.66	100.51	844.87	780.59	840.50	426.50
9	81.58	118.19	112.26	113.11	528.13	673.70	705.62	468.12
10	59.71	84.91	81.58	82.37	363.47	386.59	370.82	371.26
11	61.83	93.86	90.41	91.24	283.38	297.84	284.39	392.18
12	72.58	107.60	103.45	104.29	184.09	206.89	209.90	460.07
13	82.87	116.71	111.80	112.60	1128.71	1088.72	1183.02	456.38
14	50.90	72.77	70.22	70.92	230.91	247.93	238.66	337.74
15	59.62	85.70	81.67	82.40	224.96	177.94	183.78	380.33
16	69.07	102.34	98.16	98.96	190.00	202.11	213.24	446.62
17	64.32	93.97	89.86	90.55	252.41	234.37	238.50	413.70
18	74.58	108.27	103.52	104.31	307.72	285.05	295.11	471.51
19	51.70	73.70	71.14	71.83	219.04	241.09	230.14	338.24
20	68.58	97.11	93.34	94.15	184.81	216.48	230.48	407.86
21	108.83	151.90	146.45	147.68	254.80	264.55	271.32	545.55
22	114.35	159.28	152.83	154.00	845.97	769.56	734.17	551.15

3.2. QSAR-quality calculations

Dipole polarizabilities are often used in QSAR studies, where the aim is to give a reliable but quick estimate of $\langle\alpha\rangle$. DFT polarizability calculations are prohibitively expensive in a QSAR context, even for such simple molecules. One therefore looks to less rigorous but reliable procedures.

The relationship mean polarizability and molecular volume (V_{mol}) is defined as [38];

$$\langle\alpha\rangle = 4\pi\epsilon_0 V_{mol}$$

The molecular volume can be estimated very easily from molecular mechanics without the cost of a full quantum mechanical calculation. The molecular volumes are routinely determined in QSAR studies, and typical values shown in **Table 1**. The correlation coefficient was found as 0.94 between the molecular volumes and B3LYP mean polarizabilities. The AM1 mean polarizability calculations give values that correlate well with the B3LYP (with a correlation coefficient of 0.99).

Polarizabilities can be accurately calculated for molecules of modest size, and it is generally accepted that ab initio calculations can effectively replace experiment. The field has recently been reviewed by Marroulis[39].

Finally DFT polarizability calculations at B3LYP/6-311++G(3d,3p) level of theory are adequate for this molecules. However, we consider the likely reliability of various easily-computed indices such as the molecular volume and AM1 polarizabilities discussed above. According to obtained results of linear regression coefficients R^2 are given in **Table 2**.

Table 2 Linear regression coefficients R^2 for the studied molecules

Correlation of $\langle\alpha\rangle_{B3LYP}$ with	
Molecular volume	$R^2 = 0.94$ ($Y = 0.3585X - 53.185$)
$\langle\alpha\rangle_{AM1}$	$R^2 = 0.99$ ($Y = 1.2881X + 7.1264$)

4. Conclusion

In the present study, linear and nonlinear optical properties of aminopyridines, aminopyrimidines and aminopyrazines calculated with different DFT methods. Comparison of the calculated and previous semi-empirical and HF data for 4-aminopyridine indicates that the semiempirical PM3 values are overestimated, and B3LYP hyperpolarizability result is very compatible with the ab initio STO-3G level value for 4-aminopyridine. The largest hyperpolarizability values obtained for **6**, **8**, **13** and **22** among the studied molecules. This study reveals that these molecular systems (**6**, **8**, **13** and **22**) have large first static hyperpolarizabilities and may have potential applications in the development of NLO materials.

We consider the likely reliability of various easily computed indices such as the molecular volume and AM1 polarizabilities discussed above. AM1 polarizability calculations are in poor quantitative agreement with the B3LYP results. Nevertheless, AM1 average polarizability gives a correlation coefficient of 0.99 when compared to the B3LYP results.

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