Heterocyclic Letters
Vol. 6| No.3 |361-369|May-July| 2016
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

DETERMINATION OF BIOLOGICAL ACTIVITIES AND pKa AT DRUG ACTIVE SUBSTANCE IN SOME BISBENZIMIDAZOLES DERIVATIVES

Fatih İslamoğlu*, Naciye Erdoğan and Emre Menteşe

Recep Tayyip Erdoğan University Department of Chemistry,Rize, 53100, Turkey.
E-mail: fatih.islamoglu@erdogan.edu.tr

Abstract

Bisbenzimidazole derivatives have known different structures as drug active substance were evaluated for their biological activities such as antiviral and anti-tumor activities. In addition, acid dissociation constants (pKa) were determined experimentially with potentiometric titration method and theoretically with SPARC computer programme about state acidity for these five compounds at 25^{o}C.

Keywords: Bisbenzimidazole derivatives, Drug active substance, Acid dissociation constants, Potentiometric titration.

Introduction

Benzimidazoles are significant for many areas of chemistry[i]. They are contained in agrochemicals, dyestuffs, and high-temperature polymer products, and they have interesting biological and pharmaceutical activities[ii-vi]. These kinds of heterocycles have also shown different pharmacological activities against gram-positive drug-resistant bacteria and some fungi, which are responsible for some infections in acute systems[vii].

Benzimidazoles are the most prominent heterocycles with diverse biological functions[viii-x]. Multiple previous reports have suggested that benzimidazoles to be very good cytotoxic agents against different types of cancer cell lines[xi]. Recently bisbenzimidazole conjugates have been reported to target mitochondria in cancer cells and induce their antiproliferative activity by caspase dependent apoptosis[xii]. In addition, bisbenzimidazoles bind to minor groove of the DNA to instigate its anti-proliferative effect and many DNA minor groove binders have entered clinical trials in cancer treatment[xiii,xiv]. Furthermore, bisbenzimidazoles possess topoisomerase-115[xv] and serine protease inhibition[xvi], antiviral[xvii], antileishmanial[xviii], and several other biological properties[xix].

Benzimidazoles are heterocyclic compounds which display a wide spectrum of biological activities and thus have been a point of attraction in the eyes of synthetic organic chemists due to their use as potential pharmacopheres[xx,xxi]. Properties of benzimidazole and its derivatives have been studied for more than hundred years and keen interest of researchers has been triggered by the discovery of 5,6-dimethylbenzimidazole as a constituent unit in

vitamin B12[xxii]. Several antihelminthic, antacid and antibacterial drugs are known which have benzimidazole moiety as their essential constituent[xxiii].
Acidity constants, or pKa values, are one of the most important chemical properties which are very useful for understanding many fundamental reactions in chemistry and biochemistry. Thesevalues reveal the tendency of a molecule for deprotonating in a particular solvent. There is a great of interest to introduce different theoretical and semiempirical methods to calculate the pKa values for many different types of molecules[xix].

Results and Discussion

Antiviral Activity Results

All compounds tested were low toxicity only compound 1 and 2 at 25 and 50 µg/cm^3 in Vero and MDCK cells used to grow HSV-1 and influenza A virus, respectively. No anti-influenza virus activity of the compounds was detected. The results are given below in the **Table 1**.

Table 1. Anti-HSV and anti-influenza A virus activity of the compounds.

