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Research Article

Determination of pKa of some benzimidazole derivatives using drug as active substance by different methods

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ABSTRACT

pKa values of twelve benzimidazole derivatives (Phenyl[2-(substitutedbenzyl)-1*H*-1,3-benzimidazole-5-il]metanone) in isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile mixtures were determined as experimentally in potentiometric measurements according to the half-neutralization method. Standardization of the electrode system calibrated with 4, 7, 10 and 12 pH tampon solution. All molecules pKa values determined as theoretically by MOPAC 2012 computer program using physico-chemical semi-empirical methods (AM1, MNDO, MNDO-d, PM3, PM6, PM6-DH2, PM7 and RM1) with thermodynamic cycle and thermodynamic properties as enthalpy (ΔH°), entropy (ΔS°) and free energy (ΔG°). In addition, the values predicted by the SPARC on-line pKa calculator. All studies were performed in the same solvents and the same temperature at 25°C.The experimental pKa values were compared with corresponding values calculated by the SPARC online calculator program and MOPAC 2012 computer program. Results of all three used methods were in good correlation

Keywords: Benzimidazole derivatives, potentiometric titration, MOPAC 2012 computer program.

1. INTRODUCTION

Benzimidazole derivatives are one of the most important classes of heterocyclic molecules that occur widely in natural products. These heterocycles have shown different pharmacological and biological activities such as antibacterial, antihypertensives, anticancers, anti-histaminics, anti-HBV activity, anti-inflammatory, antimicrobial, antiviral, and antitumor[1-9]. Benzimidazole derivatives play an important role in the drug discovery process due to their potential applications in the pharmaceutical industry[10-13]. In spite of the availability of many methods for the synthesis of these molecules[14-24]. There are still many drawbacks such as the use of highly toxic reagent, strong acids and,in some cases, harsh reaction conditions. Furthermore, most of these procedures generate mono-substituted benzimidazoles as a target product. Therefore, the search for new readily available green catalysts is still being actively pursued[25].

Acid dissociation constants (pKa) are essential for understanding many fundamental reactions in chemistry and biochemistry[26-27]. pKa values are a convenient way to specify the dissociation constants for weakly acidic or basic groups, and thus are extremely informative[28]. When comparing molecules, pKa values allow scientists to compare acid strengths, base strengths, Gibbs free energy changes, and equilibrium constants of ionization reactions. In an acid-base equilibrium reaction, the pKa allows an easy prediction of the favored direction for that equilibrium as well as the concentrations of the individual species at a given pH[27].

The computer program SPARC[29] (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 electron affinity. SPARC predicts both

macroscopic and microscopic pKa values strictly from molecular structure using relatively simple reactivity models. In this paper, we describe the details of the SPARC reactivity computational methods and its performance on predicting the pKa values of various benzimidazole derivatives including many known drugs in comparison with experimental and theoretical values[30].

MOPAC is a general-purpose semiempirical molecular orbital package for the study of molecular structures and reactions. The semiempirical Hamiltonians MNDO, AM1, PM3, PM6, PM6-DH2, RM1, MNDO-d and PM7 are used in the electronic part of the calculation to obtain molecular orbitals, the heat of formation and its derivative with respect to molecular geometry[31]. Using these results MOPAC calculates the vibrational spectra, thermodynamic quantities, isotopic substitution effects and force constants for molecules, radicals, ions, and polymers. For studying chemical reactions, a transition state location routine and two transition state optimizing routines are available[31].

2. MATERIALS AND METHODS

2.1. Potentiometry

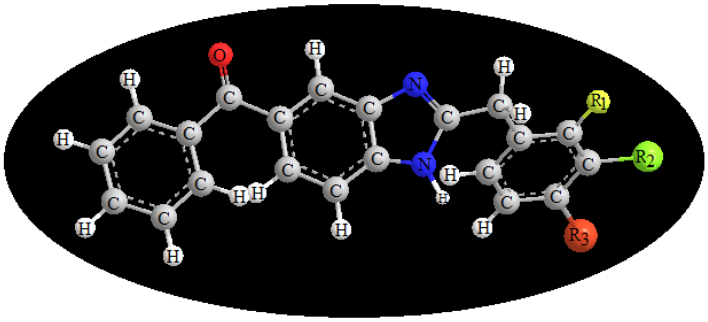
In this study, twelve benzimidazole derivatives (phenyl[2-(2-bromobenzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(1)**, phenyl[2-(3-bromobenzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(2)**, phenyl[2-(4-bromo benzyl)- 1*H*-1,3-benzimidazole-5-il]metanone **(3)**, phenyl [2-(2-florobenzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(4)**, phenyl[2-(3-florobenzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(5)**, phenyl[2-(4-florobenzyl)-1*H*-1,3-benzimidazole -5-il]metanone **(6)**, phenyl[2-(2-clorobenzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(7)**, phenyl[2-(3-clorobenzyl)- 1*H*-1,3-benzimidazole-5-il]metanone **(8)**, phenyl[2-(4-cloro benzyl)-1*H*-1,3-benzimidazole-5-il]metanone **(9)**, phenyl[2-(2-methylbenzyl)-1*H*-1,3-benzimidazole-5-il]metanone (10), phenyl[2-(3-methylbenzyl)-1H-1,3-benzimidazole-5-il]metanone (11), phenyl[2-(4-methyl benzyl)-1H-1,3-benzimidazole-5-il] metanone (12) (general molecule formules are given Figure 1) studied as experimentally and theoretically. These molecules were synthesized in Recep Tayyip Erdoğan University Organic Chemistry Research Laboratory and published32.

