A theoretical DFT study on the stability of imidazopyridine and its derivatives considering the solvent effects and NBO analysis

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Computational calculations at B3LYP/cc-pvdz level were employed in the study of the predominant tautomeric forms of imidazopyridine derivatives (H, NO_2, Cl, OH, CH_3, CF_3) in gas phase and in selected solvents like benzene, tetrahydrofuran (THF), methanol and water. The tautomers were optimized in solvents according to the polarizable continuum method (PCM) and all structures were optimized at this level. The results show that the tautomer IP1 is more stable than the other tautomers. In addition, the stability of the tautomers in different solvents shows an interesting behavior. Variations of dipole moments and NBO charges on atoms in the solvents were studied.

Keywords: DFT study, NBO charges, Imidazopyridine, Dipole moments

INTRODUCTION

Tautomeric interconversions have been investigated by chemists during the last decades. Recently, the study of tautomerism received renewed attention due to its importance for the determination of compounds' properties and their area of applications. The imidazopyridines (IPs) are a class of short-acting hypnotic, antibacterial and anticonvulsant drugs related to benzodiazepines. The IP derivatives are structurally different from benzodiazepines.[1,2] Several other papers have been devoted to their hypnotic, [3-6] analgesic and antipyretic, as well as antiviral effects. [7-9] Two highly efficient one-pot annulation reactions are described for the synthesis of imidazopyridine derivatives (IPs). The first one allows the production of simpler IPs, the second leads to IPs with functionalized imidazole moiety [10]. Synthesis and SAR studies of very potent imidazopyridine antiprotozoal agents was also reviewed.[11] Molecular structure, vibrational energy levels and potential energy distribution of 1H-imidazo[4,5-b]pyridine, 3H-imidazo[4,5-b] pyridine, 5-methyl-1H-imidazo[4,5-b]pyridine,6-methyl-1H-imidazo[4,5b]pyridine and 7-methyl-3H-imidazo[4,5-b]pyridine were determined using density functional theory(DFT) at the B3LYP/6-31G(d,p) level[12]. Thereupon compounds containing different tautomers can be the subject of

interest by theoretical chemists [13-15]. Many of the compounds possess clinically useful activity, especially as anticonvulsants (e.g., norantoin, mephenytoin, nirvanol, and methetoin). Many biological activities of hydantoin derivatives are known, as in their uses as herbicides and fungicides some N-substituted derivatives of hydantoin are employed as chlorinating or brominating agents in disinfectant/sanitizer or biocide products. Both the electron distribution and the stereochemistry of the hydantoins are important for their biological activity. For this reason and along with a research program to study the structure–activity relationships for this class of compounds, the solvent effects on the tautomerism of imidazopyridine and its derivatives were studied.

COMPUTIONAL METHOD

All calculations were carried out on a corei7 personal computer by means of GAUSSIAN09 program package. First all compounds' structures were drawn using Gauss View 03 [16] and optimized by semi-empirical methods. To characterize the optimized geometries the vibrational frequencies for all conformers were 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 procedure [17-21] to build the cavity in the polarisable continuum medium, where the solute is

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accommodated. Atomic charges in all structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital (NBO) approach [22-27].

RESULTS AND DISCUSSION

Gas phase

Structures and numbering of imidazopyridine are depicted in Fig. 1 and the results of energy comparisons of five tautomers in gas phase and in different solvents are given in Table 1. In the gas phase IP1 forms are more stable than the other forms. The order of stability of all tautomers in the gas phase is IP1>IP2>IP3. But OH substitution is an exception. If the substituted hydroxyl interacts with double bond nitrogen, as shown in Figure 2, IP2(A) is predominant to IP3, otherwise IP3(A) is [E2(Hartree)-E1(Hartree)]$_*$ 627.5096 = 4.522 kcal.mol^{-1} more predominant than IP2. The order of stability is IP1>IP3(A)>IP2.

