Research Article

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Journal of In Silico & In Vitro Pharmacology
ISSN 2469-6692

2018
Vol. 4 No.2:3

DOI: 10.21767/2469-6692.10025

Protonation of Nitrofurantoin and Furazidine Molecules in Acidic Media-Molecular Modelling Studies

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Citation: Somogi A, Dąbrowska A, Ziemba R, Pawiński T (2018) Protonation of Nitrofurantoin and Furazidine Molecules in Acidic Media-Molecular Modelling Studies. J In Silico In Vitro Pharmacol Vol. 4 No.2:3.

Abstract

The molecular modeling studies on protonation sites of Nitrofurantoin and Furazidine as well as on the stability of particular protonated forms were performed using quantum chemical MP2 method. Performed calculations show that Furazidine oxygen and nitrogen atoms are better proton acceptors than in Nitrofurantoin, therefore the acidity of the media may differentiate Nitrofurantoin and Furazidine antibacterial activity.

Keywords: Nitrofurantoin; Furazidine; Acidity; Protonation sites; Urinary tract infection; Molecular modelling

Received: September 19, 2018; **Accepted:** October 08, 2018; **Published:** October 15, 2018

Introduction

According to literature data in nitrofuran derivatives the major role in antimicrobial activity plays the acidity of physiological medium in urinary tract [1]. It was pointed out [2] that dissociation of Furazidine is hampered in the presence of ascorbic acid (vitamin C). The role of any acidifying agent like ascorbic acid is to prevent alkalization of infected urine and preserve pH close to 5.5 in which Furazidine molecule stays in non-dissociated form what enhances its antibacterial activity [1]. More acidic medium can probably cause better protonation of the Furazidine molecule than of Nitrofurantoin, what can further enhance Furazidine therapeutic efficacy. Therefore studies of possible protonation sites of Nitrofurantoin and Furazidine, along with stability of particular protonated form, can provide valuable estimate for insight into activity determinates of Furazidine moiety, and also for further modification of its structure. Selection of Nitrofurantoin and Furazidine is a wise model because those two compounds differ in two carbon atoms in the rings bridging part of molecules. Moreover there is distinct difference between their antimicrobial activities. In Escherichia coli test they display MIC ≤ 32 μg/ml and 1 μg/ml for Nitrofurantoin and Furazidine, respectively [3], as reported in information leaflets of medicine present on the market.

Methods

All quantum chemical calculations were performed with Spartan 14 V.1.1.4 software package at the MP2/6-31G*//MP2/6-31G* level [4]. The hydration energies were calculated with SM8 model.

Results and Discussion

Calculation on neutral Nitrofurantoin tautomer clearly indicates that N_1-H tautomer is the most stable form both in water medium. The same holds for Furazidine molecule.

The neutral Nitrofurantoin and Furazidine molecules can potentially exist in various tautomeric forms. As shown in **Tables 1 and 2** the N_1-H tautomer of Nitrofurantoin is the most stable.

The second most stable tautomer is the one bearing the proton on the O_2 nitrogen atom at the MP2/6-31G*//MP2/6-31G* level with hydration energy included **Table 1**. Calculation of Δ (ΔGo) yields also the O_2-H tautomer to be the most stable form after the N_1-H tautomer **(Table 2)**. The N_3-H tautomer probably does not exist. The attached proton is being transferred from N_3 to O_2 atom during optimization process yielding the O_2-H tautomer.

Table 1: Total MP_2/6-31G*//6-31G* energies, stabilization energies, ΔG0 and Δ(ΔG0) calculated for neutral and protonated Nitrofurantoin molecule.

