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Potentiometric Titrations of Some 2-Substituted 5-Nitrobenzimidazole Derivatives in Nonaqueous Solvent

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The acidity constants of 16 2-substituted 5-nitrobenzimidazole derivatives were determined in dimethyl sulfoxide, 60% (v/v) isopropyl alcohol +40% (v/v) water, and 60% (v/v) dimethyl sulfoxide +40% (v/v) water by the potentiometric method. Tetrabutylammonium hydroxide was used as the titrant for the measurements done in dimethyl sulfoxide as a solvent, and aqueous KOH was used for the measurements done in mixtures. The pK_a values were obtained from the half-neutralization potentials which were obtained from an analysis of the potentiometric titrations. The order of the acidic strengths obtained depends on the alkyl, aryl, and heterocyclic substituents on 5-nitrobenzimidazole. The acidic strengths of the alkyl-substituted 5-nitrobenzimidazoles in each solvent were in the following order: 2-(trifluoromethyl) > 2-(difluorochloromethyl) > 2-(chloromethyl) > 3-nitrobenzimidazole > 2-methyl > 2-(hydroxymethyl)-5-nitrobenzimidazole. The acidic strengths of the aryl-substituted 5-nitrobenzimidazoles in each solvent were in the following order: 2-(4′-chlorophenyl) > 2-(2′-chlorophenyl) > 2-(3′-chlorophenyl) > 2-(2′-hydroxyphenyl) > 2-phenyl > 5-nitrobenzimidazole > 2-(4′-methoxyphenyl) > 5-nitrobenzimidazole. The increasing acidic strengths of the heterocyclic-group-substituted 5-nitrobenzimidazoles for three solvent systems were in the order 2-(2′-thienyl) > 2-(2′-pyridyl) > 2-(3′-pyridyl) > 2-(2′-furyl) > 5-nitrobenzimidazole.

Introduction

Determination of pK_a values of the active constituent of certain pharmaceutical preparations is important because the distribution, transport behavior, bonding to receptors, and contributions to the metabolic behavior of the active constituent molecules depend on the ionization constants (*1*).

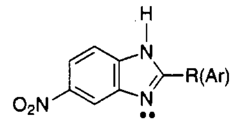
2-Substituted 5-nitrobenzimidazole derivatives which have antibacterial, anaesthetic, inflammatory, antihelminthic, and viral effects are weak acids (*2–5*). However, dissociation constants of acids depend on both their structure and the solvent in which dissociation constants are determined (*6*).

The aim of this work is to determine pK_a values of 16 2-substituted 5-nitrobenzimidazole derivatives in one nonaqueous solvent and in two mixed solvents.

Experimental Section

A Crison Micro pH 2001 model pH meter equipped with a combined glass electrode (Ingold model) was used. The pH meter can read 0.01 pH unit. A magnetic stirrer, a semimicroburet calibrated in 0.01 cm^3 and a 50 cm^3 beaker were used for titrations. The titration beaker was kept in a water bath which was controlled at 20 °C with a B. Braun Thermomix-1460 thermostat. The accuracy of the temperature control was ±0.1 K.

The 16 2-substituted 5-nitrobenzimidazole derivatives titrated in this work were synthesized by Dr. Ucucu and Dr.Işîkdağ. These compounds have the following basic structure (*7*):



R = –H, –CH$_3$, –CH$_2$OH, –CH$_2$Cl, –CF$_3$, –CF$_2$Cl
Ar = phenyl, *o*-chlorophenyl, *m*-chlorophenyl, *p*-chlorophenyl, *p*-methoxphenyl, *o*-hydroxyphenyl, 2-thienyl, 2-furyl, 2-pyridyl

Isopropyl alcohol (Merck) and dimethyl sulfoxide (Merck) were reagent grade and used as received.

KOH (0.1 mol·dm^{-3}) in water was used as the titrant for the titrations in 60% (v/v) DMSO + 40% (v/v) H$_2$O and 60% (v/v) isopropyl alcohol +40% (v/v) H$_2$O mixed solvents while 0.1 mol·dm^{-3} tetrabutylammonium hydroxide in 2-propanol was used as the titrant for the titration in DMSO. For the titrations, 10^{-3} mol·dm^{-3} solutions of the compounds were used.

Before potentiometric titrations the pH meter was calibrated according to the instructions supplied by the manufactures of the pH meter. During the titrations, the titrant was added in increments of 0.1 cm^3 after each stable recording of pH and millivolts. From the half-neutralization potential (Hnp) of S-shaped titration curves, the pK_a values were determined. Each pK_a value obtained was the average of three measurements.

