

Synthesis of 5-nitrosalicylaldehyde based hydrazones and DFT-calculations of their structure and reactivity

B. I. Nikolova-Mladenova^{1*}, S. E. Angelova²

¹Department of Chemistry, Faculty of Pharmacy, Medical University of Sofia, 2, Dunav Street, 1000 Sofia, Bulgaria

²Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Sofia 1113, Bulgaria

Received November 14, 2016; Accepted May 5, 2017

New aroylhydrazones derived from 5-nitrosalicylaldehyde, namely 5-nitrosalicylaldehyde benzoylhydrazone, 5-nitrosalicylaldehyde-4-hydroxybenzoylhydrazone and 5-nitrosalicylaldehyde isonicotinoylhydrazone were designed and synthesized. The compounds were characterized by elemental and thermogravimetric analyses, IR, ¹H and ¹³C NMR spectroscopy. Geometry optimization of the neutral hydrazones were carried out using density functional theory with Becke's three-parameter hybrid method and correlation functional of Lee, Yang and Parr with 6-31+G (d,p) basis set. The calculated bond lengths and angles of the new hydrazones are in good agreement with the experimental electron diffraction data. Molecular electrostatic potential calculations showed that the most preferred sites for iron chelation are the carbonyl oxygen atom, the imine nitrogen atom and the hydroxyl oxygen atom.

Keywords: 5-nitrosalicylaldehyde; aroylhydrazones; iron chelators; DFT calculations; molecular electrostatic potential.

INTRODUCTION

Development and synthesis of novel hydrazone derivatives continuously attracts the attention of organic and medicinal chemists due to interesting biological properties and coordinative capability of these compounds. Hydrazones demonstrate many pharmacological activities, such as anti-inflammatory [1, 2], analgesic [2], antituberculosis [3, 4], antibacterial [5], antimicrobial [6], anti-HIV [6, 7] and anticancer [6, 8–9] activity. Moreover, hydrazones are some of the most widely used ligands as they easily form stable complexes with many transition metals. Hydrazone derivatives have been intensively studied for their potential as chelating agents in medical treatment for reducing the toxic effects of metals.

Iron overload is a common clinical problem, arising as a consequence of continued blood transfusions for various blood disorders. Iron is essential for life as it plays an important role in many cellular processes. Excessive amounts of iron, however, may become very toxic to the human body. Iron ions can catalyze the generation of damaging oxygen radicals, leading to oxidative damage and subsequent cell death. Therefore, it is important to eliminate the unnecessary iron before damage can occur. The medicinal iron reduction is accomplished with chelation therapy, i.e. pharmacological removal of iron with iron-chelating agents. Only two iron chelator drugs are currently approved for administration - desferrioxamine and deferasirox. Regrettably, these medicines possess many side

effects and can affect individual people in different ways. This fact inspires the development of novel chemotherapeutic agents with potent chelating activities and reduced side effects. Very promising iron chelators are hydrazones derived from 3-hydroxy-5-(hydroxymethyl)-2-methylpyridine-4-carbaldehyde (pyridoxal) and salicylaldehyde [10–12]. Iron chelators are capable of binding the toxic metal ions to form complex structures which are easily excreted from the body.

Salicylaldehyde benzoylhydrazone (SBH) belongs to a series of iron chelators effective in chemotherapy of iron overload diseases such as β -thalassemia [13–16]. Many derivatives of SBH and their metal complexes have been synthesized to obtain new pharmacologically active compounds [17–20]. Hydrazones obtained from 3-methoxysalicylaldehyde exerted a potent antiproliferative effect on a wide spectrum of human tumor cell lines [20]. This activity may be due to the high ability of the hydrazones to chelate Fe(III) from the cells thus inhibiting the proliferation of the neoplastic cells [19]. In this paper, we describe the synthesis of new potential iron chelating agents derived from 5-nitrosalicylaldehyde and three acid hydrazides. The structures of the new aroylhydrazones are shown on Fig.1. These compounds possess several potential donor sites and can chelate metal ions in versatile manners. To predict the coordination ability and the preferred sites for binding during chelation with iron and other metal ions, the molecular electrostatic potential values were calculated and the reaction properties of the novel 5-nitrosalicylaldehyde hydrazone derivatives were evaluated.