For potentiometric titrations an Orion 720A model pH ionmeter equipped with a combined pH electrode and indicator electrode were used. System of potentiometric titration cell used in studied is given Figure 2. A magnetic stirrer, a semi-micro burette and a 25 mL beaker were also used in titrations. Before potentiometric titrations, the pH meter was calibrated according to the instructions supplied by the manufacturers of the pH meter with 4, 7, 10 and 12 pH tampon solution. During the titrations, the titrant was added in increments of 0.05 mL after each stable reading and mV values were recorded. The necessary chemicals were supplied from Merck. After purifications, isopropyl alcohol was used to prepare a 0.05 N tetra-butylammonium 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 0.05 M solution of TBAH in isopropyl alcohol, which is widely used in the titration of acids, was used as titrant. The half-neutralization potentials and the corresponding pKa values for all molecules were obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, N,N-dimethylformamide and acetonitrile. The mV values that were obtained in pH-meter were recorded. The halfneutralization potential (HNP) values and the corresponding pKa values of all molecules, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, tert-butyl alcohol, acetonitrile and N,N-dimethylformamide. Finally, HNP values were determined by drawing the mV-mL (TBAH) graphic. From the titration curves, the HNP values were measured and the corresponding pKa values were calculated.

2.2. 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[33]. 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[34].

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.

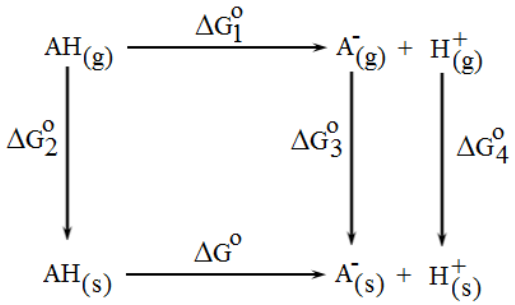


Group	1	2	3	4	5	6	7	8	9	10	11	12
R_1	-Br	-H	-H	-F	-H	-H	-Cl	-H	-H	$-CH_3$	-H	-H
R_2	-H	-Br	-H	-H	-F	-H	-H	-Cl	-H	-H	$-CH_3$	-H
R_3	-H	-H	-Br	-H	-H	-F	-H	-H	-Cl	-H	-H	$-CH_3$

Figure 1
Studied of molecules 1-12.

Figure 2

System of potentiometric titration cell used in studied.



$$\Delta G^{o} = [((\Delta G^{o}_{3} + \Delta G^{o}_{4}) - \Delta G^{o}_{2}) + \Delta G^{o}_{1}]$$

$$\Delta G^{o} = -2.303.\ R.\ T.\ \log Ka$$

Figure 3
Thermodynamic cycle.

SPARC predicts both macroscopic and microscopic pKa values strictly from molecular structure using relatively simple reactivity models[35]. SPARC computer program is based on the thermodynamic cycle (Figure 3) as shown below.

The ionization of weak acid (HA) is given for the gas and solvent phase in Figure 3. Calculation of pKa were made using the free energy changes in the thermodynamic cycle. Respectively ΔG^o_1, ΔG^o_2, ΔG^o_3 and ΔG^o_4 are calculated for find the ΔGo (in solvent phase). Then, pKa is calculated using the equation with calculated ΔG^o 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.

2.3. MOPAC 2012 Computer program

Theoretical calculations were carried out using AM1, MNDO, MNDOD, PM3, PM6, PM6-DH2, PM7 and RM1 semi empirical methods in the MOPAC 2012 computer program. Molecule **1-12** were optimized to a gradient form in isopropyl alcohol, *N*,*N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile mixtures at 25°C. The primary approximates of the geometry of all the structures were obtained by Augmented MM3 and MMFF molecular mechanic methods, followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical AM1, MNDO, MNDOD, PM3, PM6, PM6-DH2, PM7 and RM1 quantum chemical methods[36]. One of the usually used methods to search for the effect of substituent on an equilibrium proces is the practice of the Hammett equation[37]. The semi empirical calculations that were used in the present work are based on the following reaction.

$$AH_{(s)} + S_{(s)} \rightleftharpoons SH^+_{(s)} + A^-_{(s)}$$

In this reaction AH is the weak acid and SH^+ is the protonated acid. S is using solvent and A^- is conjugated base of weak acids. Semi empirical calculations were carried out using the following reactions.

$$\Delta G^o_{Reaction} = [\Delta G^o(_{SH^+}) + \Delta G^o(_{A^-})] - [\Delta G^o(_{AH}) + \Delta G^o(_S)]$$

$$pKa = \Delta G^o_{Reaction} / 2.303.R.T$$

$\Delta H^o_{Formation}$ and ΔS^o are calculated for each species involved in the reaction. In this study, $\Delta G^o_{Reaction}$ thermodynamic values were calculated from determined $\Delta H^o_{Formation}$ and ΔS^o using the semi-empirical methods.