Results and Discussion

A typical titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole using DMSO as solvent and TBAH as titrant is shown in Figure 1. The titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole in 60% (v/v) DMSO + 40% (v/v) H$_2$O and KOH in water as titrant is shown in

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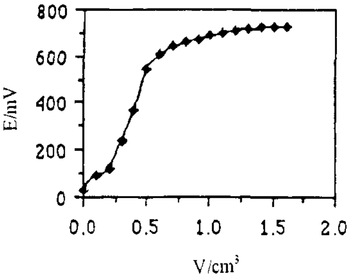


Figure 1. Titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole using DMSO as solvent and TBAH as titrant.

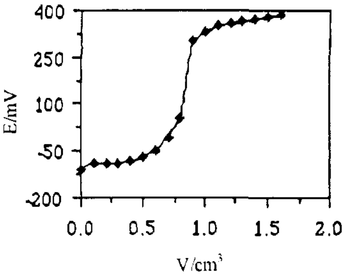


Figure 2. Titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole using 60% (v/v) DMSO + 40% (v/v) H_2O mixed solvent and KOH in water as titrant.

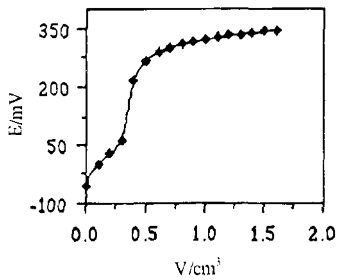


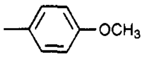
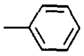
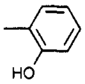
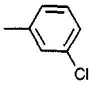
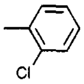
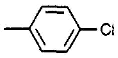
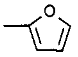
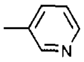
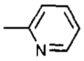
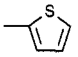
Figure 3. Titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole using 60% (v/v) isopropyl alcohol + 40% (v/v) H_2O mixed solvent and KOH as titrant.

Figure 2. Figure 3 shows the titration curve of 2-(trifluoromethyl)-5-nitrobenzimidazole in 60% (v/v) DMSO + 40% (v/v) H_2O and aqueous KOH as titrant. As seen from the figures all titration curves are good S-shaped curves having a 100–250 mV shift at the equivalence point.

Results of the titrations in DMSO, 60% (v/v) DMSO + 40% (v/v) H_2O, and 60% (v/v) isopropyl alcohol +40% (v/v) H_2O are given in Tables 1–3, respectively.

The pK_a values of 2-substituted 5-nitrobenzimidazole derivatives are classified in three different groups by considering the substituents as alkyl, aryl, or heterocylic ring groups. The pK_a values of 2-substituted 5-nitrobenzimidazole derivatives, where alkyl groups are the substituents, follow the same decreasing order in the nonaqueous and mixed solvent systems studied (Tables 1–3). The acidity order of these compounds is affected by the inductive or mesomeric effect of the substituents. The substituents which inductively or mesomerically have an electron-donating effect decrease the acidity of the compounds whereas substituents which inductively or mesomerically have an electron-withdrawing effect increase the acidity of the compounds (*6*). Due to the electron-withdrawing effect of the fluoride atom, the compound having $-CF_3$ as a substituent proved to be the most acidic compound in all solvents and solvent mixtures, while the compound having $-CH_2OH$ as a substituent is the weakest acid in all solvent systems due to the high electron-donating effect of the $-CH_2OH$ group. A similar conclusion can be made from the literature (*8*) in which the same measurements were done in aqueous media.

Table 1. Hnp, pK_a Values, and Amount of Base Required for the Equivalence Point of 2-Substituted 5-Nitrobenzimidazole Derivatives in DMSO

substituent	Hnp/mV	pK_a (σ)	amount of base required for equivalence point/cm^3	pK_a in water
$-CH_2OH$	−320	12.86(±0.024)	0.41	2.21
$-CH_3$	−343	12.77(±0.023)	0.38	5.16
−H	−315	11.75(±0.02)	0.46	3.93
$-CH_2Cl$	−273	11.36(±0.028)	0.45	2.21
$-CF_2Cl$	−280	8.97(±0.028)	0.42	−0.77
$-CF_3$	−114	8.17(±0.03)	0.40	−0.18
	−315	11.88(±0.027)	0.38	
−H	−315	11.75(±0.02)	0.46	3.93
	−290	11.41(±0.02)	0.44	2.95
	−294	11.37(±0.024)	0.46	
	−288	11.33(±0.026)	0.42	
	−281	11.05(±0.023)	0.43	
	−261	10.85(±0.02)	0.38	
−H	−315	11.75(±0.02)	0.46	3.93
	−296	11.32(±0.02)	0.40	2.64
	−314	11.19(±0.03)	0.43	
	−298	11.01(±0.024)	0.40	
	−257	11.91(±0.024)	0.44	2.36

As a result the acidic strengths of 2-alkyl-substituted 5-nitrobenzimidazoles in each solvent system are found to be as follows: 2-(trifluoromethyl) > 2-(difluoromonochloromethyl) > 2-(chloromethyl) > 2-H > 2-methyl > 2-(hydroxymethyl).