* To whom all correspondence should be sent:

E-mail: boriananik@abv.bg

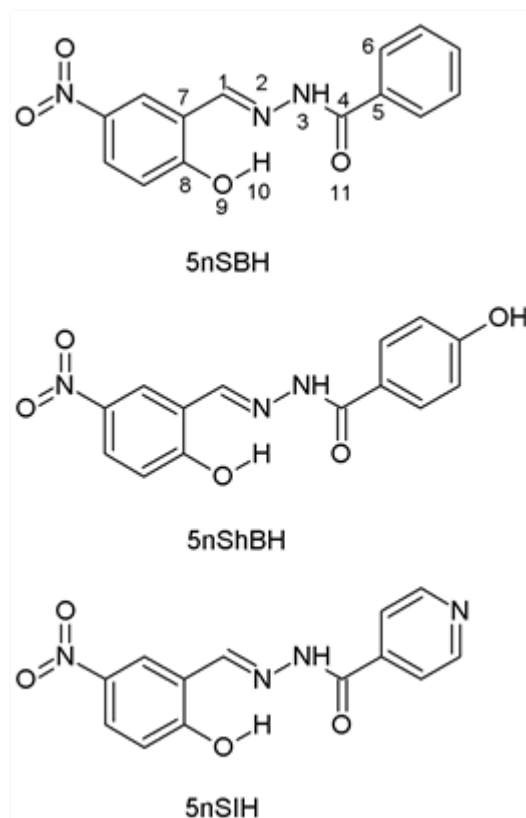


Fig. 1. Chemical structures of the synthesized hydrazones: 5-nitrosalicylaldehyde benzoylhydrazone (5nSBH), 5-nitrosalicylaldehyde-4-hydroxybenzoylhydrazone (5nShBH) and 5-nitrosalicylaldehyde isonicotinoylhydrazone (5nSIH).

EXPERIMENTAL

Materials and Measurements

All chemicals used for the synthesis of the compounds: 5-nitrosalicylaldehyde, benzhydrazide, 4-hydroxybenzhydrazide, isonicotinoyl hydrazide and 96% ethanol, were purchased from commercial sources (Merck, Sigma-Aldrich) and were used without any further purification. The carbon, nitrogen and hydrogen contents of the compounds were determined by elemental analyses on a "Euro Vector SpA" apparatus. The melting points were determined in open capillary tubes using a Büchi B-540 apparatus. The IR-spectra were recorded in solid state (in KBr pallets) on a Bruker Tensor 27 spectrophotometer in the range of 4000-400 cm^{-1} . The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 250 instrument in $\text{DMSO-}d_6$ as a solvent. Chemical shifts (δ) were reported in parts per million (ppm), J values were given in Hz. Thermal decomposition studies were carried out on a Setaram Setsys TG-DSC 15 apparatus in air atmosphere by using a corundum crucible with a sample weight of 10 mg in the temperature range of 20 - 600 $^\circ\text{C}$.

Synthesis of the hydrazones

A solution of 5-nitrosalicylaldehyde (1.671 g, 10 mmol) in 96% ethanol (30 mL) was slowly dropwise added to the solutions of the respective benzhydrazides (10 mmol) in 50% aqueous ethanol (100 mL) and immediately precipitates were formed. The mixtures were stirred for 30 min and then were left to stay for 24 h at room temperature. During this time the products fully precipitated as dark-yellow solids. The crude solids were filtered off and washed with 96% ethanol. The solid hydrazones were dried for 2 days in a vacuum desiccator.