The calculated dipole moments are presented in Table 2. For all conformer tautomers IP1 with Cl substituted has a lower dipole moment in gas phase as much as 1.3225D. Among all forms and in all phases the highest dipole moment belongs to IP3 with NO$_2$ substitution in water solution with a value of 13.1005 Debye. The largest difference of dipole moments belongs to gas and water phases for IP3 form with NO$_2$ substitution (3.2652 Debye).

The calculated values of NBO charges using the Natural population Analysis (NPA) of optimized structures of imidazopyridine derivatives in gas and solvent phases are listed in Tables 3, 4, 5 and 6. Among all positions for all structures the N9 atom has the most negative charge. For all structures, N9, N10 and N11 atoms have the most negative charge compared to the other ones. The most negative charge on the carbons belongs to C1 and C2 atoms, and these positions will most effectively interact with electrophiles.
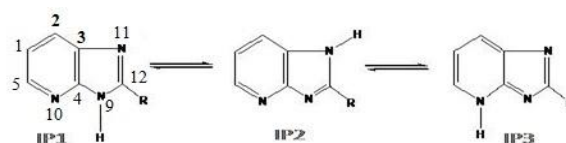

Fig.1. Tautomeric forms of imidazopyridines.

Table 1 . Total energies(Hartree**)** at B3LYP/CC-PVDZ in gas phase and in solvents.

R	Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol	Water(78.4)
	IP1	-600.447	-600.452	-600.456	-600.457	-600.457
NO2	IP2	-600.440	-600.448	-600.454	-600.455	-600.456
	IP3	-600.432	-600.444	-600.451	-600.454	-600.455
	IP1	-732.990	-732.995	-732.997	-732.998	-732.998
CF3	IP2	-732.984	-732.936	-732.995	-732.997	-732.997
	IP3	-732.977	-732.986	-732.991	-732.993	-732.994
	IP1	-855.550	-855.552	-855.557	-855.558	-855.558
CL	IP2	-855.544	-855.551	-855.555	-855.557	-855.557
	IP3	-855.539	-855.547	-855.552	-855.554	-855.555
	IP1	-395.935	-395.940	-395.944	-395.945	-395.945
H	IP2	-395.929	-395.936	-395.942	-395.943	-395.9442
	IP3	-395.920	-395.927	-395.932	-395.934	-395.934
	IP1	-435.260	-435.265	-435.268	-435.269	-435.269
CH3	IP2	-435.253	-435.261	-435.266	-435.268	-435.268
	IP3	-435.244	-435.251	-435.256	-435.257	-435.255
	IP1	-471.173	-471.179	-471.182	-471.183	-471.183
	IP1(A)	-471.173	-471.171	-471.176	-471.178	-471.767
	IP2	-471.155	-471.166	-471.174	-471.177	-471.177
OH	IP2(A)	-471.168	-471.175	-471.180	-471.182	-471.182
	IP3	-471.161	-471.169	-471.175	-471.176	-471.177
	IP3(A)	-471.162	-471.170	-471.175	-471.177	-471.177

Table 2. Calculated dipole moments of imidazopyridine (Debye).