CN[c]	HSV % Plaque reduction[a]				Anti-influenza A activity (±)[b]							
	Concentration (µg/cm^3)				Concentration (µg/cm^3)							
	6.25	12.5	25	50	100	50	25	12.5	6.2	3.1	1.5	0.7
1	0	0	13	30	-	-	-	-	-	-	-	-
2	0	0	0	0	-	-	-	-	-	-	-	-
3	0	0	0	0	-	-	-	-	-	-	-	-
4	0	0	0	0	-	-	-	-	-	-	-	-
5	0	0	0	0	-	-	-	-	-	-	-	-

[a] Percentage of plaque reduction : [(mean number of plaques is control – mean number of plaques is test)/(mean number of plaques in control)] x 100
[b] + and – indicate "no virus growth" and "virus growth", respectively, as determined by hemagglutination assay using chicken erythrocytes
[c]Compound number

Antitumor Activity Results

The tumor cell growth inhibition results in **Table 2** indicated that some of the compounds exhibited a dosedependent inhibitory effect on adenocarcinoma (CT26) and melanoma (B16F10) cells. Five of the compounds, namely 3, was active against both cancer cell lines at concentrations below 10 µg/cm^3.

Table 2. Antitumor activity of the compounds.

Compound	Tumor cell growth inhibition (GI_{50}, log µg/cm^3)	
	Cell line	
	CT26 (adenocarcinoma)	B16F10 (melanoma)
1	1.459	1.697
2	1.142	1.759
3	0.910	1.643
4	6.454	5.450
5	12.970	1.788

Acidity

In this study, all compounds were titrated potentiometrically with TBAH in isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile. The mV values read in each titration were drawn against TBAH volumes (mL) added and potentiometric titration curves were formed for all the cases. Experiments were repeated 3 times in each experiment. Standard deviations was calculated for this three experiments. Calculations were performed within 95% confidence interval. From the titration curves (**Figure 1**), the HNP (half-neutralization potential) values were measured and the corresponding pKa values were calculated. The HNP values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 MTBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile and pKa for all compounds were calculated theoretically with SPARC computer programme. All pKa and HNP values are presented in **Table 3**. Theoretical and experimental pKa values were comparisoned as an example of the compound **1**in **Figure 2**.

When the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: *N,N*-dimethylformamide (ε = 36.7) > acetonitrile (ε = 36.0) > isopropyl alcohol (ε = 19.4) >*tert*-butyl alcohol (ε = 12.0). But, in this studied that it is observed isopropyl alcohol >*tert*-butyl alcohol >*N,N*-dimethylformamide >acetonitrile for compound **2** and **3**, isopropyl alcohol >*tert*-butyl alcohol = acetonitrile >*N,N*-dimethylformamide for compound **1**, *tert*-butyl alcohol > isopropyl alcohol >*N,N*-dimethylformamide > acetonitrile for compound **4**, acetonitrile > isopropyl alcohol >*tert*-butyl alcohol >*N,N*-dimethylformamide for compound **5**.

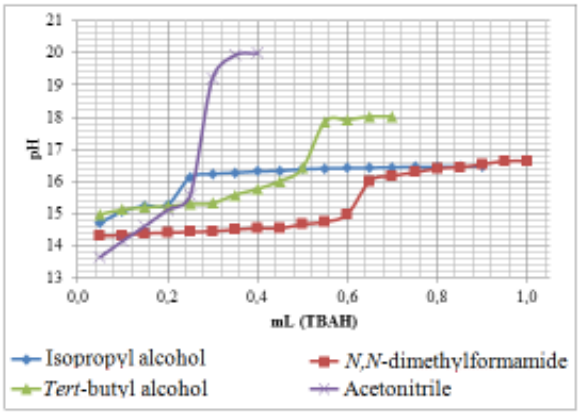
When dielectric constant is examined according to the acidity forces (amphiprotic solvents the dielectric constant of isopropyl alcohol and *tert*-butanol, respectively, 19.4 and 12.0). The acidity of the compounds are expected more acidic for high dielectric constant has solvent (isopropyl alcohol). In this study, it is obtained a result of compounds **1**, **2**, **3** and **5**data were found to be suitable in this order. When dipolar aprotic solvents is considered, the increase in strength of the acidity is expected as *N,N*-dimethyl formamide > acetonitrile. Compound **2**, **3** and **4** were observed to follow this order.