5-nitrosalicylaldehyde benzoylhydrazone (5nSBH) (1): Yield: 79%; m.p. 303-304 $^\circ\text{C}$; Color: Yellow; Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_4$: C 58.95, H 3.89, N 14.73, O 22.43. Found: C 58.92, H 3.88, N 14.80, O, 22.40. IR (KBr, cm^{-1}): 3440 (Ar-OH), 3303 (N-H), 1632 (C=O), 1602 (C=N), 1576 (C-NH), 1242 (C-O). ^1H NMR (250 MHz, $\text{DMSO-}d_6$) δ 7.12 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.17 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.59 (s, 1H, $\text{ArH}_{\text{aldehyde}}$), 7.59 (m, 3H, $\text{ArH}_{\text{hydrazide}}$), 7.95 (d, J 7 Hz, 2H, $\text{ArH}_{\text{hydrazide}}$), 8.75 (s, 1H, N=CH), 12.26 (s, 1H, N-H), 12.26 (br s, 1H, O-H). ^{13}C NMR (250 MHz, $\text{DMSO-}d_6$) δ 117.09, 119.95, 123.80, 126.51, 127.67, 127.67, 128.04, 128.04, 132.04, 132.65, 139.91 (C- NO_2), 144.39 (CH=N), 162.55 (C=O), 163.00.

5-nitrosalicylaldehyde-4-hydroxybenzoylhydrazone (5nShBH) (2): Yield: 93%; m.p. 338-339 $^\circ\text{C}$; Color: Yellow; Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_5$: C 55.82, H 3.68, N 13.95, O 26.55. Found: C 55.98, H 3.85, N 14.05, O 26.12. IR (KBr, cm^{-1}): 3440, 3400 (Ar-OH), 3300 (N-H), 1654 (C=O), 1603 (C=N), 1592 (C-NH), 1236 (C-O). ^1H NMR (250 MHz, $\text{DMSO-}d_6$) δ 7.10 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.15 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.54 (s, 1H, $\text{ArH}_{\text{aldehyde}}$), 6.88 (d, J 8.75 Hz, 2H, $\text{ArH}_{\text{hydrazide}}$), 7.84 (d, J 8.75 Hz, 2H, $\text{ArH}_{\text{hydrazide}}$), 8.69 (s, 1H, N=CH), 12.08 (s, 1H, N-H), 10.17 (s, 1H, O- $\text{H}_{\text{hydrazide}}$), 12.43 (br s, 1H, O- $\text{H}_{\text{aldehyde}}$). ^{13}C NMR (250 MHz, $\text{DMSO-}d_6$) δ 115.09, 115.09, 117.09, 119.91, 123.04, 124.02, 126.28, 129.85, 129.85, 139.89 (C- NO_2), 143.80 (CH=N), 161.00, 162.57 (C=O), 163.00.

5-nitrosalicylaldehyde isonicotinoylhydrazone (5nSIH) (3): Yield: 97 %; m.p. 318-319 $^\circ\text{C}$; Color: Yellow; Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_4$: C 54.55, H 3.52, N 19.57, O 22.36. Found: C, 54.42, H 3.50, N 19.24, O 22.84. IR (KBr): 3350 (Ar-OH), 3301 (N-H), 1664 (C=O), 1609 (C=N), 1582 (C-NH), 1243 (C-O). ^1H NMR (250 MHz, $\text{DMSO-}d_6$) δ 7.10 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.16 (d, J 9 Hz, 1H, $\text{ArH}_{\text{aldehyde}}$), 8.59 (s, 1H, $\text{ArH}_{\text{aldehyde}}$), 7.84 (d, J 6 Hz, 2H, $\text{ArH}_{\text{hydrazide}}$), 8.79 (d, J 6 Hz 2H, $\text{ArH}_{\text{hydrazide}}$), 8.75 (s, 1H, N=CH), 12.16 (s, 1H, N-H), 12.34 (br s,

^1H , O-H). ^{13}C NMR (250 MHz, DMSO- d_6) δ 117.07, 119.94, 121.48, 121.48, 123.45, 126.77, 139.81, 139.93 (C-NO $_2$), 145.07 (CH=N), 150.34, 150.34, 161.58, 162.55 (C=O).

Theoretical studies

The geometry optimizations of the neutral hydrazones were carried out using density functional theory (DFT) calculations with Becke's three-parameter hybrid functional [21] combined with the Lee-Yang-Parr [22] correlation functional - B3LYP with 6-31+G (d,p) basis set. The calculations of the studied hydrazones were performed using the Gaussian 09 program suite [23]. A tight SCF convergence criterion (10^{-8} Hartree) was employed in all calculations. Frequency calculations were carried out to examine the stationary points in the optimization procedure and no imaginary frequencies were found.