Neutral	Total energy	Stabilization energy	ΔG^0	$\Delta (\Delta G^0)$
I (N_1-H)	-900.956670	0.0	-900.823127	0.00
II (N_3-H)	-900.919856	23.10	-900.777778	28.46
III (O_1-H)	-900.928299	17.80	-900.777699	28.51
IV (O_2-H)	-900.928428	17.72	-900.786946	22.70
V (N_2-H)	-900.936229	12.83	-900.793088	18.85
VI (O_3-H)	-900.869400	54.76	-900.745721	48.57
VII (O_4-H)	-900.873576	52.14	-900.750943	48.57
Cation				
I (N_1-H; O_1-H)	-901.208345	-157.93	-901.027358	-128.15
II (N_1-H; O_2-H)	-901.369024	-258.75	-901.132061	-193.86
III (N_1-H; O_3-H)	-901.383507	-267.84	-901.150271	-205.28
IV (N_1-H; N_1-H)	-901.336768	-238.51	-901.116485	-184.08
V (N_1-H; N_2-H)	-901.364274	-255.77	-901.129443	-192.21
VI (N_1-H; N_3-H)	-901.383523	-267.85	-901.150258	-205.28
VII (N_1-H; O_4-H)	-901.355919	-250.53	-901.135881	-196.25
VIII (N_3-H; O_4-H)	-901.315992	-225.47	-901.093608	-169.73
Dication				
I (N_1-H; N_1-H; N_3-H)	-901.763484	-506.28	-901.304039	-301.77
II (N_1-H; O_1-H; N_3-H)	-901.785163	-519.88	-901.328894	-317.37
III (N_1-H; O_2-H; N_3-H)	-901.784169	-519.26	-901.329481	-317.74
IV (N_1-H; N_1-H; O_2-H)	-901.733673	-487.57	-901.289431	-292.61
V (N_1-H; O_1-H; O_2-H)	-901.767780	-508.97	-901.289982	-292.95
VI (N_1-H; N_1-H; N_2-H	-901.727780	-483.87	-901.246460	-265.64
VII (N_1-H; N_2-H; N_3-H)	-901.762048	-505.37	-901.296180	-296.84
VIII (N_1-H; N_2-H; O_1-H)	-901.482729	-330.10	-901.220942	-249.63
IX (N_1-H; N_2-H; O_2-H)	-901.734154	-487.87	-901.254361	-270.60

Table 2: Total MP_2/6-31G*//6-31G* energies, stabilization energies, ΔG0 and Δ (ΔG0) calculated for neutral and protonated Furazidine molecule.

Neutral	Total energy	Stabilization energy	ΔG^0	$\Delta(\Delta G^0)$
I (N_1-H)	-978.101505	0.00	-977.934728	0.00
II (N_3-H)	-978.047774	33.72	-977.883044	32.43
III (O_1-H)	-978.079351	13.90	-977.896975	23.69
IV (O_2-H)	-978.073821	17.37	-977.898060	23.01
V (N_2-H)	-978.065152	22.81	-977.903567	19.55
VI (O_3-H)	-978.011941	56.20	-977.856693	48.97
VII (O_4-H)	-978.011940	56.20	-977.856734	48.94
Cation				
I (N_1-H; O_1-H)	-978.497706	-248.62	-978.236155	-118.53
II (N_1-H; O_2-H)	-978.501750	-251.15	-978.252367	-199.32
III (N_1-H; O_3-H)	-978.501737	-251.15	-978.252361	-199.31
IV (N_1-H; N_1-H)	-978.483563	-239.74	-978.230392	-185.53
V (N_1-H; N_2-H)	-978.510679	-256.76	-978.250115	-198.55
VI (N_1-H; N_3-H)	-978.538595	-274.27	-978.274167	-213.00
VII (N_1-H; O_4-H)	-978.499000	-249.43	-978.249830	-197.73
VIII (N_3-H; O_4-H)	-978.460211	-225.09	-978.215781	-176.36
Dication				
I (N_1-H; N_1-H; N_3-H)	-978.913382	-509.45	-978.438447	-316.08
II (N_1-H; O_1-H; N_3-H)	-978.940486	-526.46	-978.466285	-333.55
III (N_1-H; O_2-H; N_3-H)	-978.937012	-524,28	-978.463007	-331.50
IV (N_1-H; N_1-H; O_2-H)	-978.878684	-487.68	-978.434441	-313.57
V (N_1-H; O_1-H; O_2-H)	-978.899957	-501.03	-978.403282	-294.02
VI (N_1-H; N_1-H; N_2-H	-978.866915	-480.29	-978.370630	-273.53
VII (N_1-H; N_2-H; N_3-H)	-978.914768	-510.32	-978.431724	-311.86
VIII (N_1-H; N_2-H; O_1-H)	-978.894982	-497.91	-978.395595	-289.19
VIII (N_1-H; N_2-H; O_2-H)	-978.874654	-485.15	-978.380531	-279.94

When proton is placed on O_3 oxygen atom then it relocates to one of the atoms of the nitro group. The relative stability of Nitrofurantoin tautomers in water medium is as: N1-H>O_2-H>O_1-H>O_4-H form. The same trend is observed when the Δ (ΔGo) values are considered.

In the case of Furazidine molecule also the N_1-H tautomer appeared to be the most stable. Here however the N_2-H and N_3-H tautomers exist. The N_3-H tautomer is stabilized through C-H interaction of more flexible bridging chain with O_2 atom of five membered rings. As in Nitrofurantoin, when proton is placed on O_3 oxygen atom then it relocates to one of the atoms of the nitro group.