3. RESULTS AND DISCUSSION

In this study, twelve benzimidazole derivatives (Phenyl[2-(substitutedbenzyl)-1*H*-1,3-benzimidazole-5-il]metanone) were titrated potentiometrically with TBAH in four non-aqueous solvents such as isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide. The mV values read in each titration were plotted against TBAH volumes added (mL), and potentiometric titration curves were formed for all the cases. Potentiometric titration curves for molecule **1** is given in Figure 4. From the titration curves, the HNP values were measured, and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of molecules **1-12**, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide, are presented in Table 1.

When the dielectric permittivity of the solvents is taken into consideration, the following arrangement in order of decreasing acidity may be expected: *N*,*N*-dimethylformamide (ε=36.7) > acetonitrile (ε=36) > isopropyl alcohol (ε=19.4) >*tert*-butyl alcohol (ε=12). As seen in Table 1, the acidic arrangement for molecules **1.**,**2.**, **3.**, **7.**, **8.**, **9.**,**11.** and **12**. are show isopropyl alcohol > *tert*-butyl alcohol > *N*,*N*-dimethylformamide > acetonitrile, for **4.** and **5.** are show > *N*,*N*-dimethylformamide > isopropyl alcohol >*tert*-butyl alcohol > acetonitrile, for 6. and 10. are show isopropyl alcohol > N,N-dimethylformamide > tert-butyl alcohol > acetonitrile, In isopropyl alcohol, all these molecules generally show the strongest acidic properties, while they show the weakest acidic properties in acetonitrile. This situation may be attributed to the hydrogen bonding between the negative ions formed and the solvent molecules.

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 molecules are expected more acidic for high dielectric constant has solvent (isopropyl alcohol). In this study, it is obtained a result of all moleculesdata 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. All molecules 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 molecules**9**) is showed in acetonitrile (pKs: 33.0) for all molecules. By the time analyzed according to the functional group (-R) effect, it has showed very small effect for acidic protons due to the distance.

Table 1

The half-neutralization potentials (HNP) and the corresponding pKa values of molecules

Molecule	Solvent	pKa (Experiential)	HNP (mV)
1	Isopropyl alcohol	13.40 ± 0.14	-378.7 ± 8.1
	N,*N*-Dimetilformamid	14.63 ± 0.05	-451.7 ± 3.3
	Tert-Butily alcohol	14.25 ± 0.02	-430.5 ± 2.5
	Acetonitrile	14.88 ± 0.04	-466.7 ± 2.3
2	Isopropyl alcohol	13.26 ± 0.14	-370.2 ± 7.8
	N,*N*-Dimetilformamid	14.67 ± 0.02	-454.1 ± 1.4
	Tert-Butamol	14.02 ± 0.02	-415.0 ± 1.0
	Asetonitril	14.90 ± 0.04	-468.5 ± 1.0
3	Isopropyl alcohol	13.12 ± 0.06	-361.5 ± 3.9
	N,*N*-Dimetilformamid	14.35 ± 0.03	-434.4 ± 2.0
	Tert-Butily alcohol	14.13 ± 0.07	-420.5 ± 4.7
	Acetonitrile	15.29 ± 0.07	-489.9 ± 3.9
4	Isopropyl alcohol	13.24 ± 0.14	-369.4 ± 8.9
	N,*N*-Dimetilformamid	13.10 ± 0.18	-362.2 ± 9.2
	Tert-Butily alcohol	13.84 ± 0.09	-404.4 ± 5.4
	Acetonitrile	14.33 ± 0.15	-433.9 ± 9.1
5	Isopropyl alcohol	13.39 ± 0.14	-378.2 ± 9.1
	N,*N*-Dimetilformamid	13.03 ± 0.13	-356.8 ± 8.0
	Tert-Butily alcohol	13.74 ± 0.03	-399.2 ± 1.3
	Acetonitrile	13.91 ± 0.09	-409.0 ± 5.0
6	Isopropyl alcohol	13.55 ± 0.05	-387.3 ± 2.2
	N,*N*-Dimetilformamid	14.23 ± 0.12	-428.2 ± 7.3
	Tert-Butily alcohol	14.26 ± 0.11	-430.0 ± 6.0
	Acetonitrile	14.90 ± 0.08	-468.4 ± 3.3
7	Isopropyl alcohol	13.14 ± 0.06	-363.8 ± 3.7
	N,*N*-Dimetilformamid	14.30 ± 0.07	-432.1 ± 4.0
	Tert-Butily alcohol	14.05 ± 0.02	-416.9 ± 1.3
	Acetonitrile	14.80 ± 0.09	-461.9 ± 5.1
8	Isopropyl alcohol	12.80 ± 0.13	-342.9 ± 7.8
	N,*N*-Dimetilformamid	14.07 ± 0.08	-418.0 ± 6.0
	Tert-Butily alcohol	13.69 ± 0.02	-395.8 ± 1.3
	Acetonitrile	14.14 ± 0.06	-423.3 ± 4.2
9	Isopropyl alcohol	13.21 ± 0.01	-366.5 ± 0.2
	N,*N*-Dimetilformamid	14.63 ± 0.03	-451.0 ± 2.7
	Tert-Butily alcohol	14.25 ± 0.01	-427.9 ± 0.7
	Acetonitrile	15.04 ± 0.01	-476.4 ± 0.4
10	Isopropyl alcohol	14.01 ± 0.10	-414.6 ± 6.1
	N,*N*-Dimetilformamid	14.85 ± 0.05	-464.3 ± 2.5
	Tert-Butily alcohol	15.07 ± 0.12	-475.4 ± 6.4
	Acetonitrile	15.27 ± 0.10	-489.0 ± 5.9
11	Isopropyl alcohol	13.62 ± 0.05	-391.5 ± 2.7
	N,*N*-Dimetilformamid	14.64 ± 0.04	-451.7 ± 2.3
	Tert-Butily alcohol	14.62 ± 0.13	-450.9 ± 7.8
	Acetonitrile	15.08 ± 0.12	-477.5 ± 7.1
12	Isopropyl alcohol	13.91 ± 0.05	-408.7 ± 2.8
	N,*N*-Dimetilformamid	15.05 ± 0.06	-477.0 ± 3.4
	Tert-Butily alcohol	14.58 ± 0.06	-448.7 ± 3.5
	Acetonitrile	15.08 ± 0.06	-478.1 ± 3.6