Further, the molecular electrostatic potential (MEP) was calculated. The electrostatic potential created by the nuclei and electrons of a molecule in the surrounding space is well established as a guide to the interpretation and prediction of the chemical reactivity of a number of biological systems which take part in both electrophilic and nucleophilic reactions [24–28]. The electrostatic potential study also explains the electronic distribution and structure formation in a molecule. The MEP of a molecule is a real physical property that can be experimentally determined by diffraction methods, as well as computationally. At present, however, computational approaches are more often used as a practical alternative. The calculated values were used to predict the reactive behavior and the potential donor sites of the new hydrazones as ligands for iron chelation.

RESULTS AND DISCUSSION

Chemistry

5-Nitrosubstituted hydrazones were synthesized by condensation of 5-nitrosalicylaldehyde with three benzhydrazides as previously described [20, 29] according to Scheme 1.

The structures of the isolated products were confirmed on the basis of their respective analytical

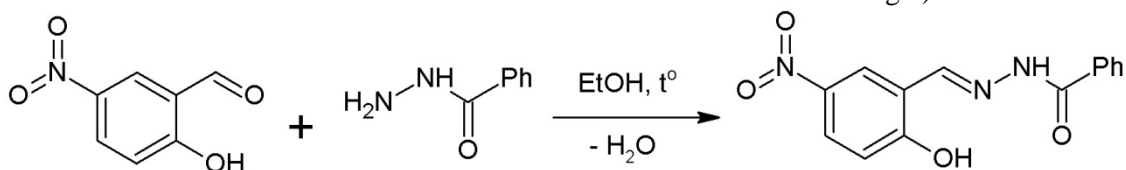
and spectral data. The water content was determined thermogravimetrically. The DTA and TGA data showed that the three hydrazones are anhydrous. The structures of the new compounds were characterized using IR, ^1H NMR and ^{13}C NMR spectral analyses and by comparison with the available literature data.

The IR spectra of all compounds show a medium intensity band at 3350-3440 cm^{-1} due to $\nu(\text{O-H})$ of the phenolic groups. The stretching vibration of the NH group appears as a weak broad band at 3300-3303 cm^{-1} . The above band, accompanied by a C=N absorption band between 1602-1609 cm^{-1} , is a good evidence for the presence of an azomethine linkage. The strong band in the region 1632-1664 cm^{-1} was assigned to stretching vibration of the carbonyl group of amide $\nu(\text{C=O})$. Another important band at 1576-1592 cm^{-1} was attributed to $\nu(\text{C-NH})$.

The hydrazones were further studied by their ^1H NMR and ^{13}C NMR spectra in deuterated dimethyl sulfoxide. ^1H NMR spectra revealed the presence of the aromatic protons in the region of δ from 6.88 to 8.79. Signals for the protons of the azomethine group HC=N- (characteristic for hydrazones) were observed between δ 8.69 and 8.75. The broad singlets around δ 12.26-12.43 were assigned to the protons of the hydroxyl group from the aldehyde ring. ^{13}C NMR spectra demonstrated signals corresponding to the carbon atoms of azomethine group between δ 143.80 and 150.34. The peaks at δ 162.55-162.57 were assigned to the C=O group.

Computational study

The molecular structures of the new compounds were studied theoretically and quantum-chemical calculations were carried out. The structural parameters were computed at B3LYP level of theory using a 6-31+G (d, p) basis set. This level of calculations was tested in our previous study on 3-methoxysalicylaldehyde hydrazones and the results obtained showed a very good agreement with the experimental structural parameters available [20]. The calculated bond lengths and angles of the new hydrazones were compared with the experimental crystallographic data for SBH and 5nSBH. The experimental data and the calculated structural parameters are presented in Table 1 (the atomic numbers are shown in Fig.1).



Ph = C $_6$ H $_5$, 4-hydroxy-C $_6$ H $_4$, 4-Pyr

Scheme 1. Synthesis of the hydrazones.

