



A Theoretical Study of NBO Analysis and Solvation Effects on Tautomerism Stability of 4,8-dioxygenated 1,5-naphthyridine

ZABIALAH HEIDARNEZHAD^{1*}, IZATULLO GANIEV¹, ZIYODULLO OBIDOV¹,
FATEMEH HEIDARNEZHAD² and MARYAM SEYED SHARIFI³

¹Chemistry Institute, Tajikistan Academy of Sciences, Dushanbe, Tajikistan.

²Andimeshk Branch, payame noor University, Iran.

³Department of Chemistry, University of Isfahan, Iran.

*Corresponding author E-mail: Z.heidarnezhad@gmail.com

(Received: September 01, 2012; Accepted: October 15, 2012)

ABSTRACT

Computational calculations at B3LYP/CC-PVDZ level were employed in the study of the tautomeric forms of 4,8-dioxygenated 1,5-naphthyridine (DN) derivatives (7-CF₃, 7-CL, 7-H, 7-CH₃, 7-OH) in the gas phase and solution using PCM model. For electron withdrawing and electron releasing derivatives in the gas phase and solution DN1 form is more stable and dominant than other forms. In the gas phase the stability order is: DN1>DN3>DN2. But in solution phase the stability domination depends on polarity and substituent groups. In addition variation of dipole moments and charges on atoms in the solvents are studied.

Key words: NBO analysis, PCM model, 4,8 -dioxygenated 1,5- naphthyridine, Tautomerism.

INTRODUCTION

Tautomerism interconversions^{1,2}. have been investigated by chemists during last decades. Recently, study of tautomerism received renewed attention due to its importance on the determination of compounds properties and their area of applications. The importance of tautomerism is revealed more since in recent years the investigation about tautomerism has been the major topic in theoretical chemistry. For example, tautomerism in keto-enol^{3,4}. imine-enamine^{5,6}.

purine⁷. pyrimidine⁸. and many other systems⁹. have been studied during the past decades. Thereupon, compounds containing different tautomers can be the subject of interest by theoretical chemists¹⁰. The density functional theory (DFT) method where electron correlation is taken into account by means of non- local exchange and correlation functional is emerging as a cost-effective alternative sophisticated MP2 computations¹¹⁻¹⁷. In the case of uracil, the DFT method is shown to provide a similar vibrational mode to those obtained at the MP2 level^{18,19}. DFT studies have been

investigated by chemists during last decades by chemist. Molecular Recognition Studies on Naphthyridine Derivatives are reported and ¹H-NMR titrations under two different concentration conditions have been employed to determine the association constants K_b .²⁰ A series of substituted 1,8-naphthyridine derivatives were synthesized from 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide. Compounds 4-11 were studied theoretically using the density functional theory (DFT) with B3LYP/6-31(d) level of calculations, and the electronic properties of these compounds were related to their biological activity.²¹ A series of 4,8-substituted 1,5-naphthyridines have been successfully synthesised by a Suzuki cross-coupling between 4,8-dibromo-1,5-naphthyridine. Quantum chemical calculations using DFT B3LYP/6-31G* showed nearly identical the lowest unoccupied molecular orbital (LUMO) of -2.39 to -2.19 eV and the highest occupied molecular orbitals (HOMO) of -5.33 to -6.84 eV. These results demonstrate the 4,8-substituted 1,5-naphthyridines with a simple architecture might be promising blue-emitting (or blue-green-emitting) materials, electron-transport materials and hole-injecting/hole-transport materials for applications for developing high-efficiency OLEDs.²² also theoretical treatment of vibronic coupling of 1,5-naphthyridine have been done²³ in the present paper we studied tautomerism of 4,8-dioxygenated 1,5-naphthyridine in the gas phase and solution using polarisable continuum method (PCM) at the B3LYP/6-311++G(d,p) level of theory.