As we know, the acidic and basic behaviors and the dielectric constants of solvents play an active role in the observed pK_a values of the compound (*9*). If we compare the measured pK_a values of the three solvent systems, we see that the pK_a values measured in DMSO are found to be greater than those of the 60% (v/v) isopropyl alcohol + 40% (v/v) H_2O system. In turn the pK_a values measured in the 60% (v/v) isopropyl alcohol +40% (v/v) H_2O system are found to be greater than those of the 60% (v/v) DMSO + 40% (v/v) H_2O system with the exception of unsubstituted and 2-CH_2Cl-substituted 5-nitrobenzimidazole; these results are logical if we remember that the isopropyl alcohol is more basic than DMSO. On the other hand the lower pK_a values of the studied compounds in the 60% (v/v) DMSO + 40% (v/v) H_2O system can be attributed to the higher dielectric constant of this solvent system compared to others. With this analogy we expect that the pK_a values of those compounds which were measured in water should be lower than the present values. This can easily be seen from Tables 1–3.

The acidic strengths of 2-aryl-substituted 5-nitrobenzimidazole derivatives are found to be dependent on the

Table 2. Hnp, pK_a Values, and Amount of Base Required for the Equivalence Point of 2-Substituted 5-Nitrobenzimidazole Derivatives in 60% (v/v) Isopropyl Alcohol + 40% (v/v) H_2O

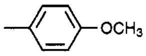
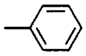
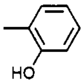
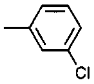
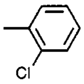
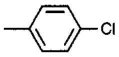
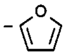
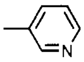
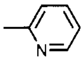
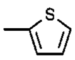
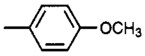
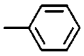
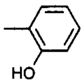
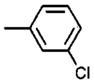
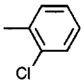
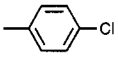
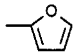
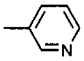
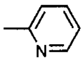
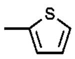
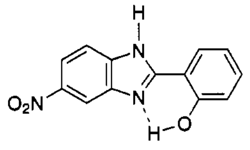
substituent	Hnp/mV	pK_a (σ)	amount of base required for equivalence point/cm^3	pK_a in water
$-CH_2OH$	−234	9.94(±0.026)	0.42	2.21
$-CH_3$	−210	9.67(±0.023)	0.42	5.16
−H	−133	8.70(±0.022)	0.46	3.93
$-CH_2Cl$	−140	8.58(±0.03)	0.30	2.21
$-CF_2Cl$	−34	6.60(±0.027)	0.42	−0.77
$-CF_3$	−22	6.54(±0.02)	0.37	−0.18
	−156	8.81(±0.03)	0.49	
−H	−133	8.70(±0.022)	0.46	3.93
	−98	7.30(±0.024)	0.46	2.95
	−74	7.23(±0.03)	0.58	
	−27	6.62(±0.028)	0.47	
	−30	6.51(±0.024)	0.47	
	−24	6.24(±0.03)	0.48	
−H	−133	8.70(±0.022)	0.46	3.93
	−69	7.21(±0.022)	0.50	2.64
	−71	7.17(±0.026)	0.44	
	−61	7.03(±0.023)	0.42	
	−47	6.72(±0.027)	0.38	2.36

Table 3. Hnp, pK_a Values, and Amount of Base Required for the Equivalence Point of 2-Substituted 5-Nitrobenzimidazole Derivatives in 60% (v/v) DMSO + 40% (v/v) H_2O