Table 1. Selected bond lengths (Å) and angles (°) for SBH and 5-nitro derivatives.

Selected geometric parameters (Å, °)	SBH Meas.	SBH calc.	5nSBH Meas.	5nSBH calc.	5nShBH calc.	5nSIH calc.
C1-N2	1.291	1.291	1.266	1.288	1.289	1.289
N2-N3	1.365	1.360	1.382	1.355	1.354	1.357
N3-C4	1.332	1.388	1.338	1.392	1.394	1.388
C4-C5	1.502	1.501	1.489	1.498	1.492	1.503
C1-C7	1.432	1.452	1.464	1.455	1.455	1.454
C4-O11	1.221	1.222	1.233	1.221	1.222	1.220
C8-O9	1.356	1.346	1.339	1.336	1.336	1.336
O9-H10	-	1.291	0.850	0.990	0.990	0.989
C1-N2-N3	118.2	118.7	115.2	119.5	119.6	119.3
N2-N3-C4	118.9	120.1	119.9	119.6	119.5	119.6
N3-C4-O11	123.1	122.3	122.3	121.8	121.4	122.5
N3-C4-C5	116.9	114.8	116.8	114.9	115.2	114.7
C5-C4-O11	119.9	122.9	120.9	123.2	123.3	122.7
C1-C7-C8	122.6	121.9	119.8	121.9	121.9	121.9

The average calculated bond length C1-N2 in the three 5-nitro-compounds is 1.289 Å, very close to the experimentally measured one for SBH (1.291 Å) and perfectly matches the length of the double bond C = N equal to 1.29 Å. The calculated length of the bond N3-C4 is slightly above that experimentally determined for 5nSBH and SBH, whereas the average calculated distance N2-N3 (1.355 Å) is slightly shorter than the experimental one in 5nSBH (1.382 Å). An excellent match exists between the experimentally measured and calculated distances of the carbonyl group C4-O11 for the three compounds (1.221 Å) and the typical length of a double bond C = O (1.22 Å).

The values of the calculated angles are very close to the experimentally measured ones and reveal that all carbon atoms are in sp² hybridization. Minor differences of about ± 3 ° were observed in the calculated angles C1-N2-N3, N3-C4-C5 and C5-C4-O11.

Despite the small differences obtained, the optimized geometries of nitro-hydrazones are in good agreement with the experimental electron diffraction data. The substituents at the 4th position in the hydrazide ring insignificantly affect the bond lengths and angles and all 5-nitrosalicylaldehyde hydrazone derivatives have similar geometry. The optimized structures of the 5-nitro derivatives are presented in Fig.2.

Aroylhydrazones can act as polydentate ligands depending on the reaction conditions, the nature of metal ion and hydrazone ligand, and the pH of the medium. Salicylaldehyde benzoylhydrazone and its substituted derivatives have four donor atoms N2, N3, O9 and O11 which allow binding to a central metal ion in a versatile manner. However, in most of their complex compounds, they react as tridentate ligands in mono-anionic form after deprotonation of

the phenolic hydroxyl group [32–35]. Deprotonation equilibrium between the neutral and the deprotonated form occurs in weak basic medium (Scheme 2) and the phenolic hydroxyl group loses its proton [36].

In general, the most negative value of the electrostatic potential in the neutral molecules LH is focused on the carbonyl oxygen O11, whereas the other donor atoms have a higher, even positive value of the electrostatic potential. So it is practically impossible to realize a complex compound with the neutral forms of the hydrazones. Deprotonation of O9 brings about considerably negative values of the electrostatic potential for it, as well as the appearance of such over N2. Appearance of a NO₂-group in the salicylaldehyde moiety slightly increases the value of the electrostatic potential, probably due to its negative inductive effect.

In view of these observations it can be concluded that the hydroxyl oxygen atom O9, the imine nitrogen atom N2 and the carbonyl oxygen atom O11 will be the preferred sites for complex formation with metal ions. Compounds 5nSBH and 5nSIH will have similar activity like SBH, 5nShBH being the most potent chelating agent among the new compounds.