Computational methods

All these calculations were carried out on a core i7 personal computer by means of GAUSSIAN09 program suite. To characterize all the optimized geometries the vibrational frequencies for all the conformers have been done at B3LYP levels. The stationary structures are confirmed by ascertaining that all ground states have only real frequencies. The tautomers were also optimized in solvents according to the polarisable continuum method of Tomasi and co-workers, which exploits the generating polyhedra procedure²⁴⁻²⁸ to build the cavity in the polarisable continuum medium, where the solute is accommodated. Atomic charges in all obtained using the Natural Population

Analysis (NPA) the structures were method within the Natural Bond Orbital (NBO) approach²⁹.

RESULTS AND DISCUSSION

Gas phase

Structures and numbering of DN derivatives are depicted in figure 1. and the results of energy comparisons of three tautomers in the gas phase and different solvents are given in Table 1. In agreement with previous results, in the gas phase all DN1 form is more stable than other forms. And stability order is: DN1>DN3>DN2. The major difference between DN1 and DN2, DN3 forms in gas phase was found for 7-H position with 16.7 kcal mol⁻¹. The order of stability of DN1 tautomer over DN2 and DN3 tautomers in the gas phase is 7-OH > 7-CF₃ > 7-CL > 7-CH₃ > 7-H This indicates that the stability of DN2 and DN3 forms does not relate to the nature of substituents. The calculated dipole moments for the DNs are presented in Table 2. It is notable that dipole at the 7th position. In all forms of tautomers, electron releasing derivatives have smaller dipole moments than electron withdrawing ones. This maybe explained by consideration of charge values on atoms of DN ring. It is well known that in DN1, N12, N13 and C9 atoms carry the most negative charge. The DN1 isomer of 7-OH derivative has the least charge density on N12 and N13. However as it can be seen from Table 3 in the DN2 and DN3 derivatives C2, N12 and N13 have the most charge density and therefore charge distribution has occurred. The calculated values NBO charges using the Natural Population Analysis (NPA) of optimized structures of 4,8-dioxygenated 1,5-naphthyridine derivatives are listed in Table 3. As it was noticed previously, DNs nitrogen atom at position 12 or 13 carry the largest negative charge and these positions will most effectively interact with electrophiles^{30,31}. There is no uniform trend for the variation of charges to relate to the different substituents of DN in the gas phase, Table 3.

Solvent effects

Solvent effects are relevant in tautomer stability phenomena, since polarity differences among tautomers can induce significant changes in their relative energies in solution We decided to use of PCM/B3LYP calculations to analyze the solvent effects on tautomerism of 4,8-dioxygenated

1,5-naphthyridine derivatives. It is important to stress that the PCM model does not consider the presence of explicit solvent molecules; hence specific solute–solvent interactions are not described and the calculated solvation effects arise only from mutual solute–solvent electrostatic polarization. The data presented in Table 1 show

that polar solvents increase the stability of all DN_s in compare to gas phase. In solvent phase DN₁ tautomer is more stable than other forms. The plots of relative stability of DN₁, DN₂ and DN₃ tautomers are depicted in Figure 2. The difference between the total energies of DN₂ and DN₃ with electron withdrawing and electron releasing substituents do

Table 1: Total energies^a at B3LYP/6-311++G in the gas phase and solvents**

R	Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol(33)	Water(78.4)
CF3	DN1	-905.5337	-905.5424	-905.5479	-905.5499	-905.5503
	DN2	-905.5082	-905.5202	-905.5283	-905.5314	-905.5320
	DN3	-905.5167	-905.5232	-905.5271	-905.5286	-905.5288
CL	DN1	-1028.0876	-1028.0961	-1028.1014	-1028.1034	-1028.1074
	DN2	-1028.0617	-1028.0733	-1028.0814	-1028.0844	-1028.0850
	DN3	-1028.0736	-1028.0796	-1028.0833	-1028.0847	-1028.0849
H	DN1	-568.4756	-568.4835	-568.4884	-568.4902	-568.4905
	DN2	-568.4489	-568.4600	-568.4675	-568.4704	-568.4709
	DN3	-568.4598	-568.4657	-568.4693	-568.4706	-568.4708
CH3	DN1	-607.7958	-607.8033	-607.8081	-607.8098	-607.8101
	DN2	-607.7693	-607.7798	-607.7870	-607.7898	-607.7903
	DN3	-607.7789	-607.7847	-607.7883	-607.7896	-607.7898
OH	DN1	-643.7060	-643.7135	-643.7182	-643.7198	-643.7201
	DN2	-643.6823	-643.6923	-643.6990	-643.7015	-643.7020
	DN3	-643.6849	-643.6913	-643.6953	-643.6967	-643.6969

^aHartree.