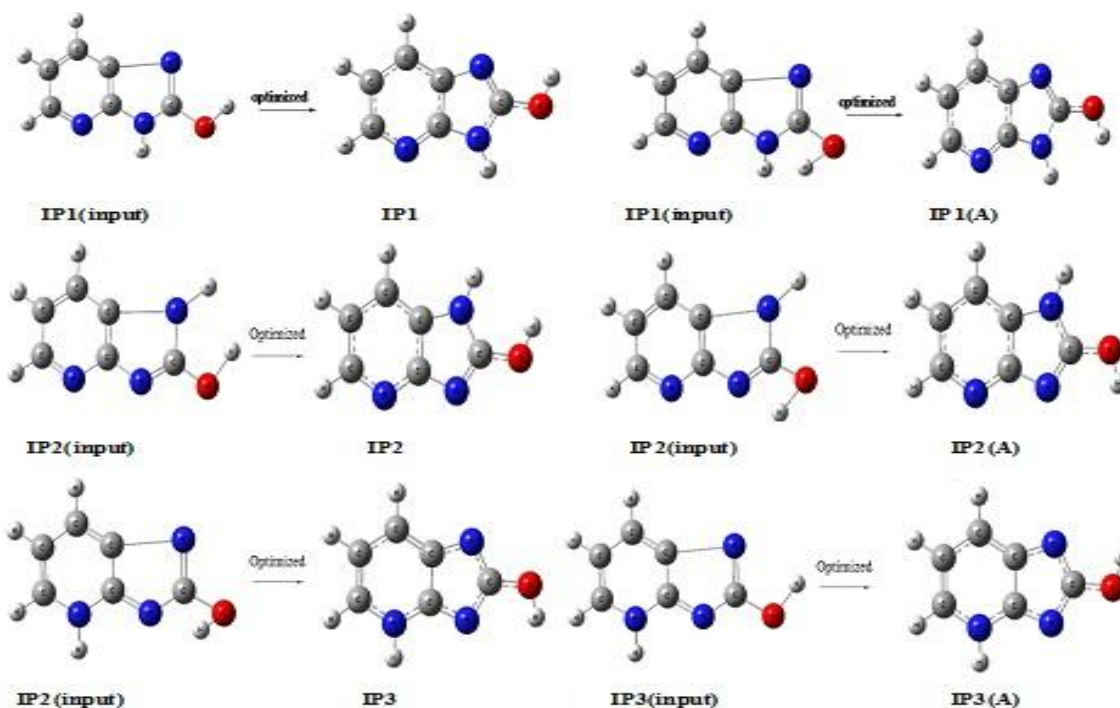| R	Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol	Water(78.4)
NO2	IP1	4.017	4.495	4.830	4.961	4.984
	IP2	6.234	7.210	7.910	8.186	8.236
	IP3	9.835	11.415	12.562	13.018	13.101
CF3	IP1	2.085	2.294	2.438	2.493	2.503
	IP2	5.419	6.353	6.924	7.168	7.212
	IP3	7.846	9.057	9.911	10.243	10.302
CL	IP1	1.323	1.505	1.632	1.681	1.690
	IP2	5.291	6.172	6.796	7.039	7.083
	IP3	6.544	7.759	8.634	8.977	9.039
H	IP1	1.611	1.854	2.023	2.088	2.100
	IP2	5.458	6.353	6.984	7.230	7.274
	IP3	5.093	6.051	6.747	7.022	7.071
CH3	IP1	2.045	2.385	2.623	2.715	2.731
	IP2	5.482	6.448	7.186	7.406	7.454
	IP3	4.420	5.296	5.931	6.182	6.227
	IP1	1.486	1.701	1.849	1.906	1.916
	IP1(A)	1.1 86	1.391	1.536	1.592	1.536
OH	IP2	6.898	7.995	8.762	9.060	9.113
	IP2(A)	4.267	5.020	5.555	5.736	5.801
	IP3	5.292	6.223	6.893	7.156	7.203
	IP3(A)	3.934	4.746	5.340	5.575	5.618

Fig.2. Optimized structures of IP1, IP2 and IP3 for 8-OH position.

Table 3. Calculated NBO charge on ring atoms of IP1.