Table 2
Studied theoretical the corresponding pKa values of molecules 1-12 in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N,N*-dimethylformamide with the computer program MOPAC 2012 and SPARC.

Molecule	Solvent	SPARC	MOPAC 2012							
			AM1	MNDO	MNDOD	PM3	PM6	PM6-DH2	PM7	RM1
1	Isopropyl alcohol	12.57	11.2487	13.0989	13.9812	13.7896	13.4737	12.1337	12.4301	13.0950
	N,N-dimethylformamide	16.84	13.4777	14.1169	14.9544	13.9266	13.3348	13.3575	12.9398	11.0905
	Tert-butyl alcohol	14.20	10.3152	12.8937	13.7479	12.9670	12.8795	11.5228	10.8030	12.6220
	Acetonitrile	15.78	19.1033	16.1863	18.1276	16.3400	14.3870	13.1109	15.4594	13.7657
2	Isopropyl alcohol	12.58	11.2929	10.6811	11.8770	12.2769	9.7373	9.8580	10.4493	11.5564
	N,N-dimethylformamide	16.86	11.2979	11.2882	12.0453	12.0079	10.9997	11.1956	10.6017	9.6455
	Tert-butyl alcohol	14.21	11.0837	10.6479	11.7928	12.0498	9.3889	9.4986	9.5678	11.4166
	Acetonitrile	15.80	11.1561	11.2008	12.2442	11.1007	10.1474	10.2553	10.4872	10.8045
3	Isopropyl alcohol	12.59	11.3835	12.0089	13.0584	13.1636	11.7216	11.1058	11.5541	12.4490
	N,N-dimethylformamide	16.86	12.5117	12.8296	13.6348	13.0969	12.2889	12.3993	11.8885	10.4717
	Tert-butyl alcohol	14.22	10.8064	11.8885	12.8981	12.6335	11.2455	10.6158	10.2873	12.1395
	Acetonitrile	15.81	15.2810	13.8305	15.3378	13.8576	12.3899	11.7999	13.1030	12.4080
4	Isopropyl alcohol	12.54	14.4381	15.7493	15.7107	17.0630	15.2352	15.8587	15.3334	16.7201
	N,N-dimethylformamide	16.81	14.1150	14.5731	14.3621	15.7330	14.6631	14.9855	14.0904	13.5545
	Tert-butyl alcohol	14.16	14.1154	15.6448	15.6047	17.1972	15.5204	16.3730	15.1149	17.3149
	Acetonitrile	15.76	14.0206	11.2524	11.2743	11.5404	10.1476	9.3602	10.3596	10.1580
5	Isopropyl alcohol	12.56	11.4591	11.1632	11.0925	12.3465	9.8967	9.8228	10.5710	11.5082
	N,N-dimethylformamide	16.83	11.4392	11.6985	11.3776	12.0672	11.1354	11.1656	10.7053	9.6045
	Tert-butyl alcohol	14.19	11.2429	11.1095	11.0416	12.1164	9.5416	9.4649	9.6843	11.3705
	Acetonitrile	15.78	11.3011	11.6212	11.5599	11.1615	10.2865	10.2245	10.5933	10.7625
6	Isopropyl alcohol	12.57	13.0781	13.5908	13.5356	14.8518	12.6916	12.9692	13.0817	14.2553
	N,N-dimethylformamide	16.84	12.9049	13.2672	12.9985	14.0391	13.0282	13.2063	12.5218	11.6953