In Nitrofurantoin and Furazidine molecules there is 8 potential protonation centers, 3 oxygen atoms and 3 nitrogen atoms and two oxygen atoms of the nitro group **(Figure 1)**. Nevertheless the nitro group, in each of two equivalent resonance structures, can potentially interact via the hydrogen bonding.

Protonation of neutral form yields mostly the other than H-N_1-H+ cations what prevents the change of charge distribution and electrostatic potential pattern around non ionized fragment of neutral molecule believed to be necessary for Furazidine activity.

For Nitrofurantoin molecule the most stable is the N_1-H; N_3-H cation. The N_1-H; O_3-H cation rearranges also to that tautomer **(Figure 1)**. For Furazidine molecule cation N_1-H O_3-H does not exist because it rearranges to N_1-H; O_2-H tautomer. The most stable like in Nitrofurantoin stays the N_1-H; N_3-H form **Table 2**.

The dication of Nitrofurantoin with the highest stability is the one formed from the most stable N_1-H; N_3-H cation by protonation of O_1 or O_2 oxygen atom. The same holds for Furazidine molecule **(Table 1)**.

Formation of the most stable monocation N_1-H N_3-H is more preferred in Furazidine then in Nitrofurantoin by ca. 7.75 kcal/mole. The most stable dication of Nitrofurantoin is N_1-H; O_2-H; N_3-H, however very close in energy to N_1-H; O_1-H; N_3-H. In Furazidine molecule formation of intramolecular hydrogen bonding yields the N_1-H; O_2-H; N_3-H dication the most stable. This is due to the higher flexibility of the bridging chain, than in Nitrofurantoin.

The nitro group can be protonated at each of the oxygen atoms yielding resonance structure -NOOH+ similar to -COOH [4]. Further protonation of -NO_2 could lead to reduction of –NO_2 yielding the -NH_2 derivative. This is one of the mechanisms that activate Furazidine active substance in the living organism [5,6].

If additional proton is placed on O_3 oxygen of five membered ring of neutral Furazidine, then it relocates to O_2 oxygen atom. It means that formation of cation III is very unlikely. Cation II gets additional stabilization due to intramolecular bonding with one of the oxygen atoms of -NO_2 group. The most stable cation is the N-$_1$H, N_3-H. The total energy and thermodynamics (ΔG) analysis leads to the same conclusions.

Similar conclusions regarding possible protonation sites appear from analysis of electron charges on the atoms that are eager to accept proton **(Table 3)**.

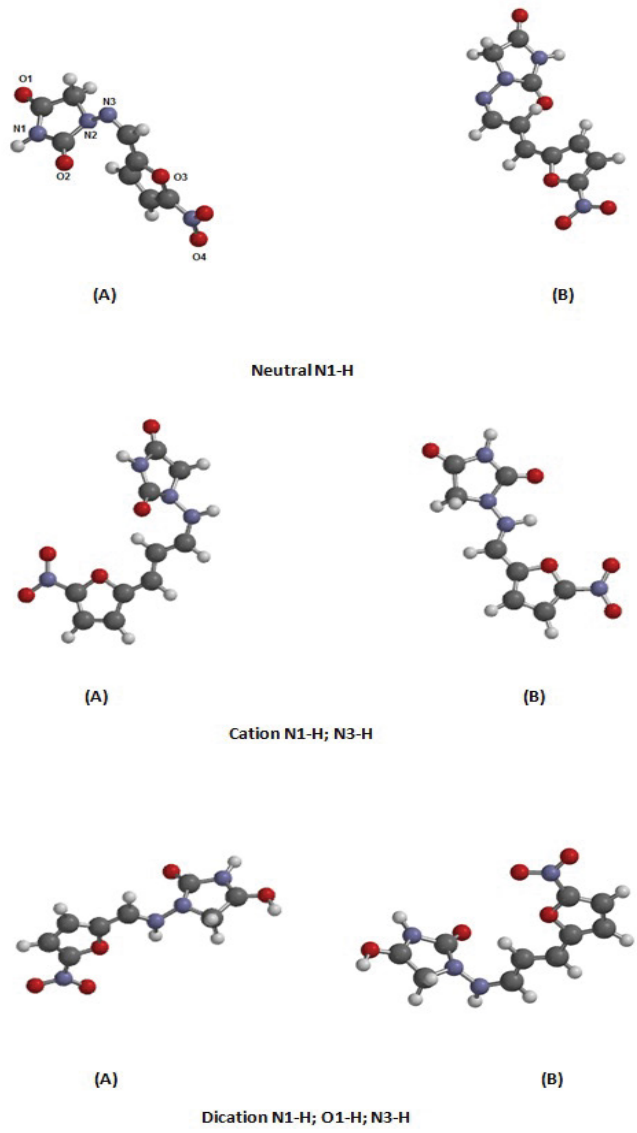

Figure 1 The most stable neutral and protonated forms of Nitrofurantoin (A) and Furazidine (B) molecules.