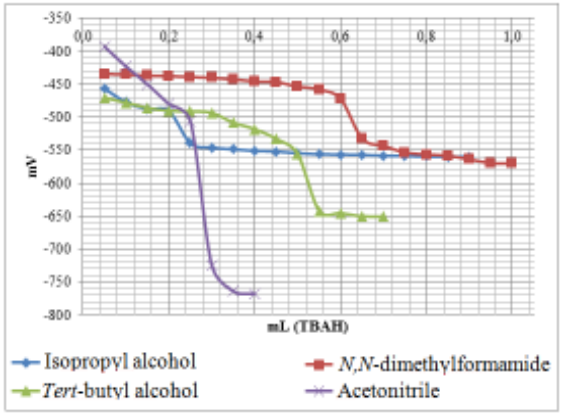
When analyzed according to autoprotolysis constant, weak acidic property is showed in isopropyl alcohol (pKs: 20.6), *N,N*-dimethylformamide (pKs: 18.0) and *tert*-butanol (pKs: 22.0) but strong acidic property (except compound **3**) is showed in acetonitrile (pKs: 33.0) for all compounds. By the time analyzed according to the functional group (-R) effect, it has showed very small effect for acidic protons due to the distance. By the time compounds were analyzed by each solvent, acidity strength decrease; **4**>**3**>**2**>**1**>**5** in isopropyl alcohol, 3>1>2>4>5 in *N,N*-dimethylformamide, 4>3>2>1>5 in *tert*-butyl alcohol and 1>5>4> 2>3 in acetonitrile as observed. Differentiated all compounds showed in the studied solvents when investigated the effect of the leveling and differentiated. When compared theoretical results with potentiometric results was obtained by the half-neutralization method, errors were found to be between 0.24% (compound **3** in acetonitrile) and -17.35% (compound **3** in *N,N*-dimethylformamide). Percentage error values of between the theoretical values and the experimental values are given in **Table 3**.

Table 3. Half-Neutralization Potential (HNP) values, experimential and theoretical the corresponding pKa values of all studied molecules.

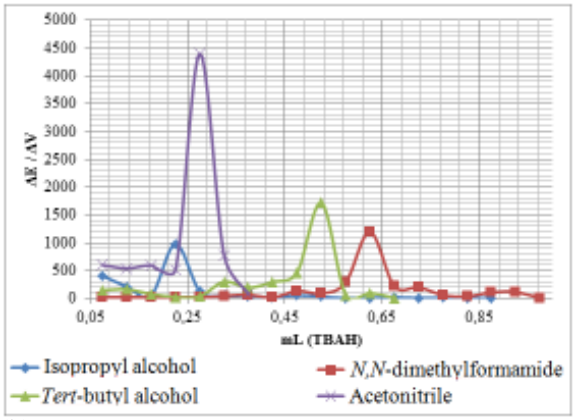
Comp.	Solvent	pKa (Experiential)	HNP (mV)	pKa (Theoretical)	Relative Error, %
1	Isopropyl alcohol	15.19 ± 0.08	-485.6 ± 6.0	13.23	12.90
	N,N-Dimetilformamid	15.40 ± 0.08	-502.1 ± 9.2	17.50	-13.64
	Tert-Butily alcohol	15.30 ± 0.02	-492.3 ± 1.3	14.86	2.88
	Acetonitrile	15.30 ± 0.04	-491.0 ± 5.8	16.45	-7.52

