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Microwave assisted synthesize of new some benzimidazole derivatives and determination of protonation constant of these compounds in non-aqueous media

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ABSTRACT

A series of 2-substituted benzimidazole derivatives have been synthesized via microwave mediated process. Different benzimidazole derivatives were titrated with tetrabutylammonium hydroxide in four non-aqueous solvents (isopropyl alcohol, *N*,*N*-dimethylformamide,tert-butyl alcohol and acetonitrile), using potentiometric method. The half neutralization potential values and the corresponding pKa values were determined for all cases.

1. Introduction

Benzimidazole ring takes an important place in the field of medicinal chemistry because of pharmacological properties such as anti-cancer, anti-microbial, anti-fungal, anti-ulcer, anti-viral and lipase inhibition [1-3]. Furthermore, some benzimidazole derivatives are constituent of important drugs thiabendazole [4] (anti-helmintic), astemizole [5] (anti-hismaminic) and omeprazole [6] (antiulcer). Also, it is found naturally in the structure of vitamin B_{12} [7]. Although, these compounds have been attracted attention of scientists, less work has been reported on pKa values of benzimidazoles [8].

Acidity measurements of organic compounds have a long history dating back to the end of the 19thcentury, when the pKa was measured for the first time. Since then, a vast body of data on acidities in various solvents has been collected [9-12]. The measurements have mostly been limited to polar solvents, however, with water being by far the most exploited medium, followed by alcohols and dipolar aprotic solvents. Several studies, involving the formation and investigation of biological activities of some benzimidazole derivatives, have been reported [13-23]. It is known that these derivatives have weak acidic properties.

The acidity of a compound in a given medium is influenced by both the electronic effects of the substituents and the solvent effects of the medium. Moreover, it is sometimes extremely difficult to assess how much each effect contributes to the acidity. Small differences in acidity between similar molecules are also extremely difficult to interpret and one care must be considered in deciding which structural effect has the main influence on acidity. A number of studies have been reported on the protonation constants of these derivatives in different media [24-27], however, little information on the protonation constants of these derivatives in water and organic solvent-water mixtures has been published so far [28-34].

The aim of this work is to determine pKa value of some benzimidazol derivatives because of their biological importance. Because, relationships between acidity constant, pKa and structure may behelpful in drug design studies and in explaining solubility, absorption, distribution, metabolism and elimination [35]. The structure of all synthesized compounds was confirmed by ^{1}H-NMR and elemental analysis. Synthesis of the compounds **1**-**10** has been carried out as depicted in Scheme 1.

2. Experimental

2.1. Instrumentation

All the chemicals were supplied from Merck, Aldrich and Fluka. Melting points were determined on capillary tubes on a Büchi oil heated melting point apparatus and uncorrected. ^{1}H NMR spectra were performed on Varian-Mercury 200 MHz spectrophotometer in DMSO-d_6 using TMS as internal. The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer; the experimental values were in agreement (±0.4%) with calculated ones. A mono-mode CEM-Discover microwave was used to carry out microwave reactions in 30 mL microwave process vials with temperature control by infrared detection temperature sensor. All reactions were monitored by TLC using pre-coated aluminum sheets (silica gel 60 F_{254} 0.2 mm thickness).

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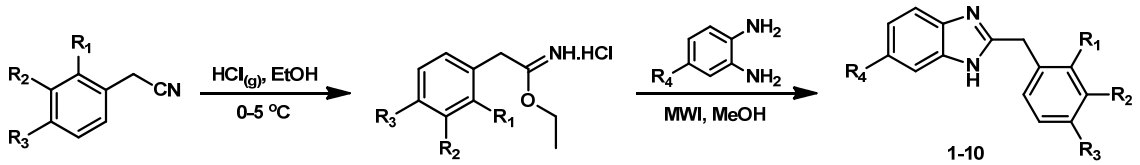

Compound no	1	2	3	4	5	6	7	8	9	10
R_1	F	Cl	Br	H	CH_3	H	H	H	Br	H
R_2	H	H	H	Cl	H	Br	H	H	H	Br
R_3	H	H	H	H	H	H	Cl	CH_3	H	H
R_4	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	NO_2	NO_2	H	H

Scheme 1

2.2. Synthesis of 2-substituted benzimidazolederivatives (1-10)

A mixture of corresponding iminoester hydrochlorides (0.012 mol) and corresponding 1,2-phenylenediamine derivatives (0.01 mol) in dry methanol (15 mL) was irradiated in closed vessels with the pressure control at 65 °C for 10 min (hold time) at 300 W maximum power. After the reaction was completed, monitored by TLC (ethyl acetate:hexane, 3:1), the mixture was cooled down to room temperature, the product was precipitated with addition of water. The obtained product was filtered, dried and recrystallized from ethanol-water (1:1) (Scheme 1).

