A DFT study of solvation effects and NBO analysis on the tautomerism of 1-substituted hydantoin

4 AUTHORS, INCLUDING:

Meisam Shabanian
Standard Research Institute
73 PUBLICATIONS   443 CITATIONS

SEE PROFILE

Hassan Moghanian
Islamic Azad University,Dezful Branch, Dezf…
46 PUBLICATIONS   576 CITATIONS

SEE PROFILE

Mohsen Hajibeygi
Arak University
56 PUBLICATIONS   312 CITATIONS

SEE PROFILE

ORIGINAL ARTICLE

A DFT study of solvation effects and NBO analysis on the tautomerism of 1-substituted hydantoin

Meisam Shabanian [a],*, **Hassan Moghanian** [b], **Mohsen Hajibeygi** [c], **Azin Mohamadi** [c]

[a] *Young Researchers Club, Arak Branch, Islamic Azad University, Arak, Iran*
[b] *Department of Chemistry, Dezful Branch, Islamic Azad University, Dezful, Iran*
[c] *Department of Chemistry, Varamin Pishva Branch, Islamic Azad University, Varamin Pishva, Iran*

Abstract 1-Substituted hydantoins (1-SH) have been known as a benefit intermediate for producing agricultural and pharmaceuticals. The effect of solvent polarity on the tautomeric equilibria of 1-substituted hydantoin ring is studied by the density functional theory calculation (B3LYP/6–31 ++ G(d,p)) level for predominant tautomeric forms of hydantoin derivatives (1-NO$_2$, 1-CF$_3$, 1-Br, 1-H, 1-CH=CH$_2$, 1-OH, 1-CH$_3$) in the gas phase and selected solvents (benzene (non-polar solvent), tetrahydrofuran (THF) (polar aprotic solvent) and water (protic solvent)). For electron withdrawing and releasing derivatives in the gas phase and solution Hy1 forms is more stable and dominant form. In addition variation of dipole moments and charges on atoms in the solvents are studied.

1. Introduction

Hydantoins, glycolylurea, consist a group of compounds that has been of considerable interest. Many of the compounds

* Corresponding author. Tel.: +98 9173235388; fax: +98 21 88257969.
  E-mail address: m-shabanian@phd.araku.ac.ir (M. Shabanian).

possess clinically useful activity, especially as anticonvulsants (e.g., norantoin, mepheenytoin, nirvanol, and methetoin). Many biological activities of hydantoin derivatives are known, as in their uses as herbicides and fungicides and some N-substituted derivatives of hydantoin are used 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, this paper reviews the relevant literature on the structure of hydantoin derivatives both in solution and in the solid state (Ware, 1950; Kleinpeter, 1997).

Tautomerism interconversions (Grochowski et al., 2004; Belova et al., 2008) have been investigated by chemists during last decades. Recently, study of tautomerism received renewed attention due to its importance on the determination of
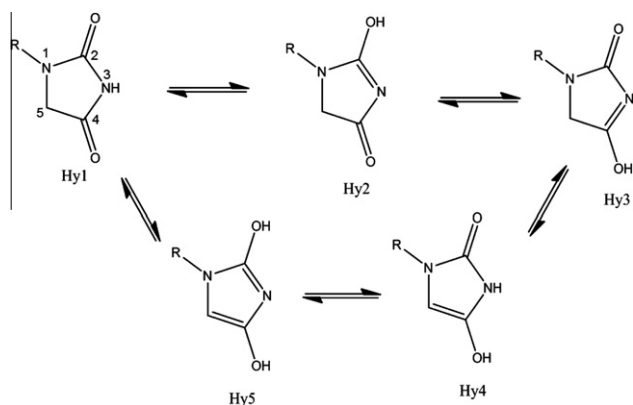
Figure 1 Tautomeric forms of hydantoin derivatives and numbering of hydantoin ring.

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, tautomerisms in keto-enol (Misra and Dalai, 2007; Zborowski and Korenova,

2004), imine–enamine (Oziminski et al., 2004; Dines and Onoh, 2006), purine (Shukla and Mishra, 2000), pirimidine (Bonacin et al., 2007) and many other systems (Ralhan and Ray, 2003) have been studied during the past decades. Thereupon, compounds containing different tautomers can be the subject of interest by theoretical chemists (Tavakol, 2010).

