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Density Functional Calculations on Heterocyclic Compounds. Part 1. Studies of Protonations of 5- and 6-Membered Nitrogen Heterocyclics

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Abstract: Density functional calculations at LSD, NLSD/6-31G, DZVP2 levels were performed on azoles, azines and their protonated forms. Geometries and dipole moments were well described by both global bases. Energies obtained at NLSD(BP)/DZVP2 level are reasonably comparable with high level ab initio and experimental data. For atomic charges, LSD/6-31G* level gave acceptable results.*

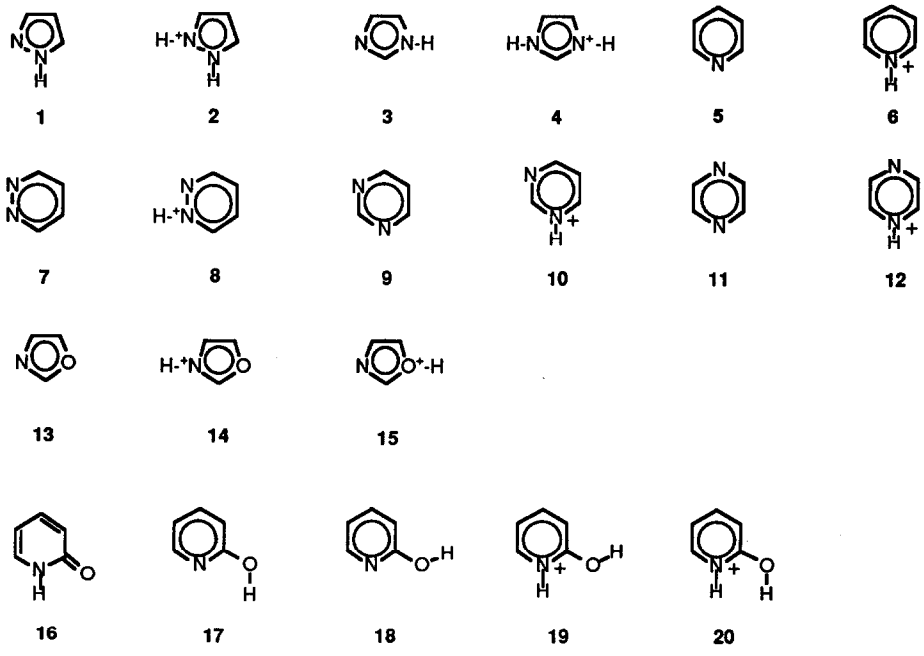
Studies on protonation of heterocyclic compounds are of great interest from not only chemical but also pharmacological points of view. The reactivity of a heterocyclic base caused by protonation may vary in characteristic way. Thus, the site of protonation is closely related to expression of biological activity and often involved directly in receptor-ligand interactions in biological systems. We have been highly motivated in these fields as being continuously interested in the mechanistic and medicinal chemistry of nitrogen heterocycles.

Recently, semiempirical,[2-5] and *ab initio*[4-8] studies on azoles and azines have been carried out in order to get quantitative and predictive tools for studying their proton affinity,[9] by which more insight into their basicities can be available. Of semiempirical procedures, the AM1 method failed to treat correctly the electrostatic proximity effects,[5] operating in the relative basicities and acidities of 1,2-azoles and -diazines.[10] Although empirical corrections were proposed to eliminate this defect,[4] further examinations seem to be necessary for proving general validity. INDO was found to be a qualitatively better approach in spite of relatively large deviations.

The experimental proton affinities could be reproduced in the correct order by high-level *ab initio* calculations, nevertheless, Møller-Plesset correlation treatment had to also be included to get approximate numerical values after taking the zero-point vibrational energy change with other energy terms into consideration.[7] However, *ab initio* calculations at high level are seriously limited by the enormous computational efforts required for polysubstituted molecules, the ordinary building blocks found in the synthetic chemistry. In this context, an alternative method, which is computationally more effective but *not* at the expense of accuracy, is really needed.