2	2-Propanol	14.59 ± 0.08	-450.6 ± 1.6	13.26	9.12
	N,N-Dimetilformamid	15.47 ± 0.03	-500.9 ± 1.8	17.52	-13.25
	Tert-Butamol	14.73 ± 0.11	-461.1 ± 6.0	14.88	-1.02
	Asetonitril	16.32 ± 0.09	-551.6 ± 5.5	16.48	-0.98
3	Isopropyl alcohol	14.39 ± 0.06	-434.0 ± 7.2	13.26	7.85
	N,N-Dimetilformamid	14.93 ± 0.05	-469.1 ± 4.9	17.52	-17.35
	Tert-Butily alcohol	14.49 ± 0.08	-443.1 ± 6.8	14.88	-2.69
	Acetonitrile	16.52 ± 0.04	-562.9 ± 5.3	16.48	0.24
4	Isopropyl alcohol	14.29 ± 0.07	-439.9 ± 5.9	13.44	5.95
	N,N-Dimetilformamid	15.77 ± 0.07	-521.2 ± 4.2	17.70	-12.24
	Tert-Butily alcohol	14.20 ± 0.09	-434.3 ± 7.3	15.06	-6.06
	Acetonitrile	16.16 ± 0.08	-546.1 ± 6.4	16.66	-3.09
5	Isopropyl alcohol	15.82 ± 0.05	-521.8 ± 6.6	13.44	15.04
	N,N-Dimetilformamid	16.42 ± 0.02	-557.1 ± 2.2	17.72	-7.92
	Tert-Butily alcohol	16.31 ± 0.04	-551.2 ± 2.9	15.08	7.54
	Acetonitrile	15.50 ± 0.06	-524.0 ± 7.3	16.67	-7.55

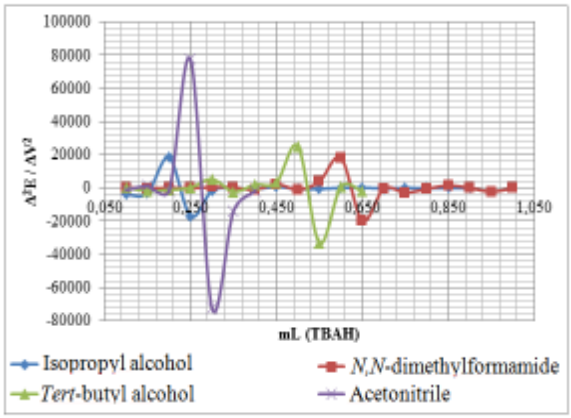




(a)



(b)



(c) (d)

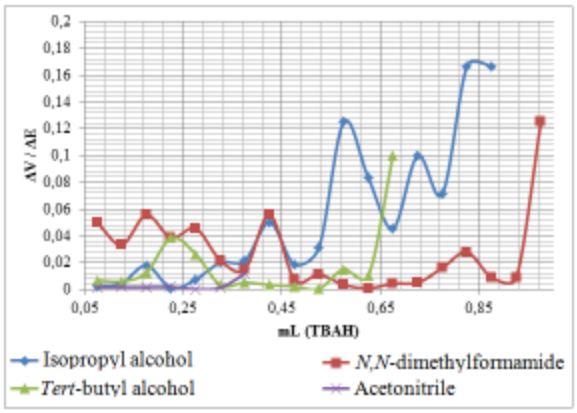


Figure 1.(a) pH-mL (TBAH), (b) mV-mL (TBAH), (c) ΔE/ΔV-mL (TBAH), (d) $\Delta^2E/\Delta V^2$-mL (TBAH) and (e) ΔV/ΔE-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **1** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile at 25°C

(e)