In this article we studied the tautomerism of seven 1-substituted hydantoins in the gas phase and solution using polarisable continuum method (PCM) at the B3LYP/6–31 ++ G(d,p) level of theory.

2. Computational methods

All these calculations were carried out on a Pentium V personal computer by means of GAUSSIAN03 program package (Frisch et al., 2004) and for our computations. First, all the compound's structures were drawn using Gauss View 03 (Dennington et al., 2003) and optimized in semi. 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 contin-

Table 1 Total energies[a] at B3LYP/6–31 + +G** in the gas phase and solvents.

R	Tautomer	Gas (1.0)	Benzene (2.2)	THF (7.6)	Water (78.4)
NO$_2$	Hy1	−581.2074691	−581.2221109	−581.2320934	−581.2367362
	Hy2	−581.1814368	−581.1932298	−581.2015427	−581.2060233
	Hy3	−581.1834681	−581.2002005	−581.2120739	−581.217642
	Hy4	−581.1711189	−581.1904285	−581.2039496	−581.2107403
	Hy5	−581.1591994	−581.1753041	−581.186004	−581.190941
CF$_3$	Hy1	−713.7845745	−713.7963805	−713.8042665	−713.8078671
	Hy2	−713.7488251	−713.7589838	−713.7683018	−713.7743826
	Hy3	−713.7610168	−713.7750443	−713.7850663	−713.7897254
	Hy4	−713.7479111	−713.7641756	−713.7753535	−713.7810888
	Hy5	−713.7376467	−713.7510511	−713.7597643	−713.7637658
Br	Hy1	−2947.821781	−2947.8339021	−2947.8420475	−2947.8455984
	Hy2	−2947.7831188	−2947.7974126	−2947.8156584	−2947.8145562
	Hy3	−2947.7956906	−2947.8101048	−2947.8203488	−2947.8249864
	Hy4	−2947.7824059	−2947.7991082	−2947.8105747	−2947.8161127
	Hy5	−2947.7746538	−2947.7883321	−2947.7971482	−2947.800963
H	Hy1	−376.7405171	−376.7556339	−376.7659129	−376.7703092
	Hy2	−376.6983782	−376.7196312	−376.7361504	−376.7441062
	Hy3	−376.7021526	−376.7221592	−376.7370945	−376.7443175
	Hy4	−376.7013924	−376.7208266	−376.7341045	−376.7402239
	Hy5	−376.6932919	−376.7100632	−376.7209578	−376.7255222
CH$_3$	Hy1	−416.0542389	−416.066013	−416.0739606	−416.0774713
	Hy2	−416.0082409	−416.0245805	−416.0369986	−416.0439921
	Hy3	−416.0158605	−416.0327035	−416.0454155	−416.0517596
	Hy4	−416.0156317	−416.0313783	−416.0421626	−416.0474911
	Hy5	−416.0059184	−416.0194233	−416.0281578	−416.0320566
CH=CH$_2$	Hy1	−454.1438696	−454.155888	−454.1638078	−454.1672786
	Hy2	−454.098425	−454.1151325	−454.1276585	−454.1351203
	Hy3	−454.1170664	−454.1311998	−454.1411281	−454.1456436
	Hy4	−454.1021849	−454.1183108	−454.1295859	−454.134804
	Hy5	−454.0907753	−454.1046771	−454.113678	−454.1175365
OH	Hy1	−451.9012817	−451.9178215	−451.9290471	−451.9339936
	Hy2	−451.86771	−451.890121	−451.9033081	−451.9092211
	Hy3	−451.8748703	−451.8769226	−451.906554	−451.912549
	Hy4	−451.860528	−451.8769226	−451.8959356	−451.9012212
	Hy5	−451.8507417	−451.8698025	−451.8823162	−451.8878452

[a] Hartree.

Table 2 Calculated dipole moments of optimized tautomers of 1-substituted hydantoin (Debye).