	Tert-butyl alcohol	14.20	12.8059	13.5109	13.4564	14.8034	12.6563	13.0481	12.5236	14.4861
	Acetonitrile	15.79	12.7875	11.5512	11.5313	11.4645	10.3192	9.8903	10.5812	10.5649
7	Isopropyl alcohol	12.54	12.1164	13.7984	13.9498	14.7168	12.4776	13.1502	13.5155	13.9533
	N,N-dimethylformamide	16.82	13.7710	14.5028	14.3811	14.4780	13.7962	14.1383	13.4964	11.6443
	Tert-butyl alcohol	14.18	11.3161	13.6040	13.7516	14.1347	11.7763	12.6676	12.2941	13.7916
	Acetonitrile	15.76	18.1162	15.7921	16.0767	15.2103	13.9798	13.1458	14.1415	12.5495
8	Isopropyl alcohol	12.56	11.4945	11.8115	11.0696	12.4118	9.9052	9.7332	10.4002	11.6582
	N,N-dimethylformamide	16.83	11.4694	11.7051	11.3582	12.1226	11.1426	11.0894	10.5598	9.7321
	Tert-butyl alcohol	14.18	11.2767	11.1169	11.0199	12.1789	9.5497	9.3791	9.5208	11.5140
	Acetonitrile	15.78	11.3319	11.6280	11.5400	11.2184	10.2940	10.1463	10.4443	10.8934
9	Isopropyl alcohol	12.56	11.9235	12.9330	12.6348	13.6999	11.3033	11.5561	12.0774	12.9338
	N,N-dimethylformamide	16.83	12.7464	13.2350	12.9983	13.4333	12.5941	12.7400	12.1484	10.7951
	Tert-butyl alcohol	14.19	11.4094	12.4841	12.5096	13.2884	10.7696	11.1336	11.0165	12.7793
	Acetonitrile	15.78	14.8713	13.8472	13.9464	13.3465	12.2583	11.7625	12.4158	11.8387
10	Isopropyl alcohol	12.78	12.0201	13.8622	13.9007	14.8796	12.8086	13.8444	13.3493	14.9386
	N,N-dimethylformamide	17.04	13.6258	14.6433	14.3697	14.5442	14.2721	15.1460	13.3767	12.5156
	Tert-butyl alcohol	14.40	11.2360	13.6625	13.7007	14.3632	12.0312	13.1976	12.0988	14.6687
	Acetonitrile	15.99	17.8542	16.1166	16.1663	14.8351	14.6994	14.6616	14.1828	14.0350
11	Isopropyl alcohol	12.74	11.2940	11.1981	11.1146	12.2540	9.8812	9.8124	10.4904	11.8056
	N,N-dimethylformamide	17.02	11.2988	11.7282	11.3965	11.9883	11.6049	11.1568	10.6366	9.8575
	Tert-butyl alcohol	14.38	11.0848	11.0628	11.6301	12.0278	9.4677	9.4550	9.6072	11.6551
	Acetonitrile	15.96	11.1571	11.6518	11.5792	11.0807	10.2730	10.2155	10.5230	11.0218
12	Isopropyl alcohol	12.76	11.7736	12.6555	12.6327	13.7025	11.4583	11.9467	12.0390	13.5058
	N,N-dimethylformamide	17.02	12.5869	13.3176	13.0119	13.3989	13.0679	13.2829	12.1267	11.2984
	Tert-butyl alcohol	14.38	11.2720	12.4863	12.7921	13.3275	10.8569	11.4396	10.9615	13.2935
	Acetonitrile	15.98	14.6507	14.0230	14.0115	13.0875	12.6111	12.5629	12.4764	12.6537