For neutral Nitrofurantoin and Furazidine nitrogen atoms the most negative is the N_3 atom of the bridging chain. Protonation at this atom leads to the most stable N_1-H; N_3-H cationic form. In the cation the most negatively charge atoms yield the most stable N_1-H; O_1-H; N_3-H dicationic form of Nitrofurantoin, and N_1-H; O_1-H; N_3-H dicationic form of Furazidine, respectively.

Consequently the N_1-H tautomer of neutral Furazidine is more stable than N_3-H, O_1-H and O_2-H tautomers. Performed calculations show that Furazidine oxygen and nitrogen atoms are good proton acceptors. Therefore it is justified to supplement Furazidine treatment with weak acids, for instance vitamin C, to keep the protonated Furazidine at satisfactory level, preventing urine alkalization. The *in vitro* studies on Furazidine acidity as function of pH are underway.

Table 3: Electrostatic, Mulliken and natural charges calculated for nitrofurantoin and furazidine at MP_2/631G*//MP_2/6-31G* level.

Atomic Charges						
Nitrofurantoin						
Neutral N_1-H Cation N_1-H; N_3-H						
Atom	Electrostatic	Mulliken	Natural	Electrostatic	Mulliken	Natural
N_1	-0.718	-0.731	-0.701	-0.544	-0.737	-0.689
N_2	-0.009	-0.444	-0.375	-0.229	-0.371	-0.310
O_1	-0.483	-0.447	-0.555	-0.404	-0.419	-0.527
O_2	-0.461	-0.428	-0.529	-0.377	-0.356	-0.458
N_3	-0.314	-0.195	-0.237	+0.215	-0.340	-0.228
O_3	-0.237	-0.441	-0.401	-0.210	-0.462	-0.416
N_4	+0.676	+0.276	+0.437	+0.631	+0.281 +0.426	+0.426
O_4	-0.356	-0.330	-0.327	-0.310	-0.298	-0.295
O_5	-0.389	-0.342	-0.345	-0.318	-0.289	-0.291
Furazidine						
Neutral N_1-H Cation N_1-H; N_3-H						
Atom	Electrostatic	Mulliken	Natural	Electrostatic	Mulliken	Natural
N_1	-0.663	-0.731	-0.699	-0.617	-0.728	-0.695
N_2	+0.013	-0.439	-0.369	-0.132	-0.422	-0.372
O_1	-0.459	-0.459	-0.568	-0.429	-0.418	-0.530
O_2	-0.451	-0.433	-0.533	-0.401	-0.372	-0.474
N_3	-0.347	-0.220	-0.246	-0.026	-0.379	-0.305
$O_3$2	-0.265	-0.405	-0.405	-0.202	-0.438	-0.401
N_4	+0.681	+0.275	+0.437	+0.653	+0.279	+0.427
O_4 -0.362	-0.362	-0.334	-0.332	-0.328	-0.307	-0.304
O_5 -0.393	-0.393	-0.346	-0.349	-0.335	-0.298	-0.300

References

1. Katzung BG (2015) Basic and Clinical Pharmacology. Lange Medical Books/McGraw-Hill.
2. Axelrod DL (1985) Ascorbic Acid and Urinary pH. JAMA 254: 1310-1311.
3. Mannisto P, Karttunen P (1979) Pharmacokinetics of furagin, a new Nitrofurantoin congener on human volunteers. Int J Pharmacol Biopharm 17: 264-270.
4. Hehre WJ, Yu J, Klunzinger PE, Lou L (2014) Spartan Pro. Wavefunction Inc. Irvine, Spartan 1.
5. Exner O, Bohm S (2005) Protonated nitro group: structure, energy and conjugation. Org Biomolec Chem 3: 1838-1843.
6. McOsker CC, Fitzpatrick PM (1994) Nitrofurantoin: Mechanism of action and implications for resistance development in common uropathogens. J Antimicrob Chemother 33: 23-30.