R	Tautomer	Gas (1.0)	Benzene (2.2)	THF (7.6)	Water (78.4)
NO_2	Hy1	2.6038	3.2247	3.7160	3.9700
	Hy2	3.0670	3.8083	4.4560	4.8578
	Hy3	6.2865	7.8248	9.0553	9.6786
	Hy4	6.9441	8.5545	9.8821	10.5669
	Hy5	3.6635	4.6294	5.4782	5.9043
CF_3	Hy1	1.3475	1.5638	1.7249	1.7905
	Hy2	5.0520	6.3704	7.2312	8.0778
	Hy3	5.5358	6.8991	8.0413	8.6616
	Hy4	5.9082	7.1693	8.1428	8.6173
	Hy5	1.7713	2.1689	2.4807	2.5991
Br	Hy1	1.9298	2.2431	2.4729	2.5882
	Hy2	7.0953	8.8554	6.7323	11.0407
	Hy3	5.0617	6.3101	7.3319	7.8312
	Hy4	5.1598	6.3006	7.2013	7.6384
	Hy5	1.3389	1.5940	1.7887	1.8825
H	Hy1	2.7821	3.2723	3.6437	3.8137
	Hy2	7.6712	9.8882	11.8194	12.5808
	Hy3	7.8371	9.6297	11.0666	11.7583
	Hy4	5.2094	6.3199	7.1838	7.5898
	Hy5	1.8784	2.2479	2.5263	2.6560
CH_3	Hy1	3.0149	3.4165	3.7002	3.8320
	Hy2	8.8193	10.6037	12.0025	12.7320
	Hy3	7.7192	9.4854	10.9136	11.6196
	Hy4	4.9890	6.0886	6.9381	7.3840
	Hy5	2.3506	2.5999	2.7825	2.8707
$CH{=}CH_2$	Hy1	1.8262	2.0860	2.2985	2.3802
	Hy2	7.4423	9.2216	10.6757	11.4296
	Hy3	4.6670	5.8457	6.8213	7.3045
	Hy4	3.7335	4.5451	5.2161	5.5522
	Hy5	1.4103	1.5789	1.7212	1.7831
OH	Hy1	2.0019	2.5576	3.0234	3.2656
	Hy2	7.2315	6.0234	7.0601	7.5663
	Hy3	4.5590	5.9384	7.1507	7.8244
	Hy4	4.4355	5.5754	6.9989	5.4223
	Hy5	2.0633	2.3916	2.6936	2.8601

uum method of Tomasi and co-workers, which exploits the generating polyhedra procedure (Miertus et al., 1981; Cances et al., 1997; Cossi et al., 1998; Barone and Cossi, 1998; Barone et al., 1998) to build the cavity in the polarisable continuum medium, where the solute is accommodated. Atomic charges in all the structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital (NBO) approach (Reed et al., 1988; Najafi Chermahini et al., 2007).

3. Results and discussion

3.1. Gas phase

Structures of hydantoin derivatives are depicted in Fig. 1 and the results of energy comparisons of five tautomers in the gas phase and different solvents are given in Table 1. In agreement with previous results, in the gas phase all Hy1 forms are more stable than the other forms. The major difference between Hy1 and the other forms in the gas phase was found for 1-methyle hydantoin with 24.07 kcal mol^{-1}. The order of stability of Hy1 tautomer over the other tautomers in the gas phase is $CH_3 > H > CH{=}CH_2 > OH > Br > NO_2 > CF_3$.

This indicates that the stability of Hy1 form decreases with the increase withdrawing effect of substituents. The calculated

dipole moments for the hydantoins are presented in Table 2. In the Hy2 tautomers, the electron withdrawing derivatives have smaller dipole moments than the electron releasing ones; but in Hy4 forms electron donating derivatives have lower dipole moments values than electron withdrawing substituents. This maybe explained by the consideration of charge values on the atoms of hydantoin ring. It is well known that in haydantoin N1 and N3 atoms carry the most negative charge. The Hy2 isomer of 1-NO_2 derivative has the least charge density on N1 and N3. It is noticeable that the differences between the dipole moments of 1-H and 2-H forms are related to nature substituents.

The calculated values of NBO charges using the Natural Population Analysis (NPA) of optimized structures of hydantoin derivatives are listed in Table 3. As it was noticed previously, the hydantoin's nitrogen atoms at position 1 or 3 carry the largest negative charge and these positions will most effectively interact with electrophiles. There is no uniform trend for the variation of charges to relate to the different substituents of hydantoins in the gas phase, Table 3.

3.2. Solvent effects

Solvent effects are relevant in the tautomers stability phenomena, since polarity differences among the tautomers can induce

Table 3 Calculated NBO charges on ring atoms of 1-substituted hydantoin.