Table 2: Calculated dipole moments of optimized tautomers of 4,8-dioxygenated 1,5-naphthyridine (Deby)

R	Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol(33)	Water(78.4)
CF3	DN1	2.8212	3.0857	3.2556	3.3185	3.3295
	DN2	10.0189	11.6795	12.874	13.3444	13.4292
	DN3	5.8159	6.5571	7.0721	7.2714	7.3072
CL	DN1	1.6042	1.87	2.0542	2.1252	2.1379
	DN2	9.1793	10.8629	12.0881	12.5732	12.6609
	DN3	4.6097	5.3286	5.8384	6.0377	6.0735
H	DN1	0.0017	0.002	0.0022	0.0023	0.0023
	DN2	8.2121	9.7145	10.8116	11.2471	11.3257
	DN3	2.95	3.4096	3.7388	3.8682	3.8916
CH3	DN1	0.5202	0.5539	0.5764	0.585	0.5865
	DN2	7.7758	9.267	10.3652	10.8033	10.8826
	DN3	2.4313	2.8282	3.1144	3.2272	3.2476
OH	DN1	1.4062	1.6081	1.7516	1.8079	1.818
	DN2	7.6106	8.997	10.0111	10.4141	10.487
	DN3	3.0952	3.6125	3.9889	4.1381	4.1652

Table.3: Calculated NBO charges on ring atoms of 4,8-dioxygenated 1,5-naphthyridine

R	e= Atom	DN1					DN2					DN3						
		1.0	2.2	7.6	33	78.4	1.0	2.2	7.6	33	78.4	1.0	2.2	7.6	33	78.4		
CF ₃	C1	0.385	0.485	0.486	0.487	0.487	0.393	0.364	0.369	0.371	0.372	0.427	0.407	0.407	0.406	0.406	0.406	
	C2	-0.263	-0.313	-0.317	-0.319	-0.319	-0.296	-0.332	-0.328	-0.326	-0.325	-0.319	-0.358	-0.352	-0.350	-0.350	-0.350	
	C3	0.111	0.108	0.115	0.117	0.118	0.054	0.072	0.072	0.072	0.072	0.063	0.097	0.099	0.100	0.100	0.100	
	C7	0.071	0.074	0.080	0.082	0.083	0.131	0.127	0.122	0.120	0.120	0.117	0.115	0.115	0.116	0.116	0.116	
	C8	0.350	0.466	0.467	0.467	0.467	0.086	0.103	0.112	0.116	0.116	0.076	0.108	0.107	0.107	0.107	0.107	
	C9	-0.304	-0.363	-0.366	-0.368	-0.368	0.367	0.505	0.508	0.508	0.508	0.427	0.431	0.432	0.433	0.433	0.433	
	N12	-0.552	-0.545	-0.541	-0.540	-0.539	-0.416	-0.481	-0.498	-0.505	-0.506	-0.470	-0.507	-0.515	-0.518	-0.518	-0.518	
	N13	-0.577	-0.554	-0.551	-0.550	-0.549	-0.582	-0.568	-0.561	-0.559	-0.558	-0.813	-0.651	-0.657	-0.659	-0.659	-0.659	
	Cl	C1	0.350	0.455	0.456	0.456	0.456	0.395	0.363	0.368	0.371	0.371	0.428	0.408	0.407	0.407	0.407	0.407
		C2	-0.135	-0.175	-0.179	-0.180	-0.180	-0.303	-0.335	-0.331	-0.329	-0.329	-0.323	-0.364	-0.359	-0.356	-0.356	-0.356
		C3	0.079	0.059	0.065	0.068	0.069	0.052	0.070	0.070	0.070	0.070	0.064	0.096	0.098	0.099	0.099	0.099
		C7	0.071	0.074	0.080	0.082	0.083	0.125	0.120	0.116	0.115	0.114	0.121	0.121	0.122	0.122	0.122	0.122
		C8	0.351	0.467	0.468	0.468	0.468	0.052	0.049	0.059	0.063	0.064	0.053	0.077	0.076	0.075	0.075	0.075
C9		-0.306	-0.367	-0.371	-0.372	-0.372	0.349	0.479	0.480	0.480	0.480	0.388	0.380	0.381	0.381	0.381	0.382	
N12		-0.551	-0.545	-0.541	-0.539	-0.539	-0.420	-0.482	-0.500	-0.506	-0.508	-0.463	-0.500	-0.508	-0.511	-0.511	-0.511	
H	N13	-0.578	-0.555	-0.552	-0.551	-0.551	-0.579	-0.569	-0.563	-0.560	-0.559	-0.814	-0.652	-0.658	-0.660	-0.660	-0.661	
	C1	0.373	0.465	0.465	0.465	0.465	0.392	0.360	0.365	0.367	0.367	0.427	0.405	0.404	0.403	0.403	0.403	
	C2	-0.330	-0.369	-0.373	-0.375	-0.375	-0.300	-0.338	-0.334	-0.332	-0.332	-0.324	-0.365	-0.361	-0.360	-0.360	-0.359	
	C3	0.086	0.071	0.077	0.079	0.079	0.050	0.065	0.065	0.065	0.064	0.060	0.091	0.092	0.093	0.093	0.093	
	C7	0.069	0.071	0.077	0.079	0.079	0.056	0.061	0.070	0.074	0.075	0.052	0.084	0.082	0.082	0.082	0.082	
	C8	0.351	0.465	0.465	0.465	0.465	0.357	0.486	0.486	0.486	0.486	0.405	0.397	0.397	0.397	0.397	0.397	
	C9	-0.307	-0.369	-0.373	-0.375	-0.375	-0.316	-0.375	-0.383	-0.386	-0.386	-0.309	-0.340	-0.342	-0.343	-0.343	-0.343	
	N12	-0.560	-0.555	-0.553	-0.551	-0.551	-0.420	-0.485	-0.503	-0.510	-0.511	-0.480	-0.559	-0.563	-0.564	-0.564	-0.564	
	N13	-0.577	-0.555	-0.552	-0.551	-0.551	-0.587	-0.580	-0.574	-0.572	-0.571	-0.478	-0.518	-0.528	-0.532	-0.532	-0.532	