Density functional theory (DFT) has recently been recognized as an efficient tool for studying properties of molecules. The local density approximation (LDA) is the fundamental approximation of the theory,[11] and leads to the local spin density (LSD) level of theory. According to LDA, the exchange-correlation energy is a *local* functional of the density. It is important from practical point of view that in the DF methods the need for computational resources scales as $-N^3$, or close to N^2, therefore larger molecules can also be examined in reasonable computational time (*cf. ab initio* scales as N^4-N^7). Promising results have been reported so far for geometric parameters, energetics, vibrational frequencies and dipole moments of small neutral organic molecules[12-15] and calculations on large Zn-insulin fragments were also described.[12d]

In this paper, we wish to report the examination and the result of DF approaches for *protonation enthalpies*, *geometric parameters*, and *dipole moments* of a set of **azoles** and **azines** (Chart). *Charge data* of compounds containing a C(O)-N structural element, and a *tautomerism* will also be discussed. Each of them represents an important field, where the DFT has not yet been systematically tested. Full geometric optimizations were carried out at LSD/DZVP2, 6-31G* levels of the theory and NLSD (Becke-Perdew) energies were also calculated.



Chart

COMPUTATIONAL METHODS

All calculations were done on a Cray-YMP supercomputer with a DGauss program.[16] Full geometric optimizations were carried out with 6-31G* and DZVP2 global basis sets, using P1 and A2 auxiliary bases, respectively. For calculations with 6-31G* and DZVP2 bases, AM1 and 6-31G* optimized structures were used as initial geometries, respectively. Energetics were obtained at LSD, NLSD (BP)/6-31G*, DZVP2

levels of theory. The BP non-local corrections were done after the final SCF. The following computational parameters were employed, for INTACC, XCGRID, CVSCF, CVDENS, CVENER, VCGRAD 'medium' options, corresponding to 5.0E-05, 5.0E-07, and 8.0E-04 values for SCF convergence thresholds of the density, and total energy, and for convergence criterion of the largest gradient component, respectively. Typically, these calculations needed at the most several hundreds sec CPU time.

RESULTS AND DISCUSSION

The geometric data are reported in Table 1 and 2. Bond lengths and angles were generally well reproduced, and the errors are within ±0.01Å and ±1.0°, respectively. Larger deviations from experimental values were observed for carbon-nitrogen bonds of imidazole (**3**), pyrimidine (**9**), oxazole (**13**) and 2(1*H*)-pyridone (**16**), for carbon-hydrogen bonds of pyridine (**5**) and **16** as well as for the nitrogen-nitrogen bond of pyrazole (**1**). In the case of pyridone (**16**), differences between the calculated and experimental values may however be well ascribed to intermolecular interactions being present only in the crystalline state. The most striking errors were found for two angles of pyrimidine (**9**) differing the calculated values from the experimental ones by -2.6 and -2.0 degrees.

Of carbon-oxygen bonds, distances of the carbonyl bond of **16**, and one of the carbon-oxygen bond of **13** were within the ±0.01Å errors, whereas the calculated length of C(5)-O(1) in **13** slightly exceeded this limit.

Both the DZVP2 and 6-31G* bases gave similar results, and no significant differences could be observed either in the trend of errors, or in their absolute values. A reasonable agreement between these basis sets was also found for geometric parameters of protonated compounds.

Total energies, calculated and experimental protonation enthalpies are listed in Table 3. Total energies obtained at the LSD level of the theory were comparable to but slightly more negative than energies calculated by HF method at 3-21G//3-21G level. As expected, including non-local corrections, DF total energies were significantly reduced at both DZVP2 and 6-31G* levels for every compound. Since the total energies of protonated forms were even more reduced than those of the corresponding bases, the protonation enthalpies, accordingly, were decreased by *ca.* 4-5 kcal/mol upon BP treatments. Nevertheless, numerical values obtained at different levels of the theory are comparable to one anothers, and to *ab initio* enthalpies. Interestingly enough, almost the same protonation enthalpies were obtained at the LSD/6-31G* and LSD+BP/DZVP2 levels. The experimental basicity order was fully reproduced by three of the four methods. The LSD/6-31G* level failed to describe only the relative basicities of pyrazine (**11**) and oxazole (**13**).

Assuming that the zero-point energy change and other contributions for the protonation (the former one is dominating) may affect the energetics calculated by *ca.* 6-8 kcal/mol (*cf.* ref.[7]), a fairly good agreement between LSD+BP/DZVP2 energies and experimental proton affinities is observed for *every* case. For pyrazole (**1**) and its protonated form (**2**), we also calculated the zero-point energy change (8.0 kcal/mol), which agreed well with the *ab initio* datum (8.9 kcal/mol) showing the fact that the latter value is overestimated by *ca.* 10%.[7] Taken then for ΔE_t and PV the same values obtained by *ab initio*, our calculated proton affinity is 214.3 kcal/mol, which is well comparable with the experimental (212.8 kcal/mol) and *ab initio* (216.0 kcal/mol) values. The agreement is also reasonable for a number of protonations at the LSD/6-31G* level. Additionally, it is noteworthy that the relative *O, N* basicities of oxazole (**13** → **14,15**) as well as relative stabilities of the *syn* and *anti* conformers of 2-hydroxypyridine (**20** and **19**) were well predicted.