R	ε= / Atom	Hy1 1.0	2.2	7.6	78.4	Hy2 1.0	2.2	7.6	78.4	Hy3 1.0	2.2	7.6	78.4	Hy4 1.0	2.2	7.6	78.4	Hy5 1.0	2.2	7.6	78.4
NO$_2$	N1	−0.035	−0.332	−0.318	3.347	−0.319	−0.304	−0.294	3.358	−0.357	−0.336	−0.323	−0.315	−0.310	−0.293	−0.280	3.366	−0.285	−0.275	−0.267	3.372
	C2	0.821	0.834	0.842	3.420	0.769	0.788	0.802	3.401	0.799	0.811	0.817	0.819	0.798	0.806	0.811	3.404	0.719	0.731	0.740	3.371
	N3	−0.680	−0.674	−0.670	3.166	−0.545	−0.573	−0.595	3.198	−0.562	−0.583	−0.598	−0.604	−0.657	−0.654	−0.652	3.175	−0.598	−0.606	−0.609	3.197
	C4	0.685	0.697	0.705	3.352	0.656	0.668	0.674	3.335	0.617	0.638	0.654	0.662	0.479	0.490	0.500	3.253	0.457	0.461	0.465	3.233
	C5	−0.334	−0.336	−0.339	2.830	−0.345	−0.345	−0.345	2.827	−0.320	−0.323	−0.326	−0.327	−0.215	−0.220	−0.223	2.888	−0.196	−0.205	−0.212	2.892
CF$_3$	N1	−0.593	−0.587	−0.583	−0.581	−0.589	−0.577	−0.569	−0.563	−0.604	−0.598	−0.593	−0.590	−0.555	−0.552	−0.549	−0.547	−0.509	−0.510	−0.512	3.244
	C2	0.853	0.845	0.852	0.855	0.780	0.801	0.810	0.820	0.812	0.820	0.825	0.827	0.805	0.807	0.808	0.807	0.722	0.729	0.733	3.367
	N3	−0.681	−0.676	−0.673	−0.671	−0.557	−0.599	−0.614	−0.636	−0.562	−0.585	−0.603	−0.612	−0.653	−0.651	−0.649	−0.648	−0.606	−0.618	−0.625	3.187
	C4	0.685	0.696	0.703	0.707	0.657	0.665	0.672	0.670	0.612	0.632	0.647	0.654	0.462	0.467	0.471	0.473	0.442	0.440	0.439	3.219
	C5	−0.324	−0.328	−0.330	−0.331	−0.338	−0.330	−0.341	−0.332	−0.307	−0.311	−0.313	−0.312	−0.201	0.205	−0.207	−0.207	−0.186	−0.194	−0.200	2.899
Br	N1	−0.602	−0.595	−0.589	3.207	−0.586	−0.575	−0.558	−0.561	−0.612	−0.603	−0.595	−0.591	−0.559	−0.553	−0.549	−0.547	−0.507	−0.509	−0.510	3.244
	C2	0.812	0.819	0.823	3.410	0.767	0.781	0.790	0.797	0.790	0.795	0.707	0.707	0.777	0.777	0.774	0.772	0.690	0.695	0.698	3.349
	N3	−0.682	−0.678	−0.676	3.163	−0.583	−0.621	−0.670	−0.664	−0.557	−0.584	−0.603	−0.613	−0.653	−0.652	−0.651	−0.651	−0.613	−0.629	−0.639	3.180
	C4	0.686	0.696	0.702	3.350	0.657	0.662	0.665	0.663	0.605	0.624	0.638	0.645	0.456	0.460	0.463	0.465	0.440	0.436	0.434	3.215
	C5	−0.317	−0.321	−0.324	2.838	−0.330	−0.332	−0.332	−0.334	−0.305	−0.310	−0.313	−0.315	−0.204	−0.208	−0.210	−0.210	−0.194	−0.202	−0.209	2.894
H	N1	−0.694	−0.687	−0.681	−0.678	−0.696	−0.681	−0.660	−0.653	−0.707	−0.697	−0.687	−0.683	−0.644	−0.641	−0.638	−0.637	−0.597	−0.600	−0.603	−0.604
	C2	01.810	0.814	0.817	0.818	0.754	0.773	0.784	0.789	0.786	0.789	0.788	0.788	0.773	−0.769	0.764	0.761	0.683	0.685	0.686	0.687