R	e=	1.0	2.2	7.6	32.6	78.4
	Atom	IP1	IP1	IP1	IP1	IP1
	C1	-0.2604	-0.2812	-0.2800	-0.2794	-0.2793
	C2	-0.2401	-0.1765	-0.1764	-0.1764	-0.1764
	C3	0.0228	0.0969	0.0969	0.0969	0.0969
	C4	0.3677	0.4126	0.4146	0.4153	0.4155
CF3	C5	0.0581	0.0711	0.0722	0.0727	0.0728
	N9	-0.6388	-0.5974	-0.5937	-0.5924	-0.5921
	N10	-0.4831	-0.5154	-0.5208	-0.5226	-0.5229
	N11	-0.2477	-0.4949	-0.5039	-0.5073	-0.5079
	C12	0.5117	0.5579	0.5600	0.5607	0.5608
	C1	-0.2640	-0.2854	-0.2854	-0.2853	-0.2853
	C2	-0.2409	-0.1826	-0.1835	-0.1839	-0.1839
	C3	-0.0011	0.0944	0.0933	0.0928	0.0928
	C4	0.3650	0.4037	0.4045	0.4048	0.4049
NO2	C5	0.0521	0.0583	0.0576	0.0574	0.0574
	N9	-0.6204	-0.5925	-0.5891	-0.5878	-0.5876
	N10	-0.4935	-0.5183	-0.5238	-0.5256	-0.5259
	N11	-0.2747	-0.5146	-0.5246	-0.5284	-0.5290
	C12	0.2707	0.3337	0.3357	0.3364	0.3365
	C1	-0.2759	-0.2870	-0.2874	-0.2875	-0.2875
	C2	-0.2456	-0.1903	-0.1914	-0.1919	-0.1920
	C3	-0.0521	0.0956	0.0941	0.0935	0.0934
Cl	C4	0.3665	0.4030	0.4037	0.4040	0.4040
	C5	0.0404	0.0484	0.0473	0.0469	0.0469
	N9	-0.6325	-0.6197	-0.6167	-0.6155	-0.6153
	N10	-0.5176	-0.5214	-0.5269	-0.5288	-0.5291
	N11	-0.4225	-0.5479	-0.5586	-0.5625	-0.5632
	C12	-0.0663	0.4283	0.4302	0.4309	0.4310
	C1	-0.2678	-0.2919	-0.2929	-0.2933	-0.2933
	C2	-0.2421	-0.1913	-0.1935	-0.1943	-0.1945
	C3	-0.0259	0.0881	0.0862	0.0855	0.0854
	C4	0.3590	0.3954	0.3953	0.3953	0.3953
H	C5	0.0464	0.0464	0.0443	0.0435	0.0434
	N9	-0.6257	-0.6112	-0.6083	-0.6073	-0.6071
	N10	-0.5024	-0.5251	-0.5310	-0.5330	-0.5334
	N11	-0.3121	-0.5513	-0.5643	-0.5691	-0.5699
	C12	0.2026	0.2831	0.2880	0.2898	0.2902
	C1	-0.2701	-0.2936	-0.2948	-0.2953	-0.2954
	C2	-0.2425	-0.1956	-0.1982	-0.1992	-0.1993
	C3	-0.0279	0.0953	0.0935	0.0928	0.0927
	C4	0.3657	0.4017	0.4016	0.4016	0.4016
CH3	C5	0.0451	0.0409	0.0384	0.0375	0.0373
	N9	-0.6365	-0.6165	-0.6139	-0.6129	-0.6127
	N10	-0.5048	-0.5280	-0.5341	-0.5362	-0.5366
	N11	-0.3119	-0.5633	-0.5756	-0.5801	-0.5809
	C12	0.4087	0.4823	0.4876	0.4895	0.4898

Table 4. Calculated NBO charge on ring atoms for IP2.