Table 1. Bond lengths (Å) and selected bond angles (deg) of compounds **1** - **10**.

Compound	**1**			**2**	**3**			**4**	**5**		**6**	**7**			**8**		**9**			**10**
Bond	Calcd 6-31G*	Calcd DZVP2	Exp[a]	Calcd 6-31G*	Calcd 6-31G*	Calcd DZVP2	Exp[a]	Calcd 6-31G*	Calcd 6-31G*	Exp[b]	Calcd 6-31G*	Calcd 6-31G*	Calcd DZVP2	Exp[c]	Calcd 6-31G*	Calcd DZVP2	Calcd 6-31G*	Calcd DZVP2	Exp[d]	Calcd 6-31G*
1-2	1.337	1.340	1.349	1.338	1.361	1.366	1.349	1.334	1.334	1.3402	1.347	1.327	1.328	1.330	1.315	1.319	1.333	1.338	1.34	1.352
2-3	1.332	1.337	1.331	1.340	1.314	1.312	1.326	1.339	1.392	1.3945	1.380	1.335	1.339	1.341	1.325	1.329	1.333	1.338	1.33	1.310
3-4	1.406	1.410	1.416	1.388	1.368	1.371	1.378	1.373	1.390	1.3944	1.393	1.392	1.398	1.393	1.402	1.306	1.334	1.338	1.36	1.338
4-5	1.381	1.385	1.373	1.388	1.372	1.380	1.358	1.363	1.390	1.3944	1.393	1.382	1.387	1.375	1.385	1.388	1.389	1.394	1.38	1.397
5-6(1)	1.354	1.357	1.359	1.340	1.371	1.374	1.369	1.372	1.392	1.3945	1.380	1.392	1.398	1.393	1.389	1.393	1.389	1.394	1.41	1.377
6-1									1.334	1.3402	1.347	1.335	1.339	1.341	1.336	1.338	1.334	1.338	1.35	1.348
1-H	1.021	1.022		1.027	1.022	1.022		1.027			1.030				1.034	1.035				1.033
2-H				1.027	1.095	1.094		1.093	1.103	1.0843	1.097						1.103	1.101		1.100
3-H	1.094	1.093		1.095				1.027	1.030				1.100		1.100	1.099				
4-H	1.092	1.091		1.092	1.095	1.093		1.031	1.099	1.0773	1.097	1.098	1.098	1.064	1.098	1.099	1.097	1.097		1.098
5-H	1.094	1.092		1.095	1.091	1.091		1.031	1.098	1.0843	1.098	1.098	1.098		1.098	1.097	1.097	1.097		1.033
6-H									1.103	1.0843	1.097	1.101	1.100		1.098	1.097	1.103	1.101		1.098
1-2-3	104.1	104.3	104.1	109.2	111.5	111.2	111.3	106.8	123.5	123.9	119.3	119.5	119.5	119.3	115.9	115.9	127.1	127.1	129.7	122.3
2-3-4	112.0	111.7	111.9	107.8	105.4	105.7	105.4	110.1	118.5	118.5	119.3	123.6	123.7	123.7	123.1	123.0	115.9	116.0	115.0	117.8
3-4-5	104.9	104.6	104.5	106.1	110.7	110.5	109.8	106.5	118.6	118.3	119.7	116.9	116.8	117.1	118.4	118.6	122.2	122.1	121.3	122.8
4-5-6(1)	106.0	105.9	106.4	107.8	105.1	105.0	106.3	106.5	118.5	118.5	119.3	116.9	116.8	117.1	117.5	117.4	116.6	116.6	118.6	117.4
5-6(1)-1(2)	113.6	113.5	113.1	109.2	107.4	107.6	107.2	110.1	123.5	123.9	119.3	123.6	123.8	123.7	118.5	118.5	122.2	122.1	121.3	118.1
6-1-2									117.5	116.8	123.2	119.5	119.5	119.3	126.6	126.6	115.9	116.0	115.0	121.6

References: a) [17a]; b) [22]; c) [17c]; d) [17d]; Data obtained by gas-phase electron diffraction and/or microwave spectroscopy.

Table 2. Bond lengths (Å) and selected bond angles (deg) of compounds **11** - **20**.