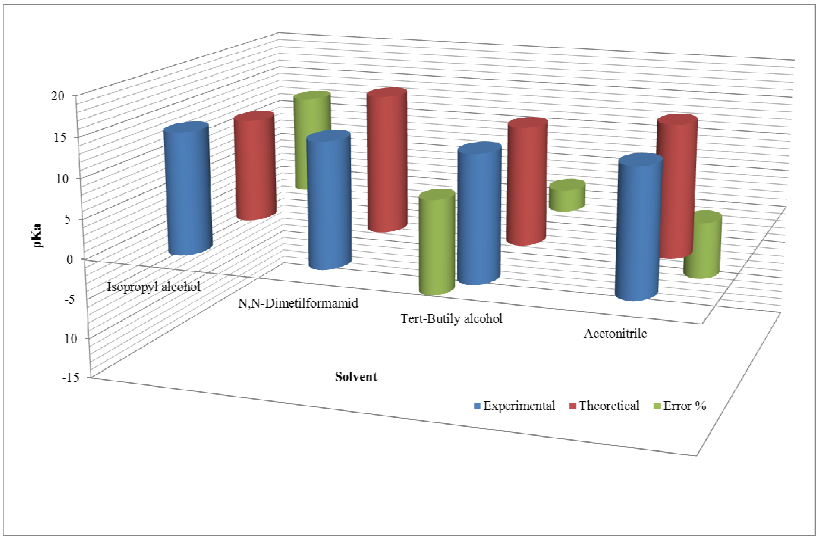


Figure 2. Experimental and theoretical results compared with Error % for compound **1**.

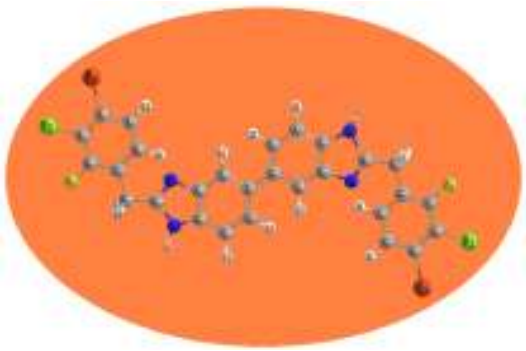
Conclusion

The acidity of a compound depends on mainly two factors, i.e. solvent effect and molecular structure. Half-neutralization potential (HNP) values and corresponding pKa values obtained from the potentiometric titrations as experimentaly rely on the non-aqueous solvents and as theoreticaly with SPARC computer program. These benzimidazole derivatives will evaluated for biological activities except antiviral and antitumor activities.

Experimental

Methods

In this study, five benzimidazole derivatives (2,2′-bis(2-chlorobenzyl)-1*H*,1′*H*-5,5′-bisbenzimidazole (**1**), 2,2′-bis(3-chlorobenzyl)-1*H*,1′*H*-5,5′-bisbenzimidazole (**2**), 2,2′-bis(4-chlorobenzyl)-1*H*,1′*H*-5,5′-bisbenzimidazole (**3**), 2,2′-bis(3-methylbenzyl)-1*H*,1′*H*-5,5′-bisbenzimidazole (**4**), 2,2′-bis(4-methylbenzyl)-1*H*,1′*H*-5,5′-bisbenzimidazole (**5**) (molecule formules are given **Figure 3**) studied as biological activities and acidity. These molecules were synthesized in Recep Tayyip Erdoğan University Organic Chemistry Research Laboratory and published[xxv].



Group	1	2	3	4	5
R_1	-Cl	-H	-H	-H	-H
R_2	-H	-Cl	-H	$-CH_3$	$-CH_3$
R_3	-H	-H	-Cl	-H	-H

Figure 3.Studied of compounds **1-5**.

Pharmacology

Antiviral Activity Testing

Antiviral activity of the compounds against HSV-1 (wal strain) and influenza A virus (A/PR/8, H1N1) was tested by plaque reduction and hemagglutination assays using Vero and MDCK cells, respectively, as described[xxvi,xxvii]. For the anti-HSV-1 activity test, briefly monolayers of Vero cells grown in 24-well plates were infected with the virüs (ca. 100 pfu/well). After incubation for 1 h to allow viral adsorption, the inoculum was aspirated and the infected cells were overlaid with 0.8% methylcellulose in maintenance medium (minimal essential medium with 2% fetal bovine serum) containing various concentrations of the compounds in duplicate. Controls included mock-infected wells with and without compounds. After 72 h of incubation, the cell monolayers were washed with phosphate buffer and then stained with naphthol blue black dye. The plaques were counted and the percentage of plaque reduction was calculated as follows: [(mean number of plaques in control - mean number of plaques in test)/(mean number of plaques in control)] x 100. For the antiinfluenza activity test, briefly monolayers of MDCK cells were grown in 96-well plates and infected with 0.1 cm^3 of x 100 TCID50 of influenza A virus (A/PR/8, H1N1) prepared in a maintenance medium (minimal essential medium with no serum but containing 1 µg/cm^3 trypsin). After incubation for 1 h to allow viral adsorption at 37°C, the inoculum was decanted and the infected cells were overlaid with fresh maintenance medium containing various concentrations (200, 100, 50, 25, 12.5, 6.2, 3.1, 1.5 µg/cm^3) of the compounds in triplicate. After 72 h of incubation at 37°C and 5 %CO_2, 50 $mm^3$of culture supernatant from each well was transferred into U-bottom microwell plates to detect the presence of virus by the hemagglutination assay. The result were reported as the presence (+) or absence (-) of the virus growth[xxviii].