R	e= Atom	1.0 IP2	2.2 IP2	7.6 IP2	32.6 IP2	78.4 IP2
	C1	-0.2604	-0.2812	-0.2800	-0.2794	-0.2793
	C2	-0.2401	-0.1765	-0.1764	-0.1764	-0.1764
	C3	0.0228	0.0969	0.0969	0.0969	0.0969
CF3	C4	0.3677	0.4126	0.4146	0.4153	0.4155
	C5	0.0581	0.0711	0.0722	0.0727	0.0728
	N9	-0.6388	-0.5974	-0.5937	-0.5924	-0.5921
	N10	-0.4831	-0.5154	-0.5208	-0.5226	-0.5229
	N11	-0.2477	-0.4949	-0.5039	-0.5073	-0.5079
	C12	0.5117	0.5579	0.5600	0.5607	0.5608
	C1	-0.2640	-0.2854	-0.2854	-0.2853	-0.2853
	C2	-0.2409	-0.1826	-0.1835	-0.1839	-0.1839
	C3	-0.0011	0.0944	0.0933	0.0928	0.0928
NO2	C4	0.3650	0.4037	0.4045	0.4048	0.4049
	C5	0.0521	0.0583	0.0576	0.0574	0.0574
	N9	-0.6204	-0.5925	-0.5891	-0.5878	-0.5876
	N10	-0.4935	-0.5183	-0.5238	-0.5256	-0.5259
	N11	-0.2747	-0.5146	-0.5246	-0.5284	-0.5290
	C12	0.2707	0.3337	0.3357	0.3364	0.3365
	C1	-0.2759	-0.2870	-0.2874	-0.2875	-0.2875
	C2	-0.2456	-0.1903	-0.1914	-0.1919	-0.1920
	C3	-0.0521	0.0956	0.0941	0.0935	0.0934
Cl	C4	0.3665	0.4030	0.4037	0.4040	0.4040
	C5	0.0404	0.0484	0.0473	0.0469	0.0469
	N9	-0.6325	-0.6197	-0.6167	-0.6155	-0.6153
	N10	-0.5176	-0.5214	-0.5269	-0.5288	-0.5291
	N11	-0.4225	-0.5479	-0.5586	-0.5625	-0.5632
	C12	-0.0663	0.4283	0.4302	0.4309	0.4310
	C1	-0.2678	-0.2919	-0.2929	-0.2933	-0.2933
	C2	-0.2421	-0.1913	-0.1935	-0.1943	-0.1945
	C3	-0.0259	0.0881	0.0862	0.0855	0.0854
H	C4	0.3590	0.3954	0.3953	0.3953	0.3953
	C5	0.0464	0.0464	0.0443	0.0435	0.0434
	N9	-0.6257	-0.6112	-0.6083	-0.6073	-0.6071
	N10	-0.5024	-0.5251	-0.5310	-0.5330	-0.5334
	N11	-0.3121	-0.5513	-0.5643	-0.5691	-0.5699
	C12	0.2026	0.2831	0.2880	0.2898	0.2902
	C1	-0.2701	-0.2936	-0.2948	-0.2953	-0.2954
	C2	-0.2425	-0.1956	-0.1982	-0.1992	-0.1993
	C3	-0.0279	0.0953	0.0935	0.0928	0.0927
CH3	C4	0.3657	0.4017	0.4016	0.4016	0.4016
	C5	0.0451	0.0409	0.0384	0.0375	0.0373
	N9	-0.6365	-0.6165	-0.6139	-0.6129	-0.6127
	N10	-0.5048	-0.5280	-0.5341	-0.5362	-0.5366
	N11	-0.3119	-0.5633	-0.5756	-0.5801	-0.5809
	C12	0.4931	0.4829	0.4888	0.4910	0.4914

Table 5. Calculated **NBO** charge on ring atoms of **IP3**.