Table 3 Continue

CH ₃	C1	0.376	0.470	0.470	0.471	0.471	0.393	0.359	0.364	0.366	0.367	0.429	0.405	0.404	0.403	0.403	0.403
	C2	-0.123	-0.156	-0.158	-0.159	-0.159	-0.303	-0.340	-0.336	-0.335	-0.335	-0.329	-0.370	-0.366	-0.364	-0.364	-0.364
	C3	0.087	0.065	0.070	0.072	0.072	0.050	0.064	0.063	0.063	0.063	0.063	0.060	0.091	0.092	0.092	0.092
OH	C7	0.069	0.071	0.077	0.079	0.080	0.128	0.116	0.111	0.109	0.109	0.121	0.113	0.112	0.112	0.112	0.112
	C8	0.352	0.465	0.465	0.465	0.465	0.057	0.055	0.063	0.067	0.067	0.060	0.088	0.086	0.085	0.085	0.085
	C9	-0.310	-0.373	-0.377	-0.379	-0.379	0.361	0.493	0.493	0.493	0.493	0.402	0.399	0.399	0.399	0.399	0.399
OH	N12	-0.553	-0.551	-0.549	-0.548	-0.547	-0.422	-0.485	-0.502	-0.510	-0.511	-0.471	-0.514	-0.524	-0.528	-0.528	-0.529
	N13	-0.578	-0.555	-0.553	-0.552	-0.551	-0.580	-0.576	-0.570	-0.568	-0.568	-0.814	-0.655	-0.661	-0.664	-0.664	-0.664
	C1	0.322	0.407	0.407	0.407	0.407	0.399	0.362	0.367	0.369	0.369	0.429	0.408	0.407	0.406	0.406	0.406
OH	C2	0.283	0.242	0.239	0.238	0.238	-0.301	-0.342	-0.339	-0.338	-0.337	-0.329	-0.377	-0.373	-0.372	-0.371	-0.371
	C3	0.034	-0.017	-0.013	-0.011	-0.011	0.058	0.066	0.067	0.067	0.067	0.060	0.094	0.094	0.094	0.094	0.094
	C7	0.070	0.075	0.081	0.084	0.084	0.125	0.097	0.093	0.092	0.092	0.121	0.116	0.116	0.116	0.116	0.116
OH	C8	0.352	0.468	0.469	0.469	0.469	0.053	-0.029	-0.021	-0.018	-0.017	0.060	0.036	0.033	0.032	0.032	0.032
	C9	-0.311	-0.378	-0.382	-0.384	-0.384	0.326	0.440	0.439	0.438	0.438	0.402	0.310	0.312	0.312	0.312	0.312
	N12	-0.554	-0.540	-0.537	-0.537	-0.536	-0.421	-0.484	-0.502	-0.509	-0.510	-0.471	-0.499	-0.509	-0.513	-0.514	-0.514
OH	N13	-0.579	-0.557	-0.554	-0.553	-0.553	-0.562	-0.564	-0.559	-0.557	-0.556	-0.814	-0.655	-0.661	-0.663	-0.664	-0.664