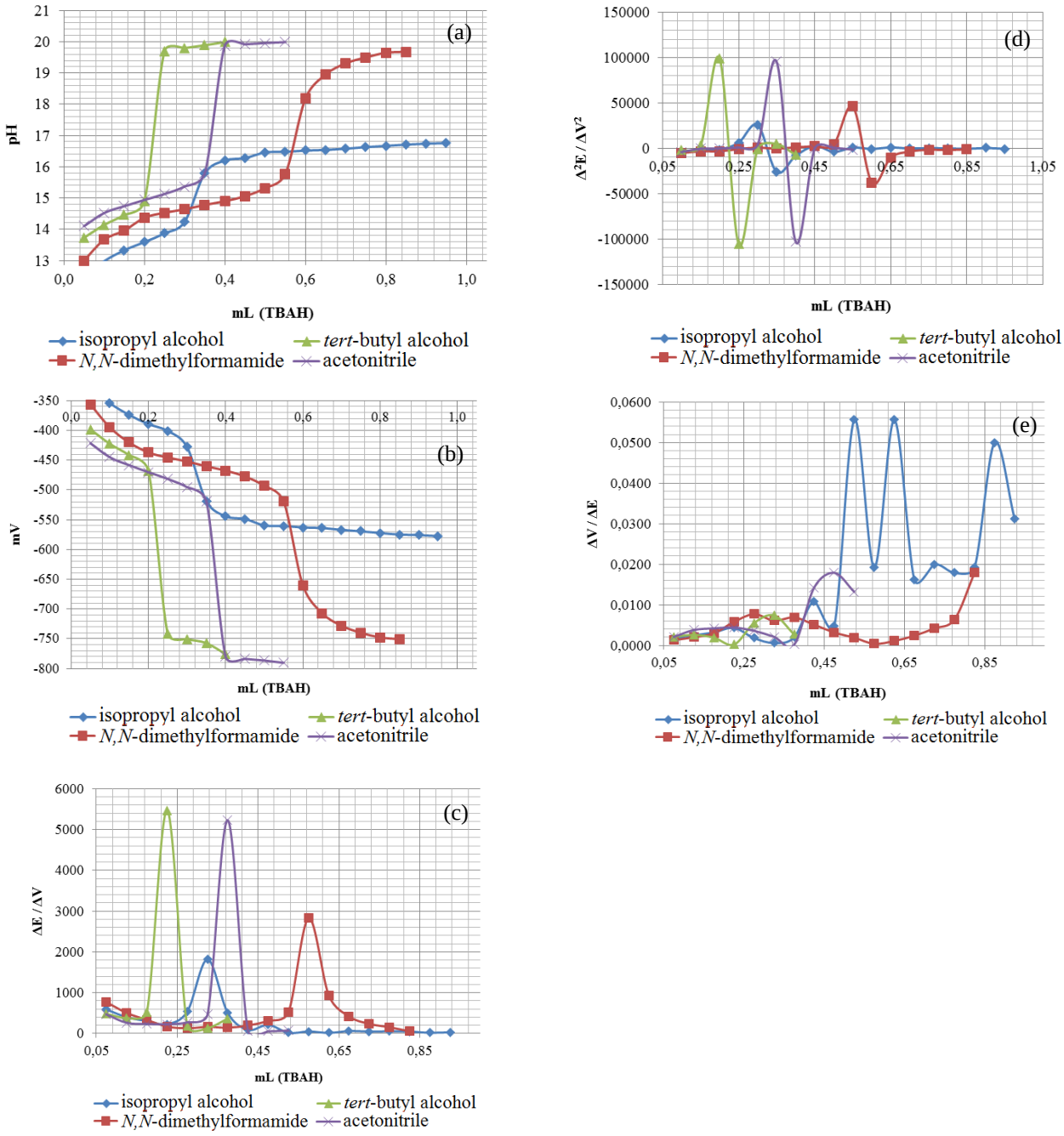


Figure 4

(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.

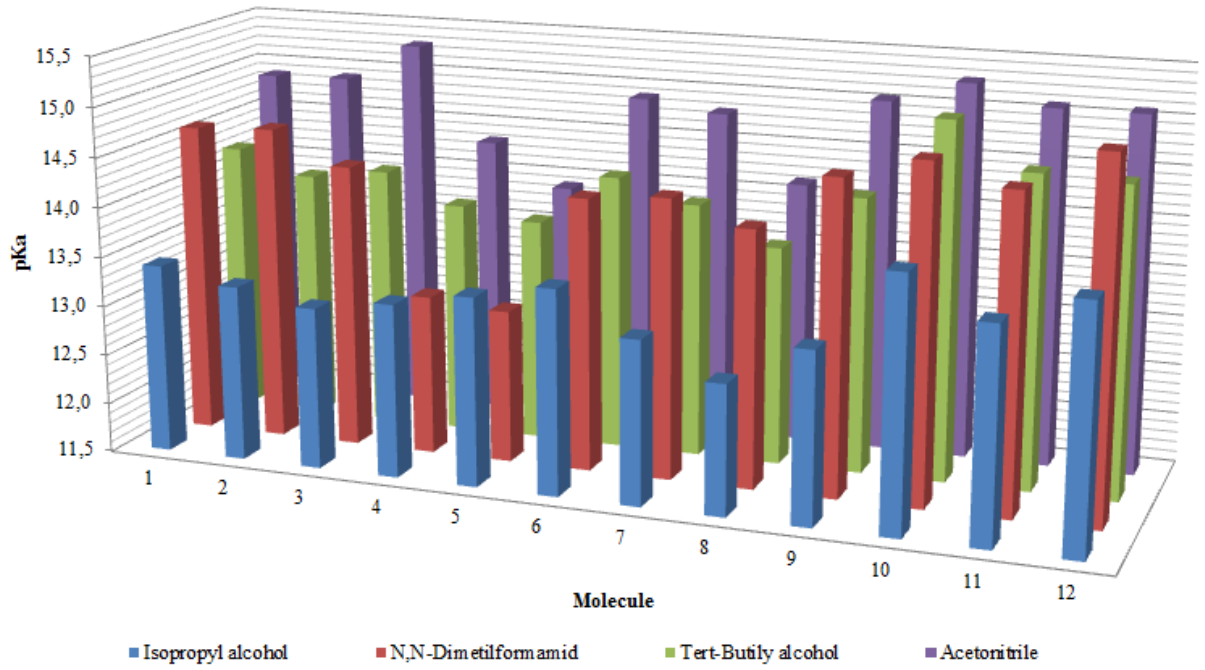


Figure 5
Comparison of all results in studied as experimentally at 25°C.