R	e= Atom	1.0 IP3	2.2 IP3	7.6 IP3	32.6 IP3	78.4 IP3
	-0.2801	-0.2942	-0.2908	-0.2891	-0.2888	-0.2801
	-0.1998	-0.1478	-0.1452	-0.1443	-0.1441	-0.1998
	-0.0763	0.1071	0.1041	0.1029	0.1027	-0.0763
CF3	0.4167	0.4195	0.4209	0.4214	0.4215	0.4167
	0.0644	0.0720	0.0848	0.0900	0.0910	0.0644
	-0.6156	-0.5846	-0.5917	-0.5942	-0.5947	-0.6156
	-0.5616	-0.5213	-0.5175	-0.5160	-0.5157	-0.5616
	-0.2197	-0.5396	-0.5504	-0.5545	-0.5552	-0.2197
	0.5130	0.5398	0.5329	0.5300	0.5295	0.5130
	-0.2840	-0.2979	-0.2958	-0.2948	-0.2946	-0.2840
	-0.2043	-0.1571	-0.1558	-0.1554	-0.1553	-0.2043
	-0.0869	0.1058	0.1013	0.0995	0.0992	-0.0869
NO2	0.4136	0.4213	0.4219	0.4220	0.4220	0.4136
	0.0605	0.0613	0.0717	0.0759	0.0767	0.0605
	-0.6170	-0.5998	-0.6077	-0.6106	-0.6111	-0.6170
	-0.5631	-0.5248	-0.5213	-0.5200	-0.5197	-0.5631
	-0.2440	-0.5525	-0.5635	-0.5677	-0.5684	-0.2440
	0.2705	0.3212	0.3133	0.3100	0.3095	0.2705
	-0.2847	-0.2957	-0.2942	-0.2934	-0.2932	-0.2847
	-0.2071	-0.1739	-0.1719	-0.1712	-0.1711	-0.2071
	-0.0922	0.1120	0.1072	0.1054	0.1050	-0.0922
CI	0.4162	0.4251	0.4256	0.4257	0.4257	0.4162
	0.0572	0.0475	0.0580	0.0623	0.0630	0.0572
	-0.6396	-0.6172	-0.6248	-0.6276	-0.6281	-0.6396
	-0.5655	-0.5289	-0.5251	-0.5236	-0.5233	-0.5655
	-0.2575	-0.5844	-0.5960	-0.6004	-0.6011	-0.2575
	0.3301	0.4117	0.4057	0.4032	0.4027	0.3301
	-0.2876	-0.3016	-0.3005	-0.2999	-0.2997	-0.2876
	-0.2101	-0.1741	-0.1738	-0.1737	-0.1737	-0.2101
	-0.1011	0.1026	0.0975	0.0955	0.0951	-0.1011
H	0.4079	0.4145	0.4146	0.4145	0.4145	0.4079
	0.0544	0.0461	0.0553	0.0590	0.0597	0.0544
	-0.6391	-0.6248	-0.6330	-0.6359	-0.6364	-0.6391
	-0.5664	-0.5292	-0.5261	-0.5249	-0.5246	-0.5664
	-0.2705	-0.5884	-0.6011	-0.6058	-0.6067	-0.2705
	0.2019	0.2748	0.2674	0.2643	0.2637	0.2019
	-0.2882	-0.3019	-0.3016	-0.3013	-0.3013	-0.2882
	-0.2113	-0.1843	-0.1843	-0.1844	-0.1844	-0.2113
	-0.1079	0.1124	0.1071	0.1050	0.1046	-0.1079
CH3	0.4155	0.4254	0.4254	0.4253	0.4253	0.4155
	0.0514	0.0383	0.0468	0.0503	0.0509	0.0514
	-0.6483	-0.6326	-0.6406	-0.6434	-0.6439	-0.6483
	-0.5670	-0.5342	-0.5312	-0.5301	-0.5299	-0.5670
	-0.2781	-0.5978	-0.6102	-0.6149	-0.6158	-0.2781
	-0.2801	-0.2942	-0.2908	-0.2891	-0.2888	-0.2801

Table 6. Calculated NBO charge for (OH) substituted.