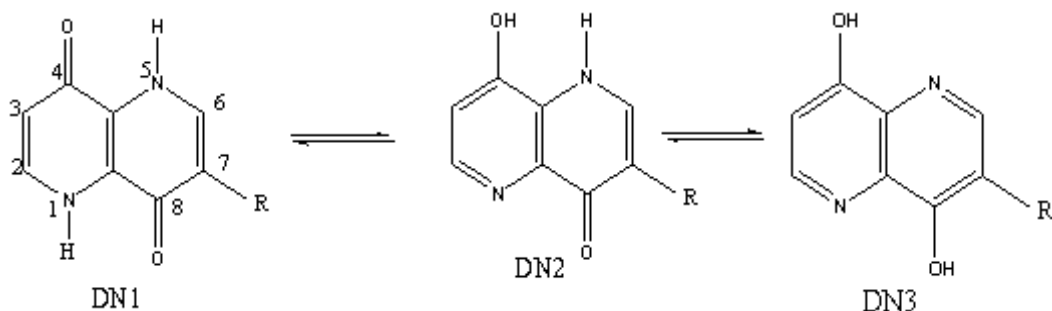


Fig. 1: Tautomeric forms of 4,8-dioxygenated 1,5-naphthyridine

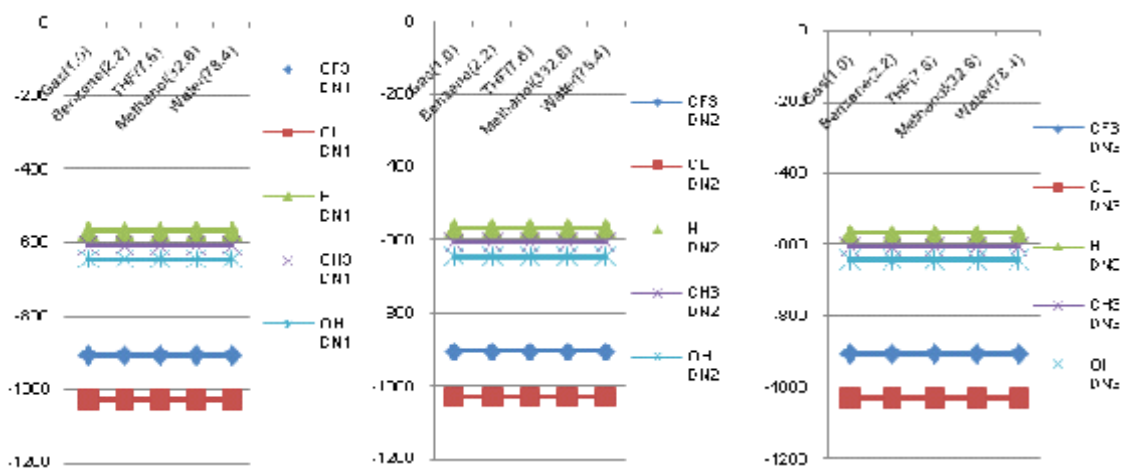


Fig. 2: Relative stability of DN1, DN2 and DN3 tautomers from left to right respectively