The nitro-group withdraws electron density from the aldehyde ring, thus the replacement of the hydrogen in SBH with a nitro group in nitro-derivatives will result in partially positive charges at *ortho*- and *para*-positions. Additionally, this will increase the polarity of the phenolic group on *para*-position and will influence and facilitate its deprotonation during complexation.

To predict the reactivity of the new hydrazones as iron-chelators, MEP was calculated. The negative regions in the molecules with negative values of electrostatic potential were related to the

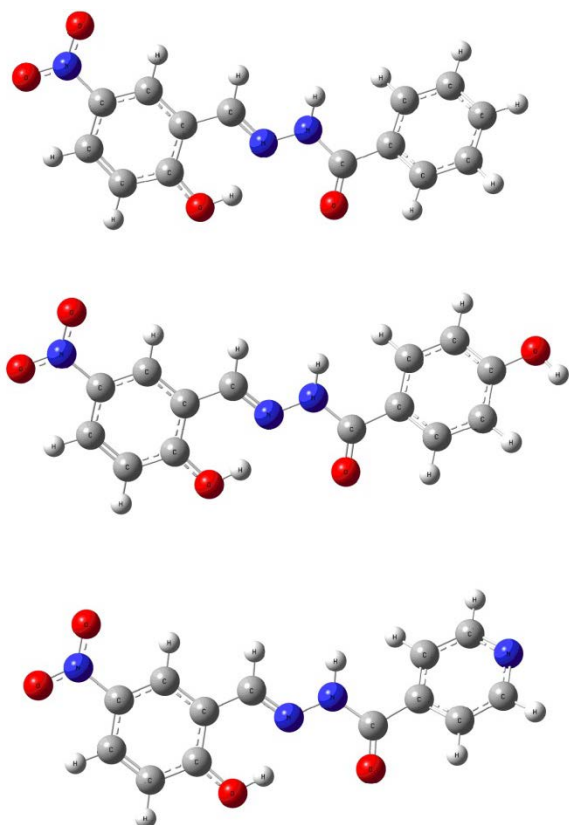
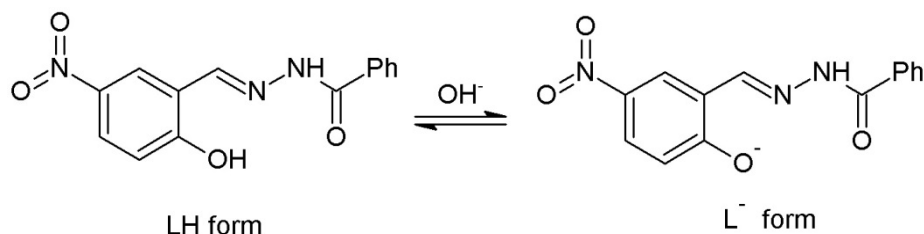


Fig. 2. B3LYP/6-31+G (d,p) optimized structures of 5nSBH, 5nShBH and 5nSIH.

electrophilic reactivity and were found as the reactive sites where the metal ion will prefer to coordinate. An approaching iron ion will be attracted to the region of the molecule with the most negative values, i.e., where the effects of the electrons are dominant [24]. Table 2 presents recently calculated minima of the molecular electrostatic potentials V_{min} for the nitro-derivatives, compared with these of SBH [37]. Both of the oxygen atoms - O9 and O11 have two values of the electrostatic potential due to the presence of two electron pairs around them. The values for O9 in the neutral form LH are identical and only one is shown.

CONCLUSIONS

In conclusion, three hydrazones, 5-nitroderivatives of salicylaldehyde benzoyl hydrazone were synthesized. The molecular formulas of the substances were confirmed by elemental, thermogravimetric and spectral analyses such as IR, ^1H NMR and ^{13}C NMR. Computational studies were carried out in order to evaluate the molecular structure. The substitutions in the aromatic nuclei insignificantly influenced the geometries and all derivatives have similar structure. The DFT-calculated molecular electrostatic potentials for all molecules indicate the favorable sites for iron chelation - hydroxyl oxygen atom, imine nitrogen atom and carbonyl oxygen atom.