substituent	Hnp/mV	pK_a (σ)	amount of base required for equivalence point/cm^3	pK_a in water
$-CH_2OH$	−159	9.54(±0.03)	0.35	2.21
$-CH_3$	−116	9.33(±0.027)	0.34	5.16
−H	−128	9.15(±0.025)	0.62	3.93
$-CH_2Cl$	−122	9.08(±0.025)	0.38	2.21
$-CF_2Cl$	+31	6.36(±0.024)	0.42	−0.77
$-CF_3$	+82	5.51(±0.021)	0.85	−0.18
	−172	9.36(±0.024)	0.38	
−H	−128	9.15(±0.025)	0.62	3.93
	−161	8.63(±0.021)	0.40	2.95
	−133	8.32(±0.027)	0.31	
	−94	7.85(±0.024)	0.48	
	−98	7.58(±0.02)	0.30	
	−90	7.24(±0.023)	0.55	
−H	−128	9.15(±0.025)	0.62	3.93
	−124	8.10(±0.022)	0.53	2.64
	−102	7.78(±0.024)	0.44	
	−98	7.62(±0.021)	0.53	
	−86	7.49(±0.03)	0.42	2.36

character of the substituent which is located on the aryl ring. As can be seen from Tables 1−3 phenyl itshelf increased the acidity of the molecule. That means it acted as an electron-withdrawing group. The *o*-hydroxyphenyl and *o*-, *p*-, and *m*-chlorophenyl groups also acted as electron-withdrawing groups. This is of course expected. The only surprise can be the effect of the *o*-hydroxyphenyl group. However, we can easily say that this is a possibility of hydrogen bonding in this molecule.



In this way the proton uptake on the azo nitrogen atom is hindered and becomes difficult.

Only the *p*-methoxyphenyl group was found to decrease the acidic strength of the molecule. This is also expected if we consider the strong mesomeric electron-donating effect of the methoxy group.

Comparison of the three solvent systems indicated that the pK_a values of these groups of compounds were more affected by the basic behavior of the solvent in comparison with the dielectric constant of the solvents. The acidic strengths of the aryl-substituted benzimidazoles in each solvent system are as follows: 2-(4′-chlorophenyl) > 2-(2′-chlorophenyl) > 2-(3′-chlorophenyl) > 2-(2′-hydroxyphenyl > 2-phenyl > −H > 2-(4′-methoxyphenyl).

Heterocyclic substituents of the third group of compounds are either π-deficient or π-rich. π-Deficient heterocyclic substituents were found to act as electron-withdrawing groups, so the pK_a values of pyridyl-substituted 5-nitrobenzimidazole derivatives are lower than those of unsubstituted 5-nitrobenzimidazole. The position of the hetero atom (e.g., ortho or meta) in pyridyl also alters the acidity of 2-substituted 5-nitrobenzimidazole. When the hetero atom is in the ortho position, the pK_a value is lower than the pK_a value when it is in meta position. The compounds with π-rich heterocyclic substituents due to the possibility of H bonding of unpaired electrons on the hetero atom cause an increase in acidity. Thienyl-substituted compounds are more acidic than furyl-substituted compounds. This behavior originates from the fact that the atomic radius of the sulfur atom is greater than that of oxygen atom. The acidity order of these 2-heterocyclic-ring-substituted 5-nitrobenzimidazoles for the three solvent systems are as follows: 2-(2′-thienyl) > 2-(2′-pyridyl) > 2-(3′-pyridyl) > 2-(2′-furyl) > −H in all the solvent systems.

The pK_a values of 2-aryl- and 2-heterocyclic-ring-substituted compounds which were measured in aqueous media are given in Tables 1−3 (*8*). As is expected the higher dielectric constant of water caused the decrease of the pK_a values.

Literature Cited

(1) Frey, P. A.; Kokesh, F. O.; Westheimer, F. H. *J. Am. Chem. Soc.* **1971**, 7266.
(2) Khrizanova, T.; Torlakov, I.; Zhelyazko, L. *Chemotherapy* **1972**, 449.
(3) Theodorides, V. J.; Gyurik, R. J.; Kingsbury, W. D. *Experienta* **1967**, 702.
(4) Sharp, J. W.; Wescott, R. B. *Lab. Anim. Sci.* **1976**, 222.
(5) Otaki, K.; Inoje, J.; Yamazaki, Z. *Yakugahu Zasshi* **1965**, 926.
(6) Cram, D. J.; Hendrickson, J. B.; Hammond, G. S. *Organic Chemistry*, 3rd ed.; McGraw-Hill Kogakusha, Ltd.: Tokyo, 1970; p 207.
(7) Işıkdağ, I.; Uçucu, Ü.; Demirayak, Ş. *Turk. J. Chem.* **1989**, 33.
(8) Öğretir, C.; Demirayak, Ş. *Turk. J. Chem.* **1986**, 118.
(9) Latinen, H. A.; Harris, V. E. *Chemical Analysis*, 2nd ed.; McGraw-Hill Kogakusha, Ltd.: Tokyo, 1975; p 56.

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