Compound	**11**			**12**	**13**			**14**		**15**	**16**			**17**		**18**	**19**	**20**
	Calcd		Exp[a]	Calcd	Calcd		Exp[b]	Calcd		Calcd	Calcd		Exp[c]	Calcd		Calcd	Calcd	Calcd
Bond	6-31G*	DZVP2		6-31G*	6-31G*	DZVP2		6-31G*	6-31G*	6-31G*	6-31G*	DZVP2		6-31G*	DZVP2	6-31G*	6-31G*	6-31G*
1-2	1.333	1.336	1.339	1.343	1.349	1.358	1.357	1.306	1.313	1.472	1.409	1.406	1.401	1.329	1.330	1.326	1.351	1.353
2-3	1.393	1.398	1.403	1.389	1.296	1.301	1.293	1.320	1.324	1.251	1.442	1.444	1.444	1.400	1.401	1.404	1.394	1.395
3-4	1.333	1.336	1.339	1.332	1.379	1.383	1.395	1.381	1.383	1.389	1.366	1.372	1.334	1.384	1.389	1.386	1.383	1.379
4-5	1.333	1.336	1.339	1.332	1.358	1.365	1.353	1.353	1.356	1.344	1.417	1.422	1.421	1.396	1.401	1.393	1.402	1.404
5-6(1)	1.393	1.398	1.403	1.389	1.357	1.364	1.370	1.362	1.366	1.405	1.365	1.369	1.371	1.387	1.393	1.390	1.373	1.374
6-1	1.333	1.336	1.339	1.343							1.354	1.356	1.335	1.335	1.340	1.332	1.354	1.361
C-O[d]											1.227	1.238	1.236	1.338	1.351	1.346	1.313	1.311
O-H										1.000				0.988	0.986	0.979	0.983	0.984
1-H				1.033							1.026	1.027	1.02				1.032	1.029
2-H	1.101	1.101	1.115	1.098	1.094	1.094		1.095	1.095	1.095								
3-H	1.101	1.101	1.115	1.100				1.030	1.031		1.097	1.097	0.95	1.097	1.097	1.100	1.099	1.096
4-H					1.093	1.093		1.093	1.093	1.094	1.100	1.100	1.18	1.100	1.100	1.100	1.099	1.099
5-H	1.101	1.101	1.115	1.100	1.091	1.091		1.093	1.093	1.093	1.095	1.095	1.02	1.096	1.097	1.098	1.097	1.096
6-H	1.101	1.101	1.115	1.098							1.097	1.096	0.98	1.101	1.102	1.103	1.097	1.097
1-2-3	122.1	122.0	122.2	117.5	114.5	114.1	115.0	109.3	109.3	107.8	112.9	113.3	112.7	123.7	124.1	123.2	118.9	118.5
2-3-4	122.1	122.0	122.2	122.2	104.1	104.6	103.9	108.9	109.0	110.1	121.8	121.5	122.3	117.4	117.5	118.0	118.8	119.4
3-4-5	115.9	115.9	115.6	118.3	109.2	108.9	109.1	105.2	105.1	110.9	121.3	121.3	122.2	119.6	119.3	119.3	120.8	120.5
4-5-6(1)	122.1	122.0	122.2	122.2	107.7	107.8	108.1	108.2	108.4	1105.1	118.0	117.9	116.0	118.1	118.1	117.7	118.7	118.8
5-6(1)-1(2)	122.1	122.0	122.2	117.5	104.5	104.6	103.9	108.4	108.2	106.1	120.3	120.4	121.8	123.2	123.2	123.9	119.5	119.6
6-1-2	115.9	115.9	115.6	122.3							125.5	125.6	125.1	118.0	117.7	117.9	123.4	123.1

References: a) [17e]; b) [17a]; c) [18]. Data obtained by gas-phase electron diffraction and/or microwave spectroscopy (**11**, **13**), or X-ray crystallographic method (**16**).
d) In compounds **16** - **20**.

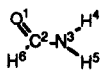
Table 3. Total energies (a.u.)[a] and protonation enthalpies (kcal/mol) of compounds **1** -**20**.