6-Methyl-2-(2-fluorobenzyl)-1H-benzimidazole (**1**): Yield: 85%. Cas no: 1308531-67-0. M.p.: 150-151 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.05 (s, 1H, NH exchangeable with D_2O), 7.23-7.98 (m, 7H, Ar-H), 4.35 (s, 2H, CH_2), 2.44 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{13}FN_2$: C, 74.98; H, 5.45; N, 11.66. Found: C, 75.03; H, 5.50; N, 11.60%.

6-Methyl-2-(2-chlorobenzyl)-1H-benzimidazole (**2**): Yield: 83%. Cas no: 1306230-94-3. M.p.: 174-175 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.65 (s, 1H, NH exchangeable with D_2O), 7.13-7.84 (m, 7H, Ar-H), 4.23 (s, 2H, CH_2), 2.39 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{13}ClN_2$: C, 70.18; H, 5.10; N, 10.91. Found: C, 70.13; H, 5.14; N, 10.98%.

6-Methyl-2-(2-bromobenzyl)-1H-benzimidazole (**3**) :Yield: 86%. M.p.: 168-169 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.22 (s, 1H, NH exchangeable with D_2O), 7.13-7.69 (m, 7H, Ar-H), 4.23 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.85; N, 9.30. Found: C, 59.89; H, 4.89; N, 9.38%.

6-Methyl-2-(3-chlorobenzyl)-1H-benzimidazole (**4**): Yield: 85%. M.p.: 156-157 °C. ^{1}HNMR (200 MHz, DMSO-d_6, δ, ppm): 12.25 (s, 1H, NH exchangeable with D_2O), 7.13-7.98 (m, 7H, Ar-H), 4.25 (s, 2H, CH_2), 2.44 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{13}ClN_2$: C, 70.18; H, 5.10; N, 10.91. Found: C, 70.22; H, 5.14; N, 10.98%.

6-Methyl-2-(2-methylbenzyl)-1H-benzimidazole (**5**): Yield: 85%. M.p.: 168-170 °C [36]. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.25 (s, 1H, NH exchangeable with D_2O), 7.19-7.84 (m, 7H, Ar-H), 4.23 (s, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.25(s, 3H, CH_3). Anal. calcd. for $C_{16}H_{15}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.28; H, 6.84; N, 11.94%.

6-Methyl-2-(3-bromobenzyl)-1H-benzimidazole (**6**):Yield: 86%. M.p.: 130-131 °C. ^{1}HNMR (200 MHz, DMSO-d_6, δ, ppm): 12.27 (s, 1H, NH exchangeable with D_2O), 7.18-7.95 (m, 7H, Ar-H), 4.25 (s, 2H, CH_2), 2.44 (s, 3H, CH_3). Anal. calcd. for $C_{15}H_{13}BrN_2$: C, 59.82; H, 4.85; N, 9.30. Found: C, 59.87; H, 4.80; N, 9.33%.

6-Nitro-2-(4-chlorobenzyl)-1H-benzimidazole (**7**): Yield: 90%. M.p.: 169-170 °C (M.p.: 169-171°C [37]).

6-Nitro-2-(4-methylbenzyl)-1H-benzimidazole (**8**): Yield: 89%. M.p.: 177-178 °C (M.p.: 176-177 °C [37]).

2-(2-Bromobenzyl)-1H-benzimidazole (**9**): Yield: 90%. M.p.: 225-227 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.32 (s, 1H, NH exchangeable with D_2O), 7.10-7.64 (m, 8H, Ar-H), 4.32 (s, 2H, CH_2). Anal. calcd. for$C_{14}H_{11}BrN_2$: C, 58.56, H, 3.86,N, 9.76. Found: C, 58.63, H, 3.90, N, 9.73%.