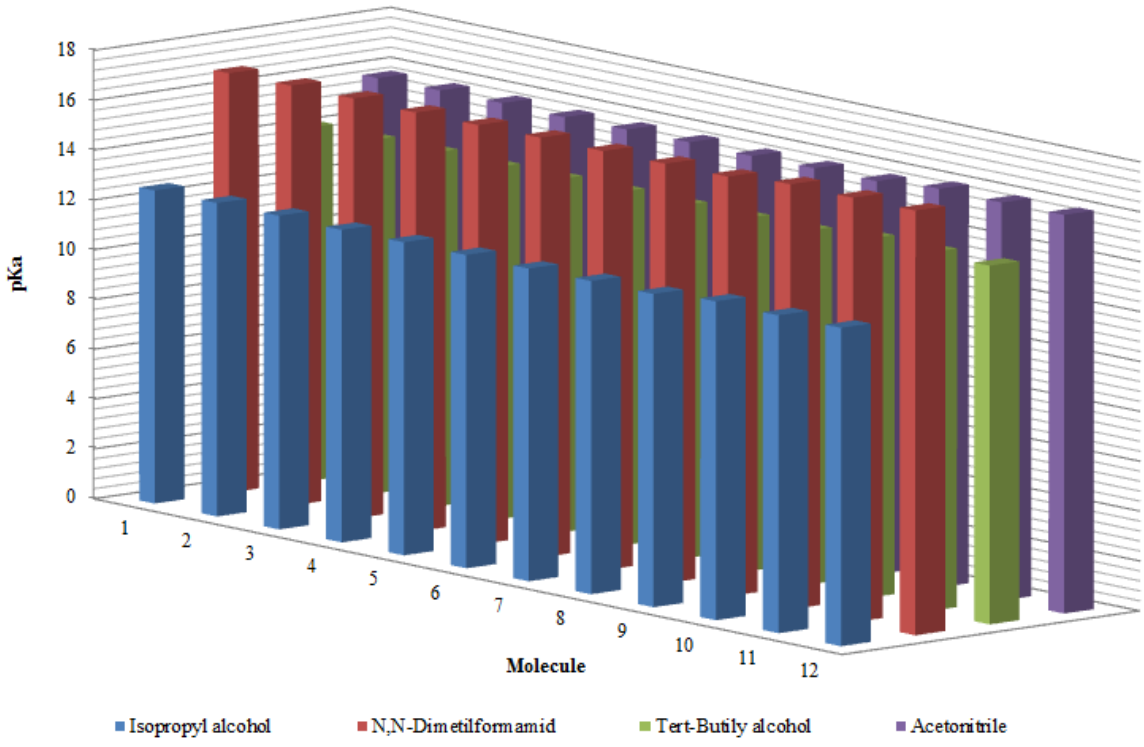


Figure 6
The corresponding pKa values of molecules as theoretically obtained from the SPARC online calculator program at 25°C.

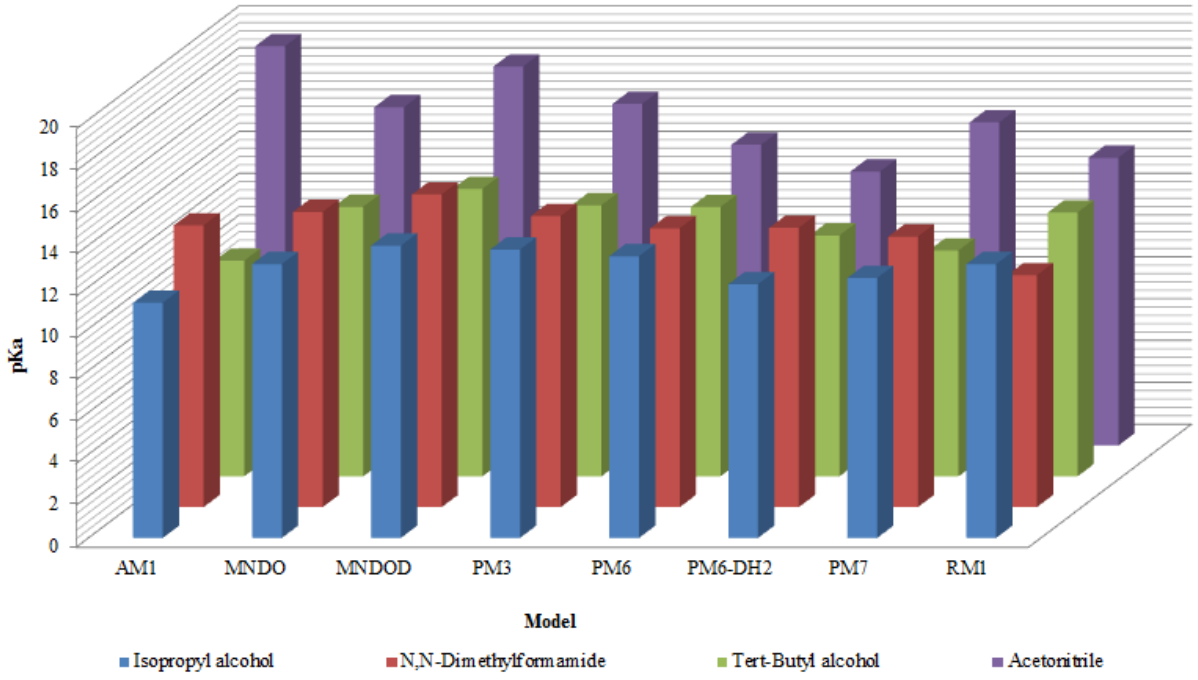


Figure 7
The corresponding pKa values of molecule 1 as theoretically obtained from the MOPAC 2012 computer program at 25°C.