Scheme 2. Equilibrium of 5-nitrohydrazones in basic media.

Table 2. Calculated minima of the molecular electrostatic potentials V_{min} / kcal mol $^{-1}$ for selected atoms in the neutral molecules LH and deprotonated molecules L $^-$.

Molecule	LH				L $^-$			
	V_{min} O9	V_{min} N2	V_{min} N3	V_{min} O11	V_{min} O9	V_{min} N2	V_{min} N3	V_{min} O11
SBH	-44.43	-21.27	-5.65	-53.02 -50.32	-179.0 -157.6	-175.7	-87.7	-145.0 -119.9
5nSBH	-31.75	-13.55	+1.76	-37.96 -37.96	-158.6 -138.3	-150.7	-80.2	-125.8 -100.4
5nShBH	-31.69	-10.67	+7.53	-45.81 -44.18	-208.6 -177.0	-200.9	-138.7	-194.8 -177.0
5nSIH	-25.98	+1.88	+18.45	-38.84 -37.90	-155.4 -133.1	-144.6	-76.1	-125.8 -101.0

REFERENCES

1. Z. A. Kaplancikli, M. D. Altintop, A. Ozdemir, G. Turan-Zitouni, S. I. Khan, N. Tabanca, *Lett. Drug Des. Discovery*, **9**, 310 (2012).
2. W. B. Júnior, M. S. Alexandre-Moreira, M. A. Alves, A. Perez-Rebolledo, G. L. Parrilha, E. E. Castellano, O. E. Piro, E. J. Barreiro, L. M. Lima, H. Beraldo, *Molecules* **16**, 6902 (2011).
3. A. Ozdemir, G. Turan-Zitouni, Z. A. Kaplancikli, G. Revial, *Marm. Pharm. J.*, **14**, 79 (2010).
4. B. Koçyiğit-Kaymakçioğlu, E. E. Oruç-Emre, S. Unsalan, S. Rollas, *Med. Chem. Res.*, **18**, 277 (2009).
5. T. Govindasami, A. Pandey, N. Palanivelu, A. Pandey, *Int. J. Org. Chem.*, **1**, 71 (2011).
6. L. Savini, P. Massarelli, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino, M. B. Pisano, *Eur. J. Med. Chem.*, **39**, 113 (2004).
7. P. Vicini, M. Incerti, P.L. Colla, R.E. Loddo, *Eur. J. Med. Chem.*, **44**, 1801 (2009).
8. T. B. Chaston, R. N. Watts, J. Yuan, D. R. Richardson, *Clin. Cancer Res.*, **10**, 7365 (2004).
9. D. K. Johnson, T. B. Murphy, N. J. Rose, W. H. Goodwin, L. Pickart, *Inorg. Chim. Acta*, **67**, 159 (1982).
10. J.T. Edward, *BioMetals*, **11**, 203 (1998).
11. J.T. Edward, P. Ponka, D.R. Richardson, *BioMetals*, **8**, 209 (1995).
12. E.M. Becker, D.R. Richardson, *J. Lab. Clin. Med.*, **134**, 510 (1999).
13. P. Ponka, D. Richardson, E. Baker, H. M. Schulman, J. T. Edward, *Biochim. Biophys. Acta*, **967**, 122 (1988).
14. E. Baker, D. R. Richardson, S. Gross, P. Ponka, *Hepatology*, **15**, 492 (1992).
15. D. R. Richardson, P. Ponka, *J. Lab. Clin. Med.*, **131**, 306 (1998).
16. J. L. Buss, E. Arduini, P. Ponka, *Biochem. Pharmacol.*, **64**, 1689 (2002).
17. D. B. Lovejoy, D. R. Richardson, *Blood*, **100**, 666 (2002).
18. D. R. Richardson, K. Milnes, *Blood*, **89**, 3025 (1997).
19. D.R. Richardson, *Antimicrob. Agents Chemother.*, **41**, 2061 (1997).
20. B. Nikolova-Mladenova, N. Halachev, R. Iankova, G. Momekov, D. Ivanov, *Arzneim.-Forsch.*, **61(12)**, 714 (2011).
21. A. D. Becke, *J. Chem. Phys.*, **98**, 5648 (1993).
22. C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B*, **37**, 785 (1998).
23. M. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji. Gaussian 09, revision A. 02; Gaussian, Inc. Wallingford, CT, **19**, p. 227 (2009).
24. P. Politzer, J. S. Murray, in: K. B. Lipkowitz, D. B. Boyd (Eds.): *Reviews in Computational Chemistry*, vol. 2, VCH Publishers, New York, 1991, p. 273.
25. P. Politzer, J. S. Murray, *Theor. Chem. Acc.*, **108**, 134 (2002).
26. C. Munoz-Caro, A. Nino, M. L. Senent, J. M. Leal, S. Ibeas, *J. Org. Chem.*, **65**, 405 (2000).
27. N. Okulik, A. H. Jubert, *Internet Electron. J. Mol. Des.*, **4**, 17 (2005).
28. R. Soliva, F. J. Luque, M. Orozco, *Theor. Chem. Acc.*, **98**, 42 (1997).
29. J.T. Edward, M. Gauthier, F.L. Chubb, P. Ponka, *J. Chem. Eng. Data*, **33**, 538 (1988).
30. A. Lyubchova, A. Cossé-Barbi, J.P. Doucet, *Acta Cryst. C51*, 1893 (1995).
31. H. M. Ali, S. Puvaneswary, S. W. Ng, *Acta Cryst. E61*, 3464 (2005).
32. R. M. El-Bahnasawy, S. E. El-Meleigy, A. El-Tawansi, *Trans. Met. Chem.*, **19**, 270 (1994).
33. B. Mladenova, D. S. Ivanov, M. H. Umbreit, J. Klos, S. Konstantinov, M. Karaivanova, *Pharmacy*, **3-4**, 3 (2003).
34. B. Nikolova-Mladenova, D. Ivanov, *Pharmacia*, **61(4)**, 7 (2014).
35. S. A. Yasrebi, H. Mobasheri, I. Sheikhshoae, M. Rahban, *Inorg. Chim. Acta*, **400**, 222 (2013).
36. Yi-H. Lu, Yu-W. Lu, C.-Li Wu, Q. Shao, X.-L. Chen, R. Bimbong, *Spectrochim. Acta Mol. Biomol. Spectrosc.*, **65**, 695 (2006).
37. N. Halachev, R. Iankova, St. Manolov, B. Nikolova-Mladenova, D. S. Ivanov, *Annual Assen Zlatarov University*, **XXXVI (1)**, 44 (2007).