2-(3-Bromobenzyl)-1H-benzimidazole (**10**): Yield: 88%. M.p.: 185-186 °C. ^{1}H NMR (200 MHz, DMSO-d_6, δ, ppm): 12.30 (s, 1H, NH exchangeable with D_2O), 7.13-7.67 (m, 8H, Ar-H), 4.31 (s, 2H, CH_2). Anal. calcd. for$C_{14}H_{11}BrN_2$: C, 58.56, H, 3.86,N, 9.76. Found: C, 58.61, H, 3.92, N, 9.77%.

2.3. Potentiometric titrations

Potentiometric titrations (Figure 1), an Orion 720A model pH-ionmeter equipped with a combined pH electrode (Ingold) and indicator electrode were used. 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 manufactures of the pH meter. In this section, the pH electrode calibrated 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.

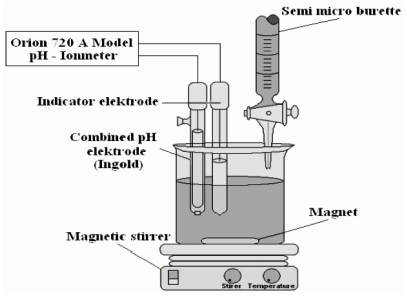

Figure1. Potentiometric titration cell.

The necessary chemicals were supplied from Fluka and Merck. After purifications, isopropyl alcohol was used to prepare 0.05 N tetrabutylammonium hydroxide. For all potentiometric titrations, 0.05 N tetrabutylammonium hydroxide in isopropyl alcohol, which was prepared from 0.1 N tetrabutylammonium hydroxide (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 mV values,that were obtained via pH meter, were recorded. Finally, the half-neutralization potential (HNP) values were determined by drawing the mL (TBAH)-mV graphic.

3. Results and discussion

In this search, iminoester hydrochlorides (**1a-d**) were prepared according to the reported literature procedures [3,38]. Iminoester hydrochlorides could be useful intermediates for the synthesis of benzimidazole derivatives by

microwave irradiation [3]. Firstly, iminoester hydrochlorides reacted with corresponding 1,2-phenylenediamine derivatives under microwave irradiation gave to the compound **1-10** within short reaction times. The structures of new compounds were confirmed by ^{1}H NMR and elemental analyses. Spectroscopic investigations of newly synthesized compounds are accordance with the proposed structure.

Second part of 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. From the titration curves (Figure 2-6), the HNP values were measured and the corresponding pKa values were calculated. The half-neutralization potential (HNP) values and the corresponding pKa values of all triazole derivatives, obtained from the potentiometric titrations with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide,*tert*-butyl alcohol and acetonitrile and, are presented in Table1.

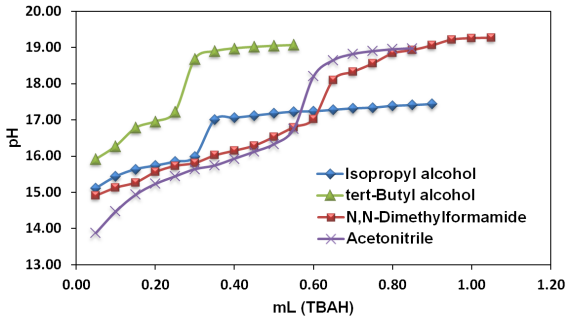

Figure 2. pH-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

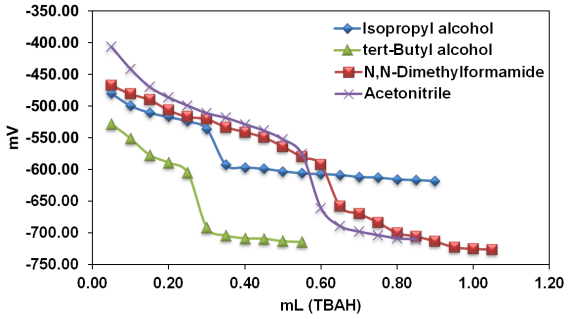

Figure 3. mV-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

The pHs of the weak acids are given by the equation 1.