	N3	−0.689	−0.686	−0.684	−0.683	−0.583	−0.635	−0.678	−0.693	−0.526	−0.569	−0.604	−0.622	−0.660	−0.661	−0.661	−0.661	−0.629	−0.651	−0.666	−0.673
	C4	0.682	0.691	0.696	0.698	0.653	0.658	0.658	0.658	0.586	0.606	0.622	0.630	0.447	0.446	0.446	0.447	0.431	0.424	0.418	0.415
	C5	−0.330	−0.333	−0.335	−0.335	−0.351	−0.348	−0.345	−0.345	−0.331	−0.333	−0.334	−0.335	−0.215	−0.217	−0.217	−0.216	−0.208	−0.215	−0.220	−0.222
CH$_3$	N1	−0.519	−0.509	−0.501	−0.497	−0.514	−0.476	−0.215	−0.469	−0.533	−0.519	−0.507	3.251	−0.474	−0.467	−0.461	3.272	−0.428	−0.426	−0.425	−0.425
	C2	0.821	0.826	0.830	0.831	0.774	0.798	0.626	0.803	0.798	0.801	0.802	3.398	0.785	0.783	0.780	3.386	0.693	0.698	0.701	0.702
	N3	−0.685	−0.681	−0.697	−0.678	−0.602	−0.671	−0.553	−0.685	−0.523	−0.565	−0.599	3.193	−0.656	−0.658	−0.658	3.171	−0.631	−0.651	−0.664	−0.670
	C4	0.684	0.693	0.699	0.701	0.653	0.658	−0.407	0.658	0.588	0.608	0.624	3.314	0.458	0.455	0.456	3.226	0.434	0.428	0.423	0.421
	C5	−0.315	−0.319	−0.322	−0.323	−0.330	−0.332	−0.236	−0.333	−0.315	−0.318	−0.321	2.839	−0.206	−0.209	−0.210	2.895	−0.196	−0.203	−0.208	−0.210
CH=CH$_2$	N1	−0.502	−0.496	−0.491	−0.489	−0.490	−0.478	−0.469	−0.464	−0.512	−0.505	−0.499	−0.496	−0.467	−0.463	−0.460	−0.459	−0.431	−0.432	−0.433	3.287
	C2	0.825	0.833	0.837	0.839	0.772	0.789	0.800	0.807	0.803	0.808	0.810	0.811	0.795	0.795	0.793	0.793	0.707	0.711	0.714	3.356
	N3	−0.681	−0.678	−0.675	−0.673	−0.580	−0.620	−0.650	−0.665	−0.563	−0.590	−0.610	−0.619	−0.668	−0.666	−0.662	−0.661	0.619	−0.636	−0.647	3.175
	C4	0.686	0.696	0.702	0.705	0.655	0.661	0.664	0.664	0.607	0.625	0.639	0.646	0.435	0.447	0.458	0.464	0.440	0.435	0.431	3.214
	C5	−0.323	−0.327	−0.330	−0.331	−0.335	−0.337	−0.339	−0.339	−0.308	−0.313	−0.316	−0.318	−0.140	−0.158	−0.176	−0.187	−0.190	−0.198	−0.203	2.897
OH	N1	−0.243	−0.237	−0.228	3.390	−0.244	−0.214	−0.203	−0.196	−0.259	−0.249	−0.238	−0.231	−0.206	−0.196	−0.177	−0.165	0.136	−0.131	−0.127	−0.125
	C2	0.807	0.814	0.817	3.406	0.755	0.770	0.781	0.789	0.785	0.790	0.791	0.791	0.782	0.779	0.771	0.764	0.678	0.682	0.684	0.685
	N3	−0.684	−0.680	−0.677	3.162	−0.566	−0.643	−0.664	−0.674	−0.569	−0.594	−0.614	−0.626	−0.661	−0.659	−0.659	−0.663	−0.626	−0.646	−0.659	−0.664
	C4	0.683	0.694	0.699	3.349	0.656	0.663	0.666	0.666	0.608	0.626	0.639	0.646	0.456	0.459	0.460	0.446	0.437	0.432	0.428	0.426
	C5	−0.334	−0.336	−0.338	2.830	−0.351	−0.348	−0.348	−0.348	−0.319	−0.323	−0.326	−0.327	−0.212	−0.218	−0.224	−0.189	−0.207	−0.217	−0.223	−0.225