СИНТЕЗ НА ХИДРАЗНИ, ПОЛУЧЕНИ ОТ 5-НИТРОСАЛИЦИЛАЛДЕХИД И DFT-ИЗЧИСЛЕНИЯ ЗА ТЯХНАТА СТРУКТУРА И РЕАКЦИОННА СПОСОБНОСТ

Б. И. Николова-Младенова^{1*}, С. Е. Ангелова²

¹ *Фармацевтичен факултет, Медицински университет София, София 1000, България*

² *Институт по органична химия с Център по фитохимия, Българска Академия на Науките, София 1113, България*

Получена на 14 ноември, 2016 г.; приета на 5 май, 2017 г.

(Резюме)

Синтезирани са нови ароилхидразони чрез кондензацията на 5-нитросалицилалдехид и три ароматни хидразида – бензхидразид, 4-хидроксibenзхидразид и изоникотиноил хидразид. Съединенията са охарактеризирани с елементарен и термогравиметричен анализ, ИЧ, ¹H и ¹³C ЯМР спектроскопия. Геометриите на неутралните хидразони са оптимизирани с методите на теория на функционала на плътността (density functional theory, DFT), като са използвани функционал B3LYP и базисен набор 6-31+G (d, p). Изчислените дължини на връзки и ъгли на новите хидразони са в добро съгласие с експерименталните данни от рентгеноструктурен анализ. Изчислените стойности на електростатичния потенциал показват, че най-предпочитаните места за хелатотерапия са кислородният атом от карбонилната група, азотният атом от имино групата и кислородният атом от хидроксилната група.