R	e= Atom	1.0	2.2	7.6	32.6	78.4	1.0	2.2	7.6	32.6	78.4
		IP1					IP2				
	C1	-0.2667	-0.2893	-0.2907	-0.2912	-0.2913	-0.2765	-0.2844	-0.2856	-0.2860	-0.2860
	C2	-0.2423	-0.2087	-0.2108	-0.2116	-0.2118	-0.2567	-0.2340	-0.2293	-0.2273	-0.2269
	C3	-0.0110	0.1023	0.1007	0.1001	0.1000	0.1536	0.1052	0.1074	0.1083	0.1085
	C4	0.3664	0.4008	0.4010	0.4011	0.4011	0.3607	0.3942	0.3910	0.3896	0.3894
OH	C5	0.0501	0.0307	0.0278	0.0268	0.0266	0.0576	0.0321	0.0279	0.0262	0.0259
	N9	-0.6589	-0.6434	-0.6419	-0.6413	-0.6412	-0.5883	-0.6039	-0.6241	-0.6318	-0.6332
	N10	-0.4965	-0.5269	-0.5335	-0.5358	-0.5362	-0.4299	-0.5056	-0.5224	-0.5289	-0.5300
	N11	-0.3162	-0.6305	-0.6382	-0.6409	-0.6414	-0.6794	-0.6516	-0.6458	-0.6434	-0.6430
	C12	0.6454	0.8097	0.8133	0.8146	0.8148	0.7731	0.8072	0.8123	0.8141	0.8145
		IP1(A)					IP2(A)				
	C1	-0.2637	-0.2889	-0.2902	-0.2907	-0.2902	-0.2818	-0.2847	-0.2862	-0.2866	-0.2867
	C2	-0.2394	-0.2069	-0.2107	-0.2122	-0.2107	-0.2371	-0.2326	-0.2286	-0.2269	-0.2265
	C3	-0.0130	0.1017	0.1001	0.0995	0.1001	0.1035	0.1054	0.1071	0.1077	0.1079
	C4	0.3644	0.3994	0.4000	0.4002	0.4000	0.3995	0.3957	0.3927	0.3914	0.3912
OH	C5	0.0495	0.0299	0.0267	0.0255	0.0267	0.0360	0.0313	0.0275	0.0259	0.0257
	N9	-0.6717	-0.6602	-0.6553	-0.6534	-0.6553	-0.6134	-0.6329	-0.6458	-0.6507	-0.6516
	N10	-0.4991	-0.5289	-0.5346	-0.5365	-0.5346	-0.4856	-0.5083	-0.5238	-0.5297	-0.5308
	N11	-0.3056	-0.6034	-0.6195	-0.6256	-0.6195	-0.6382	-0.6336	-0.6300	-0.6285	-0.6282
	C12	0 .5994	0.8072	0.8119	0.8138	0.8119	0.8027	0.8094	0.8137	0.8153	0.8156
		IP3					IP3(A)				
	C1	-0.2868	-0.2948	-0.2956	-0.2957	-0.2957	-0.2933	-0.2952	-0.2955	-0.2954	-0.2954
	C2	-0.2125	-0.2062	-0.2063	-0.2064	-0.2064	-0.2083	-0.2079	-0.2073	-0.2070	-0.2070
	C3	-0.0868	0.1221	0.1171	0.1151	0.1147	0.1285	0.1217	0.1167	0.1147	0.1143
	C4	0.4124	0.4340	0.4339	0.4339	0.4339	0.4328	0.4338	0.4339	0.4338	0.4338
OH	C5	0.0559	0.0222	0.0310	0.0345	0.0352	0.0129	0.0230	0.0310	0.0342	0.0348
	N9	-0.6430	-0.6786	-0.6820	-0.6832	-0.6834	-0.6312	-0.6482	-0.6589	-0.6629	-0.6636
	N10	-0.5690	-0.5394	-0.5362	-0.5349	-0.5347	-0.5432	-0.5389	-0.5357	-0.5345	-0.5343
	N11	-0.2368	-0.6313	-0.6470	-0.6529	-0.6540	-0.6484	-0.6614	-0.6698	-0.6729	-0.6735
	C12	0.6770	0.7877	0.7842	0.7827	0.7824	0.7929	0.7887	0.7849	0.7833	0.7830