significant changes in their relative energies in solution. PCM/
B3LYP calculations were used to analyze the solvent effects on
tautomerism of hydantoin 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 the polar solvents increase
the stability of all hydantoins in comparison to gas phase. The
difference between the total energies of Hy1 and the other
forms do not show a regular trend when changing from gas
phase to most polar solvents (water).

The solvent interactions have not pronounced an effect on
the order of stability of the tautomers in the gas phase. The
solvent represented by a polarizable continuum is found to
show significant effect on the dipole moments of the individual
solute conformers. The dipole moments (l) increase by chang-
ing the gas phase to the solution as well as by increasing the
solvent polarity. The most significant variations being ob-
tained in hydantoin in Hy2 form with 4.9096 D, Table 2. We
have examined the charge distribution of tautomers in the sol-
vent as well as gas phase by using calculated NBO charges. The
charge distribution in solvents with the increase of polarity dif-
ferently varies for any atoms.

4. Conclusion

1. In the gas phase and solution all Hy1 forms were more
   stable than the other tautomers. On the other hand,
   interestingly enough, the highly elaborate B3LYP/6–
   $31++G(d,p)$ type DFT calculations yield results in
   estimating the stability order of these tautomers as
   Hy1 > Hy2 > Hy2 > Hy4 > Hy5 (Table 1). In the solu-
   tion and with increase of polarity; Hy1 isomers were more
   stable. With increase of polarity, total energies of all com-
   pounds were more negative.

2. The dipole moments of all compounds are affected by sol-
   vent. With increase of the polarity of solvents the dipole
   moments of the tautomers were increased.
3. The charges on all five positions were affected by substitu-
   ents and solvents.

References

Barone, V., Cossi, M., 1998. J. Phys. Chem. A. 102, 1995.
Barone, V., Cossi, M., Tomasi, J., 1998. J. Comp. Chem. 19, 404.
Belova, N.V., Oberhammer, H., Girichev, G.V., Shlykov, S.A., 2008. J. Phys. Chem. A. 112, 3209.
Bonacin, J.A., Melo, D., Toma, H.E., 2007. Vib. Spectrosc. 44, 133.
Cances, M.T., Mennucci, V., Tomasi, J., 1997. J. Chem. Phys. 107, 3032.
Cossi, M., Barone, V., Mennucci, B., Tomasi, J., 1998. Chem. Phys. Lett. 286, 253.
Dennington, R., Keith, T., Millam, J., Eppinnett, K., Hovell, W.L., Gilliland, R., 2003. GaussView, Version 309. Semichem, Inc., Shawnee Mission, KS.
Dines, T.J., Onoh, H., 2006. Spectrochim. Acta A. 64, 891.
Frisch, M.J. et al. 2004. Gaussian 03, Revision CO_2, Gaussian, Inc., Wallingford CT.
Grochowski, J., Serda, P., Markiewicz, M., Kozik, B., Sepiol, J.J., 2004. J. Mol. Struct. 689, 43.
Kleinpeter, E., 1997. Struct. Chem. 8, 161.
Miertus, S., Scrocco, E., Tomasi, J., 1981. J. Chem. Phys. 55, 117.
Misra, A., Dalai, S., 2007. THEOCHEM 807, 33.
Najafi Chermahini, A., Nasr-Esfahani, M., Dalirnasab, Z., Abdol Dabbagh, H., Teimouri, A., 2007. THEOCHEM 820, 7.
Oziminski, W.P., Dobrovolski, J.C., Mazurek, A.P., 2004. THEO-CHEM 680, 107.
Ralhan, S., Ray, N.K., 2003. THEOCHEM 634, 83.
Reed, A.E., Curtiss, L.A., Wienhold, F., 1988. Chem. Rev. 88, 899.
Shukla, M.K., Mishra, S.K., 2000. Comput. J. Chem. 21, 826.
Tavakol, H., 2010. THEOCHEM 956, 97.
Ware, E., 1950. Chem. Rev. 46, 403.
Zborowski, K., Korenova, A., 2004. THEOCHEM 683, 15.