Antitumor Activity Testing

The test for inhibition of tumor cell growth in the presence of the compounds was performed essentially as described[xxix] using murine tumor cell lines CT26 (adenocarcinoma) and B16F10 (melanoma). Briefly, $1x10^5$ viable cells from each cell line in RPMI-1640 growth medium supplemented with 10% FBS were seeded in a 96-well plate and incubated for 24-48 h. When cells reached greater than 80% confluence, themedium was decanted and cells were incubated with twofold dilutions (100, 50, 25, 12.5, 6.2, 3.1, and 1.5 µg/cm^3) of the test compounds prepared in 0.5% dimethyl sulfoxide in triplicate. After 48 h of incubation at 37°C, the treated and untreated cells (controls) were fixed by the addition of 1%

glutaraldehyde solution for 15 min, washed with deionized water, and dried in air. The cells were then stained with 0.4% crystal violet for 30 min, then extensively washed with phosphate buffered saline and allowed to dry overnight before dissolving the retained dye with 75% ethyl alcohol. The absorbance of developing color was determined by measuring the optical density (OD) at 570-630 nm using a multiwell spectrophotometer. The cell growth inhibiting (GI_{50}) concentration of the compounds given as μg/cm^3 in log units was calculated by GraphPad Prim 4 software. All determinations were performed in triplicate[xxviii].

Acidity

Potentiometric Titration

In this study, Orion Model 720A pH ion meter, fitted witha combined pH electrode (Ingold) was used for potentiometric titrations. An Ingold pH electrode was preferred because of the advantage. A magnetic stirrer, a semi-micro burette and a 25 ml beaker were also used in titrations at 25^{o}C. All the chemicals were supplied from Merck. Before potentiometric titrations (**Figure 4**), the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. In this section, the pH electrode calibrated with 4, 7, 10 and 12 pH tampon solution.

Figure 4.System of potentiometric titration cell used in studied.

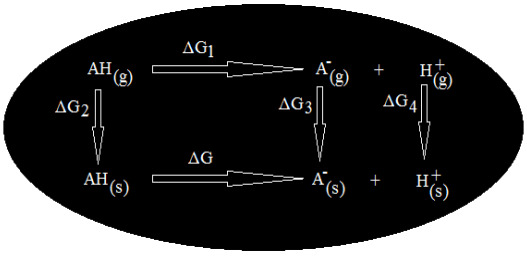
For each compound that would be titrated, the 0.001 M solution was separately prepared in each non-aqueous solvent (isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile). During the titrations, the titrant was added in increments of 0.05 mlafter each stable reading, and mV values were recorded. After purifications, isopropyl alcohol was used to prepare 0.05 N tetrabutylammonium hydroxide (TBAH). For all potentiometric titrations, 0.05 N TBAH in isopropyl alcohol, which was prepared from 0.1 N TBAH by dilution, was used. The mV values, that were obtained in pH meter, were recorded. Graphs were drawn by obtained from all data and end point is determined by ΔE/ΔV - (TBAH, mL), $\Delta^2E/\Delta V^2$ - (TBAH, mL) and ΔV/ΔE - (TBAH, mL) graphics. Finally, the half-neutralization potential (HNP) values were by drawing these graphic and pKa values were determined according to half-neutralization method.