By the time all molecules were analyzed by each solvent, acidity strength decrease; **8**>**3**>**7**>**9**>**4**>**2**>**5**>**1**>**6**>**11** >**12**>**10** in isopropyl alcohol, **5**>**4**>**8**>**6**>**7**>**3**>**1** = **9**>**11**>**2**>**10**>**12** in *N*,*N*-dimethylformamide, **8**>**5**>**4**>**2**>**7**>**3**>**1** = **9**>**6**>**12**>**11**>**10** in *tert*-butyl alcohol and **5**>**8**>**4**>**7**> **1**>**2** = **6**>**9**>**11** = **12** >**10**>**3** in acetonitrile as observed. Differentiated all molecules showed in the studied solvents when investigated the effect of the leveling and differentiated. Comparison of all results as graphical display is given in Figure 5.

The corresponding pKa values of molecules **1-12** calculated by the SPARC online calculator program and MOPAC 2012 computer program in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide at 25°C. All results is given in Table 2.As seen in Table 2, the acidic arrangement changed between the largest and smallest values for all molecules are show for SPARC, 12.57 – 16.84 for molecule **1**., 12.58 – 16.86 for molecule **2.**, 12.59 – 16.86 for molecule **3.**, 12.54 – 16.81 for molecule 4., 12.56 – 16.83 for molecule **5.**, 12.57 – 16.84 for molecule **6.**, 12.54 – 16.82 for molecule **7.**, 12.56 – 16.83 for molecule **8.**, 12.56 – 16.83 for molecule **9.**, 12.78 – 17.04 for molecule **10.**, 12.74 – 17.02 for molecule **11**. and 12.76 – 17.02 for molecule **12.** The corresponding pKa values of molecules **1-12**, obtained from the SPARC online calculator program in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide at 25°C, are compared in Figure 6.

pKa values of changes in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide are obtained with the computer program MOPAC 2012 as 10.3152 (AM1/*tert*-butyl alcohol) – 19.1033 (AM1/acetonitrile) for molecule **1.**, 9.3889 (PM6/*tert*-butyl alcohol) – 12.2769 (PM3/isopropyl alcohol) for molecule **2.**, 10.2873 (PM7/*tert*-butyl alcohol) – 15.3378 (MNDOD/acetonitrile) for molecule **3.**, 9.3602 (PM6-DH2/acetonitrile) – 17.3149 (RM1/*tert*-butyl alcohol) for molecule **4.**, 9.4649 (PM6-DH2/*tert*-butyl alcohol) – 12.3465 (PM3/isopropyl alcohol) for molecule **5.**, 9.8903(PM6-DH2/acetonitrile) – 14.8518 (PM3/isopropyl alcohol) for molecule **6.**, 11.3161 (AM1/*tert*-butyl alcohol) – 18.1162 (AM1/acetonitrile) for molecule **7.**, 9.3791 (PM6-DH2/*tert*-butyl alcohol) – 12.4118 (PM3/isopropyl alcohol) for molecule **8.**, 10.7696 (PM6/*tert*-butyl alcohol) – 14.8713 (AM1/acetonitrile) for molecule **9.**, 11.2360 (AM1/*tert*-butyl alcohol) – 17.8542 (AM1/acetonitrile) for

molecule **10.**, 9.4550 (PM6-DH2/*tert*-butyl alcohol) – 12.2540 (PM3/isopropyl alcohol) for molecule **11.** and 10.8569 (PM6/*tert*-butyl alcohol) – 14.6507 (AM1/acetonitrile) for molecule **12.** The corresponding pKa values of molecule **1**, obtained from the MOPAC 2012 computer program in isopropyl alcohol, *tert*-butyl alcohol, acetonitrile and *N*,*N*-dimethylformamide at 25^{o}C, are compared in Figure 7.

CONCLUSION

Dissociation constants (pKa) of benzimidazole derivatives (Phenyl[2-(substitutedbenzyl)-1*H*-1,3-benzimidazole-5-il]metanone) were determined potentiometrically and theoretically in isopropyl alcohol, *N*,*N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile mixtures. The accuracy of the obtained pKa values was evaluated by comparing the results with the pKa values determined by the half-neutralization method, SPARC online calculator program and MOPAC 2012 computer program. pKa values for benzimidazole derivatives in isopropyl alcohol, *N*,*N*-dimethylformamide, *tert*-butyl alcohol and acetonitrile mixtures were determined potentiometrically for the first time. In conclusion, potentiometric method is an excellently precise technique for determination of pKa values of benzimidazole derivatives.All results were observed to be compatible with each other.

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