	Density Functional Theory							*Ab Initio*					Exp.[b]
Comp	LSD/6-31G*	$-\Delta H_p$	LSD+BP/6-31G*	$-\Delta H_p$	LSD/DZVP2	$-\Delta H_p$	LSD+BP/DZVP2	$-\Delta H_p$	3-21G//3-21G[c]	$-\Delta H_p$[c]	$-\Delta H_p$[d]	ΔE_r^0[d]	$-\Delta H_p^{corr}$[d]	$-\Delta H_p$
1	-224.2636		-226.2225		-224.3308		-226.2746							
		220.0		222.5		216.1		220.8			223.5	8.9	216.0	212.8
2	-224.6142		-226.5796		-224.6751		-226.6265					8.0[h]		
3	-224.2785		-226.2368		-224.3459		-226.2896							
		232.4		236.8		228.1		232.7			238.1	9.6	230.0	222.1
4	-224.6490		-226.6141		-224.7094		-226.6605							
5	-246.0612		-248.3001		-246.1257		-248.3473		-245.33822					
		229.0		233.4		225.4		230.5		235.8				220.8
6	-246.4258		-248.6721		-246.4849		-248.7146		-245.71402					
7	-261.9989		-264.3113		-262.0673		-264.3636		-261.19032					
		225.6		229.4		221.8		226.5		229.5				215.6
8	-262.3585		-264.6768		-262.4207		-267.7245		-261.55600					
9	-262.0337		-264.3446		-262.1033		-264.3978		-261.23760					
		217.6		222.1		214.1		219.4		224.2				210.5
10	-262.3085		-264.6986		-262.4445		-264.7475		-261.59495					
11	-262.0274		-264.3388		-262.0975		-264.3923		-261.22852					
		215.0		219.9		211.7		216.9		219.9				209.0
12	-262.3701		-264.6890		-262.4349		-264.7380		-261.57896					
13	-244.0532		-246.0940		-244.1250		-246.1524							
		215.2		219.3		211.5		216.1			219.6	9.1	212.0	207.8
14	-244.3961		-246.4435		-244.4620		-246.4968							
		154.9[e]		159.9[e]							160.4	6.4	155.1	
15	-244.3001		-246.3488											
16	-320.7874		-323.5448		-320.8836		-323.6205							
17	-320.7844		-323.5400		-320.8819		-323.6186							
18	-320.7748													
		223.8[f]		227.2[f]		219.9[f]		225.0[f]						
19	-321.1440		-323.9068		-321.2340		-323.9791							
		225.6[g]		230.2[g]		220.9[g]		226.2[g]						
20	-321.1354													

a) 1 a.u. = 627.51 kcal/mol. b) Ref. [7] for **1**, **3** and **11**; ref. [19] for **5**, **7**, **9** and **12**. c) Ref. [4] d) Ref. [7], values obtained by MP2/6-31G*(d,p)//STO-3G, ΔH_p^{corr} corrected by ΔE_v^0, ΔE_t and PV terms. e) for **13** + $H^+ \rightarrow$ **15**. f) for **16** + $H^+ \rightarrow$ **19**. g) for **17** + $H^+ \rightarrow$ **19**. h) this work, at NLSD/DZVP2 level.

Table 4. Atomic charges in compounds **13 - 21**.

compound	13		14		15	16			17			18	19	20	21[b]		
atom	I[a]	II	I	II	I	I	II	III	I	II	III	I	I	I	I	II	exp
1	-0.31	-0.06	-0.24	-0.03	-0.45	-0.58	0.00	-0.77	-0.43	-0.11	-0.63	-0.38	-0.56	-0.58	-0.39	-0.30	-0.50
2	0.16	-0.11	0.31	-0.03	0.32	0.49	0.08	0.80	0.41	0.19	0.68	0.38	0.53	0.55	0.25	0.02	0.37
3	-0.35	-0.09	-0.51	0.08	-0.27	-0.22	-0.20	-0.29	-0.29	-0.17	-0.24	-0.23	-0.18	-0.17	-0.69	-0.37	-0.71
4	-0.08	-0.22	0.03	-0.18	-0.03	-0.13	-0.17	-0.06	-0.15	-0.17	-0.07	-0.14	-0.11	-0.11			
5	0.01	-0.15	0.04	-0.05	0.05	-0.20	-0.20	-0.27	-0.16	-0.18	-0.23	-0.15	-0.17	-0.17			
6						0.05	-0.21	0.21	-0.03	-0.26	0.14	-0.03	0.07	0.06			
O[c]						-0.47	-0.35	-0.65	-0.57	-0.33	-0.68	-0.55	-0.52	-0.50			
1H					0.54	0.36	0.27						0.43	0.41			
2H	0.20	0.21	0.32	0.28	0.32												
3H			0.45	0.35		0.17	0.21		0.17	0.20		0.15	0.24	0.26			
4H	0.18	0.21	0.31	0.26	0.29	0.17	0.19		0.17	0.19		0.17	0.26	0.26	0.36	0.28	0.37
5H	0.20	0.21	0.30	0.27	0.32	0.17	0.19		0.16	0.19		0.16	0.26	0.26	0.35	0.26	0.35
6H						0.19	0.19		0.17	0.19		0.17	0.28	0.27	0.12	0.16	0.12
OH[c]									0.42	0.32		0.42	0.48	0.47			