$$pH = pKa + \log [A^-]/[HA] \quad (1)$$

pH = pKa occurs when [A$^-$] is equal to [HA] at the half-neutralization point. Therefore, the pH values can be regarded as pKa at the half-neutralization points. When the dielectric permittivity of solvents is taken into consideration, the acidic arrangement can be expected as follows: *N,N*-dimethyl formamide (ε = 36.7) > acetonitrile (ε = 36.0) > isopropyl alcohol (ε = 19.4) > *tert*-butyl alcohol (ε = 12.0). But, it is not observed the acidic arrangement in this study. The degree to which a pure solvent ionizes was represented by its autoprotolysis constant, K_{SH}. For the above reaction the constant is defined by the equation 2.

$$K_{SH} = [H_2S^+].[S^-] \quad (2)$$

Autoprotolysis is an acid-base reaction between identical solvent molecules in which some act as an acid and others as a base. Consequently, the extent of an autoprotolysis reaction depends both on the intrinsic acidity and the intrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. The acidity of a compound depends on several factors. The two most important factors are the solvent effect and molecular structure. Table 1 shows that the halfneutralization potential (HNP) values and the corresponding pKa values obtained from potentiometric titrations depend on the type of non-aqueous solvents used and molecular structure of the compound.

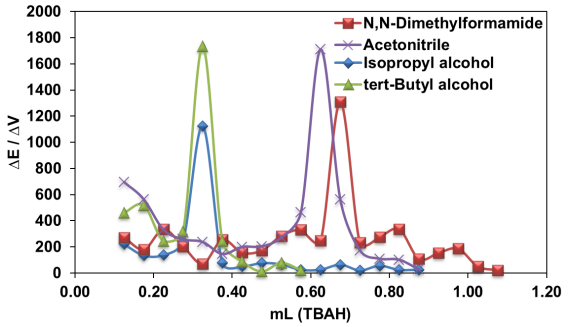

Figure 4. ΔE/ΔV-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

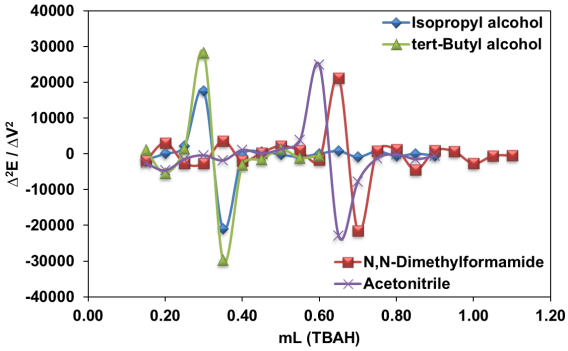

Figure 5. Δ^{2}E/ΔV^2-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

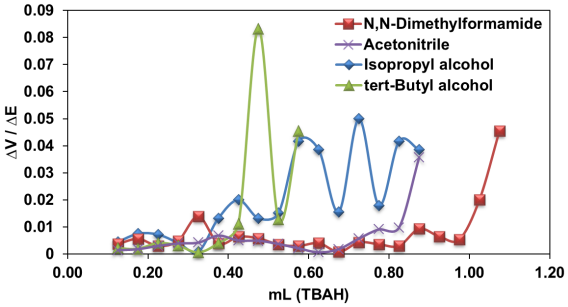

Figure 6. ΔV/ΔE-mL (TBAH) potentiometric titration curves of 0.001 M solutions of compound **5** titrated with 0.05 M TBAH in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile at 25 °C.

Table 1. Half-neutralization potential (HNP) values and the corresponding pKa values of all benzimidazole derivatives in isopropyl alcohol, *N,N*-dimethylformamide, *tert*-butyl alcohol, and acetonitrile.