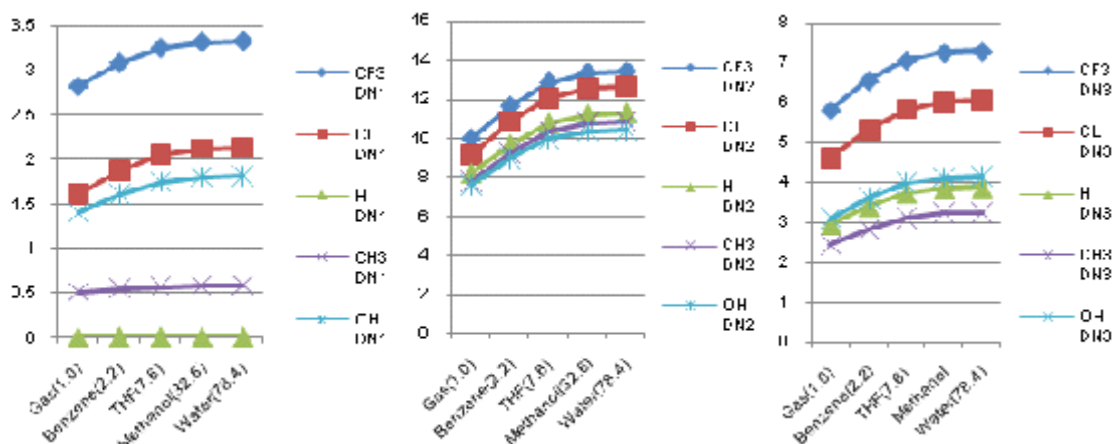


Fig. 3: Dielectric constant dependence of the dipole moments of DN1, DN2 and DN3 tautomers from left to right respectively

not show a regular trend when changing from gas phase to most polar solvents (water). The electron donating substituent at 7-OH position show a regular decrease of in the difference between DN2 and DN3 form. For benzene with small dielectric constant, the stability order of tautomers with CL, CF₃, H and CH₃ substituent group is; DN1 > DN3 > DN2. But for OH substituent DN3 is more stable than DN2. But for THF the stability order of tautomers with CF₃ and OH substituent group is; DN1 > DN2 > DN3 but for CL, H and CH₃ substituents DN3 is more stable than DN2. In methanol with a relatively high dielectric constant with CF₃, CH₃ and OH substituents the stability order is; DN1 > DN2 > DN3, and for CL and H substituents DN3 is more stable than DN2. However for a more polar solvent (water) tautomer stability order is; DN1 > DN2 > DN3 for all derivatives. The solvent represented by a polarizable continuum is found show significant effect on the dipole moments of the individual solute conformers. The dipole moment as by increasing the solvent polarity. The most significant variations being obtained in DN2 form with 7-CF₃ substituent position for water and gas phases is 3.4103 Deby. Plot of dipole moment of 4,8-dioxygenated 1,5-naphthyridine derivatives vs. dielectric constants are given in Figure 3. The curves show an asymptotic behavior. charge distributions of dipolar

compounds are often altered significantly in the presence of a solvent reaction field ³². We have examined the charge distribution of tautomers in the solvent as well as gas phase by using calculated NBO charges. The charge distribution in solvents with increase of polarity differently varies for any atoms. For example, a regular decrease of negative charge was found for N12 and N13 atoms in DN1 form when passing from gas phase to more polar solvent water, but for the DN2 form an increase of negative charge was obtained.

CONCLUSIONS

1. In the gas phase all DN1 form were more stable than the Others. The order of stability in gas phase is; DN1 > DN3 > DN2. With increase of polarity total energy of all compounds were more negative.
2. The dipole moments of all compounds are affected by solvent. With increase of the polarity of solvents the dipole moments of all DN tautomers were increased.
3. The charges on all five positions were affected by substituents and solvents In addition with increase of dielectric constant a regular variation was found.

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