a) Method I: LSD/6-31G*; Method II: LSD/DZVP2; Method III: HF/6-31G**; see ref [20]. b) Numbering for formamide: 

for experimental data, see ref [21]. c) In compounds **16 - 20**.

The 2-hydroxypyridine → 2(1*H*)-pyridone tautomeric equilibrium has been extensively investigated by experimental and theoretical methods. It was established that only high level *ab initio* calculations could accurately describe the energy difference between the tautomeric forms of **17** → **16** ($\Delta H_{exp} = 0.6 \pm 0.3$ kcal/mol, ΔH_{calcd} (6-31G*//3-21G) = 1.0 kcal/mol).[20] Our results shown in Table 3 confirm that the DF approaches studied failed to properly treat this equilibrium. Though the absolute errors, -1.1, -1.2 kcal/mol are relatively small with DZVP2 basis at both the LSD and NLSD levels, in fact, each calculation predicted incorrectly that **16** should be more stable than **17**.

Atomic charges were next investigated. We were particularly interested in the analysis of compounds containing C(O)-N structural elements, in which the charge distributions may be directly related to their ambident behaviour. Mulliken net charges for compounds **13-20** and formamide (**21**) as a structurally relating compound, are listed in Table 4. Comparison with experimental and HF/6-31G** data indicates that within the frame of DFT, the 6-31G* basis performed better. Results obtained with DZVP2 basis clearly demonstrate that the polarization of carbon-heteroatom bonds are substantially underestimated by this basis. This trend is especially noticeable in cyclic compounds as compared with the acyclic analogue, formamide (**13, 14, 16, 17** and **21**). The LSD optimized basis set is more diffuse than the 6-31G* basis leading to larger delocalization of charges,[13] and this also manifests in calculation of atomic charges. On the other hand, atomic charges seem to be well treated by 6-31G* basis, and it provides correct accounts for charge separations in amides and related systems.

Table 5. Dipole moments of compounds **1** - **20**.

	μ(D)		
compound	LSD/6-31G*	LSD/DZVP2	exp.[a]
1	2.31	2.35	2.21
2	2.57	2.55	
3	3.79	3.90	
4	1.36	1.37	
5	2.20	2.42	2.22
6	1.93	1.93	
7	4.11	4.18	3.95
8	2.39	2.43	
9	2.31	2.54	2.33
10	3.87	3.95	
11	0.00	0.00	0
12	4.62	4.74	
13	1.60	1.64	1.50
14	2.78	2.82	
15	4.96		
16	4.06	4.47	
17	1.04	1.35	
18	3.27		
19	0.25		
20	3.14		

a) References: [17f] for **1**; [17b] for **5**; [17c] for **7**; [17b] for **9**; [17e] for **11**; [17a] for **13**.

Dipole moments for compounds **1- 20** are presented in Table 5. As can be seen from the table, the calculated values are reasonably close to the experimental data, nevertheless the errors are significantly larger with the DZVP2 basis set.

CONCLUSIONS

In conclusion, our present data demonstrate that the density functional theory is a suitable investigative tool for protonation enthalpies, geometric parameters, atomic charges and dipole moments of important representatives of heterocyclic compounds. Protonation enthalpies calculated at NLSD(BP)/DZVP2 level of threory are favourably comparable with high level *ab initio* and experimental values. Relative basicity order of azoles and azines representing a wide range in the basicity scale is also correctly described by the LSD/DZVP2 as well as the NLSD/6-31G* levels. Bond lengths are generally within ±0.01Å or at most ±0.02Å, and bond angles within ±1.0° with both basis sets studied. For calculations of atomic charges and dipole moments the 6-31G* basis set seems to be more appropriate. Although the more detailed investigation is still required, it is clear that lactam-lactim tautomeric equilibria are great challenges for DFT. This field will be further investigated in a forthcoming paper. We hope that the present study might emphasize the practical and possible usage of the density functional theory in the heterocyclic chemistry as a computationally efficient quantum chemical method.

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