Compound No	Isopropyl alcohol		*N,N*-dimethylformamide		*tert*-Butyl alcohol		Acetonitrile	
	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)	pKa	HNP (mV)
1	15.26±0.09	-478.9±5.7	15.20±0.04	-486.7±6.3	16.40±0.07	-556.3±2.9	16.22±0.05	-545.6±8.4
2	15.63±0.11	-510.6±6.4	15.46±0.08	-501.2±4.6	16.58±0.10	-568.4±7.1	15.78±0.06	-521.4±5.8
3	15.03±0.13	-470.3±3.9	15.66±0.06	-511.8±5.6	16.33±0.08	-554.2±4.7	16.76±0.07	-577.9±7.8
4	15.08±0.09	-477.4±6.2	15.78±0.11	-519.0±8.4	16.47±0.10	-560.7±5.9	16.48±0.08	-561.3±7.1
5	15.75±0.10	-517.2±8.4	15.80±0.08	-525.5±6.9	16.48±0.12	-561.1±4.7	15.44±0.09	-499.8±6.3
6	14.31±0.05	-430.2±6.6	16.54±0.08	-564.9±7.8	15.71±0.09	-515.0±6.5	16.12±0.06	-539.7±7.1
7	11.91±0.05	-290.8±5.2	12.63±0.04	-332.9±5.8	12.42±0.08	-318.3±6.1	12.37±0.07	-317.1±4.9
8	12.54±0.09	-327.3±7.3	12.22±0.11	-308.7±4.3	13.02±0.07	-356.8±8.6	13.77±0.06	-399.9±5.2
9	14.54±0.07	-446.2±5.7	15.63±0.10	-511.3±6.1	14.83±0.08	-462.6±4.9	14.71±0.05	-456.2±5.5
10	15.33±0.09	-492.9±7.5	15.91±0.06	-527.4±8.2	15.53±0.05	-502.1±5.8	15.00±0.07	-472.7±6.3

As seen in Table 1, the acidic order for compounds **1** and **2** is *N,N*-dimethyl formamide> isopropyl alcohol > acetonitrile >*tert*-butyl alcohol, for compounds **3** and **4** is isopropyl alcohol > *N,N*-dimethylformamide>*tert*-butyl alcohol > acetonitrile, for compounds **7** and **9** is isopropyl alcohol > acetonitrile > *tert*-butyl alcohol > *N,N*-dimethylformamide, for compound **5** is acetonitrile > isopropyl alcohol > *N,N*-dimethylformamide>*tert*-butyl alcohol, for compound **6** is isopropyl alcohol > *tert*-butyl alcohol > acetonitrile > *N,N*-dimethylformamide, for compound **8** is *N,N*-dimethylformamide > isopropyl alcohol > *tert*-butyl alcohol > acetonitrile, for compound **10** is acetonitrile > isopropyl alcohol > *tert*-butyl alcohol > *N,N*-dimethyl formamide.

Changes of acidic properties is observed as 7 > 8 > 6 > 9 > 3 > 4 > 1 > 10 > 2 > 5 in isopropyl alcohol, as 8 > 7 > 1 > 2 > 9 > 3 > 4 > 5 > 10 > 6 in *N,N*-dimethylformamide, as 7 > 8 > 9 > 10 > 6 > 3 > 1 > 4 > 5 > 2 in*tert*-butyl alcohol and as 7 > 8 > 9 > 10 > 5 > 2 > 6 > 1 > 4 > 3 in acetonitrile. Compound **7** shows strongest acidic properties (11.91±0.05; -290.8±5.2) in isopropyl alcohol, but compound **3** shows weakest acidic properties (16.76±0.07; -577.9±7.8) in acetonitrile. All compounds protonation constant values are changed between 11.91±0.05-15.75±0.10 in isopropyl alcohol, between 12.22±0.11-16.54±0.08 in *N,N*-dimethylformamide, between 12.42±0.08-16.58±0.10 in *tert*-butyl alcohol and between 12.37±0.07-16.76±0.07 in acetonitrile.

The most important point in this study, compounds 7 and 8 shows very strongest acidic properties in isopropyl alcohol, *N,N*-dimethyl formamide, *tert*-butyl alcohol and acetonitrile media at 25 °C. This point is explained as -NO_2 group has the high electron-withdrawing character. Therefore, these compounds show very different acidic properties in all compounds. This group increases amount of acidity and it is observed as clearly in this study.

4. Conclusion

In conclusion, a series of benzimidazole derivatives have been synthesized from iminoether derivatives under microwave irradiation in short reaction times. The extent of an autoprotolysis reaction depends both on the intrinsic acidity and the instrinsic basicity of the solvent. The importance of the autoprotolysis constant in titrations lies in its effect on the completeness of a titration reaction. 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 rely on the non-aqueous solvents.

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