SPARC Computer Program

Theoretical methods presented in quantum computational chemistry are used as an effective tool for calculating the pKa values of many different types of molecules. These include molecules that have not been synthesized, those for which experimental pKa determinations are difficult, and larger molecules where the local environment changes the usual pKa values, such as for certain amino acids that are part of a larger polypeptide chain[xxx]. The main problem for calculating the pKa value in nonaqueous solvents is related to the estimation of

ΔG in these solvents. Thus, the determination of the free energy solvation of the proton in various nonaqueous solvents is a fundamental issue of central importance in solution chemistry[xxxi].

The computer program SPARC (SPARC Performs Automated Reasoning in Chemistry) was developed to predict numerous physical properties such as vapor pressure, distribution coefficient, and GC retention time as well as chemical reactivity parameters such as pKa and electronaffinity. SPARC predicts both macroscopic and microscopic pKa values strictly from molecular structure using relatively simple reactivity models[xxxii]. SPARC computer program is based on the thermodynamic cycle (**Figure 5**) as shown below.



$\Delta G = [((\Delta G_3 + \Delta G_4) - \Delta G_2) + \Delta G_1]$

$\Delta G = -2.303.\ R.\ T.\ \log Ka$

Figure 5. Thermodynamic cycle.

The ionization of weak acid (HA) is given for the gas and solvent phase in **Figure 5**. Calculation of pKa were made using the free energy changes in the thermodynamic cycle. Respectively ΔG_1, ΔG_2, ΔG_3 and ΔG_4 are calculated for find the ΔG (in solvent phase). Then, pKa is calculated using the equation with calculated ΔG at 25°C. In this paper, we describe the details of the SPARC reactivity computational methods and its performance on predicting the pKa values of these benzimidazole derivatives in comparison with experimental values.

References:

i Stevenson,C.;Davies,R.;Jeremy,H.;*Chemical Research in Toxicology***(1999)**12, 38-45.

İi Grimmett, M. R.;*Science of Synthesis***(2002)**12, 529-612.

iii Sierra-Zenteno,A.;Gal´an-Vidal,C.;Tapia-Benavides,R.;*Revista de la Sociedad Química de México***(2002)**46,125-130.

iv Küçükbay, H.;Yılmaz,Ü.;Şireci,N.;Güvenç, A.N.;*Turkish Journal of Chemistry***(2011)**35,561-571.

V Kuş, C.;Altanlar, N.;*Turkish Journal of Chemistry***(2003)**27, 35-40.

vi Utku, S.;Topal,M.;Döğen,A.;Serin, M. S.;*Turkish Journal of Chemistry***(2010)**34, 427-436.

vii Özel Güven, Ö.;Erdoğan,T.;Göker,H.;Yıldız, S.;*Bioorganic & Medicinal Chemistry Letters***(2007)**17, 2233-2236.

viii Abonia,R.;Cortés,E.;Insuasty,B.;Quiroga,J.;Nogueras,M.;Cobo, J.;*European Journal of Medicinal Chemistry***(2011)**46, 4062-4070.

ix Townsend, L.B.;Devivar,R.V.;Turk,S.R.;Nassiri, M.R.;Drach, J.C.;*Journal of Medicinal Chemistry***(1995)**38, 4098-4105.

x Ries, U.J.;Mihm, G.;Narr, B.;Hasselbach, K.M.;Wittneben, H.;Entzeroth, M.;van Meel, J.C.A.;Wienen, W.;Hauel, N.H.;*Journal of Medicinal Chemistry***(1993)**36, 4040-4051.

xi Hranjec, M.;Starčević, K.;Piantanida, I.;Kralj, M.;Marjanović,M.;Hasani, M.;Westman, G.;Karminski-Zamola, G.;*European Journal of Medicinal Chemistry***(2008)**43, 2877-2890.