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 used PCM/B3LYP calculations to analyze the solvent effects on the tautomerism of imidazopyridine 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 forms compared to gas phase. The difference between the total energies of imidazopyridine and the other forms does not show a regular trend when changing from gas phase to most polar solvents (water). If in IP2 form with substituted hydroxyl, hydrogen interacts with double bond nitrogen N9 (Fig. 2) then the order of stability is IP1>IP2 (A)>IP3 in all phases. But if hydrogen of the substituted hydroxyl does not interact with double bond nitrogen (N4) in IP2 and intra-molecular hydrogen bond is not formed, then the order of stability has two different sequences. In the first one hydrogen of the substituted hydroxyl interacts with double bond nitrogen (N7) in IP3, then the order of stability in all phases is IP1>IP3>IP2. The other sequence is when hydrogen of the substituted hydroxyl interacts with double bond nitrogen (N9) then the order of stability in gas phase, benzene, THF is IP1>IP3(A)>IP2 but in polar solvents like water and methanol is IP1>IP2>IP3. Also the dipole moment increases from gas phase to a more polar solvent, then the highest value belongs to IP3 with substituted NO_2 in water phase with 13.1005D. We have examined the charge distribution of tautomers in the solvent, as well as in gas phase by using calculated NBO charges. The charge distribution in solvents with increase in polarity differently varies for any atoms. Calculated Gibbs free energies of all structures at 298.15 K and one atmosphere at B3LYP/cc-pvdz level are illustrated in Table 7. The Gibbs free energy difference (ΔG) between IP3(A) and IP2 for (OH) substituted in gas phase is 2.58 kcal.mol^{-1}.

Table 7. Calculated Gibbs free energy of imidazopyridine (kcal.mol^{-1}).

R	Tautomer	Gas(1.0)	Benzene(2.2)	THF(7.6)	Methanol	Water(78.4)
	IP1	**46.950**	**46.920**	**46.889**	**46.876**	**46.873**
NO2	IP2	46.772	46.809	46.825	46.829	46.829
	IP3	46.222	46.829	46.958	46.986	46.991
	IP1	46.169	45.893	45.570	45.301	45.218
CF3	IP2	46.083	45.993	45.886	45.815	45.798
	IP3	46.586	48.392	48.431	48.414	48.414
	IP1	40.580	40.576	40.567	40.564	40.562
CL	IP2	40.363	40.434	40.476	40.491	40.494
	IP3	40.935	41.009	41.050	41.064	41.066
	IP1	48.037	48.084	48.109	48.116	48.118
H	IP2	47.820	47.940	48.011	48.036	48.040
	IP3	48.319	48.416	48.473	48.492	48.496
	IP1	63.583	63.620	63.632	63.635	63.635
CH3	IP2	63.279	63.431	63.517	63.546	63.551
	IP3	63.628	63.749	63.821	63.846	63.850
	IP1	50.062	50.011	49.971	49.954	49.951
	IP1(A)	49.056	50.011	49.253	49.260	49.261
OH	IP2	48.010	48.757	48.888	48.912	48.915
	IP2(A)	49.828	49.858	49.880	49.878	49.880
	IP3	50.542	50.555	50.555	50.554	50.554
	IP3(A)	50.598	50.606	50.604	50.601	50.601

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ТЕОРЕТИЧНО DFT-ИЗСЛЕДВАНЕ НА СТАБИЛНОСТТА НА ИМИДАЗОПИРИДИН И НЕГОВИ ПРОИЗВОДНИ ПРИ ОТЧИТАНЕ НА ЕФЕКТА НА РАЗТВОРИТЕЛЯ И NBO-АНАЛИЗ

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(Резюме)

Извършени са изчисления на ниво B3LYP/cc за изследването на преобладаващите тавтомерни форми на производните на имидазопиридина (H, NO_2, Cl, OH, CH_3, CF_3) в газова фаза и избрани разтворители като бензен, тетрахидрофуран (THF), метанол и вода. Всички тавтомерни форми са оптимизирани според разтворителите съгласно метода на поляризирания континуум (PCM). Резултатите показват, че тавтомерите IP1 в различни разтворители са по-стабилни от останалите. Изследвани са диполните моменти и NBO-товарите на атомите в разтворителите.