Xii Li, L.;Wong, Y.S.;Chen, T.;Fan, C.;Zheng, W.;*Dalton Trans***(2012)** 41, 1138-1141.

xiii Yang, Y.H.;Cheng, M.S.;Wang, Q.H.;Nie, H.;Liao, N.;Wang, J.;Chen, H.;*European Journal of Medicinal Chemistry***(2009)**44, 1808-1812.

xiv Mann, J.;Baron, A.;Opoku-Boahen, Y.;Johansson, E.;Parkinson, G.;Kelland,L.R.;Neidle, S.;*Journal of Medicinal Chemistry***(2001)**44, 138-144.

xv Singh, M.;Tandon, V.;"*European Journal of Medicinal Chemistry***(2011)**46, 659-669.

xvi Yeung, K.S.;Meanwell,N.A.;Qiu,Z.L.;Hernandez,D.;Zhang, S.;McPhee,F.;Weinheimer, S.;Clark, J.M.;Janc,J.W.;*Bioorganic & Medicinal Chemistry Letters***(2001)**11, 2355-2359.

xvii Roderick, W.R.;Nordeen Jr, C.W.;Von Esch, A.M.;Appell, R.N.;*Journal of Medicinal Chemistry***(1972)**15, 655-658.

xviii Mayence, A.;Pietka,A.;Collins, M.S.;Cushion,M.T.;Tekwani,B.L.;Huang, T.L.;Vanden Eynde, J.J.; *Bioorganic & Medicinal Chemistry Letters***(2008)**18, 2658-2661.

xix Hu,L.Kully,M.L.;Boykin,D.W.;Abood, N.; *Bioorganic & Medicinal Chemistry Letters***(2009)**19, 1292-1295.

xx Roth,T.;Morningstar,M.L.;Boyer,P.L.;Hughes,S.H.;Buckheit Jr, R.W.;Michejda, C.J.;*Journal of Medicinal Chemistry***(1997)**40, 4199-41207.

xxi Bhaumik,J.;Yao,Z.;Borbas,K.E.;Taniguchi,M.;Lindsey,J.S.;*The Journal of Organic Chemistry***(2006)**71, 8807-8817.

xxii Khanna,L.;Panda,S.S.;Khanna,P.;*Mini-Reviews in Organic Chemistry***(2012)**9, 381-396.

Xxiii Bhattacharya,S.;Chaudhuri,P.;*Current Medicinal Chemistry***(2008)**15, 1762-1777.

xxiv Alongi, K.S.; Shields, G.C.;Annual Reports in Computational Chemistry (**2010)** Elsevier, Amsterdam.

xxv Kahveci,B.;Menteşe,E.;Özil,M.;Yılmaz,F.;Serdar, M.;*Journal of Heterocyclic Chemistry***(2016)** 53, 975-980

xxvi Brian,W.J.M.;Kangro,H.O.;Screening antiviral agents against influenza virus. In: Virology methods manual (**1996)** Academic Press Ltd, London.

xxvii Hill, E.L.;Ellis,M.N.;Nguyen-Dinh,P.;Antiviral and antiparasitic susceptibility testing, American Society for Microbiology, Washington, DC, **1991**.

xxviii Kahveci,B.;Menteşe,E.;Özil, M.;Ülker,S.;Ertürk,M.;*Monatshefte für Chemie***(2013)**144, 993-1001.

Xxix Kueng, W.;Silber,E.;Eppenberger,U.;*Analytical Biochemistry***(1989)**182, 16-19.

xxx Alongi, K.S.;Shields,G.C.;Annual Reports in Computational Chemistry **(2010)**Elsevier, Amsterdam.

xxxi Farrokhpour,H.;Manassir, M.;*Journal of Chemical & Engineering Data***(2014)**59, 3555-3564.

xxxii Öğretir, C.;Yarligan,S.;Demirayak,Ş.;Arslan,T.;*Journal of Molecular Structure (Theochem)***(2003)** 666-667, 609-615.

Received on 3 June 2016.