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Potentiometric Study of Acid−Base Equilibria of 3,5-Disubstituted 1,2,4,5-Oxadiazaboroles in Nonaqueous Media

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The protonation constants of the amino nitrogens of some substituted 1,2,4,5-oxadiazaboroles have been determined in acetic acid by means of potentiometric titration with perchloric acid. pK_a values of the title compounds were interpreted on the basis of structural effects due to the substituents and the main skeleton by plotting p$K_{BH}{}^+$ value versus Hammett constants. Good correlations between p$K_{BH}{}^+$, σ constants, and $\delta_{C=N}$ and δ_{NH} values were also obtained.

Introduction

Potentiometric titration in nonaqueous media is a standard method for the determination of the basicity and acidity of various compounds, particularly in organic and pharmaceutical analyses. The reason for using nonaqueous solvents is that many organic compounds of pharmaceutical importance do not dissolve in water. Furthermore, since water is amphoteric, only a limited range of acid and base strengths can be determined in this solvent.[1,2]

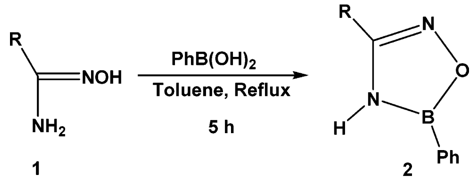
Amidoximes are versatile precursors of many heterocyclic compounds of pharmaceutical importance.[3,4] On the other hand, aryl boronic acids and their esters are highly popular as synthetic intermediates in organic synthesis with their ease of conversion to other functional groups (such as phenols and aryl halides) with a well-known reaction.[5−8] To the best of our knowledge, a literature survey of oxadiazaboroles from amidoxime and phenyl boronic acid reveals that only a limited number of reports were given in 1960s and 1970s at which no spectral data were supplied for those heterocycles.[9,10]

As a continuing part of our studies[11,12] on the acid−base equilibria of the amidoximes and related compounds, in this work we report the potentiometric determination of basicity (protonation) constants of the novel 3,5-disubstituted 1,2,4,5-oxadiazaboroles (Scheme 1) in acetic acid.

Experimental Section

Phenylboronic acid was purchased from Aldrich. Aldehydes and nitriles were purchased from Merck and Fluka. Amidoximes and oxadiazaboroles were prepared according to literature procedures described previously.[10,13−19] ^{1}H and ^{13}C NMR spectra were recorded on Bruker and Varian spectrometers (300 and 400 MHz). IR spectra were recorded on a Jasco 430 FT/IR instrument (KBr pellet). Mass spectra were measured on a Agilent GC 6890N gas chromatograph with mass detector MS 5975. Melting points were determined on a Meltemp apparatus and uncorrected. TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate, *p*-anisaldehyde, and iodine were used for visualization of the TLC spots.

Scheme 1. Structures of 1,2,4,5-Oxadiazaboroles



	R		R
a	Me	h	p-NH$_2$-C$_6$H$_4$
b	Ph	i	p-NO$_2$-C$_6$H$_4$
c	p-CH$_3$-C$_6$H$_4$	j	p-(CH$_3$)$_2$N-C$_6$H$_4$
d	p-MeO-C$_6$H$_4$	k	2-Pyridyl
e	p-Cl-C$_6$H$_4$	l	3-Pyridyl
f	p-Br-C$_6$H$_4$	m	4-Pyridyl
g	p-I-C$_6$H$_4$	n	2-Thienyl

Potentiometric Titrations. The potentiometric titrations were performed in a 50 mL glass vessel equipped with a combined pH electrode (Ingold), argon inlet and outlet tubes, a magnetic stirrer, and a titrant inlet. Titrant additions were carried out by means of a microburet with 0.01 mL graduations. The electrode was modified using saturated KCl solution in anhydrous methanol instead of aqueous KCl solution. A Thermo Orion model 720 A Plus ionmeter was used to measure the cell EMF.

Perchloric acid solution diluted with glacial acetic acid was used as titrant. The concentration of the oxadiazaboroles was maintained as 10^{-3} M in glacial acetic acid. All measurements were conducted with constant stirring of 30 mL of sample solution (magnetic stirbar) at 25.0 ± 0.1 °C. Titration curves were constructed by plotting the potential change (from the initial baseline value) versus the concentration of added titrant solution. The end points of titration were calculated by the Kolthoff method. The half-neutralization potentials (HNP) were determined by using these sigmoidal curves. In calculations of the pK_a values, ΔHNP (mV) values from the sigmoidal curves of the samples and the corresponding ΔEMF values in calibration plot were used; 59 mV was taken as corresponding to one pH unit.

Results and Discussion

p$K_{BH}{}^+$ values of nonaromatic heterocyclic compounds bearing oxygen, nitrogen, and boron in same ring, namely, oxadiaza-

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Table 1. Basicity (protonation) Constants, $\delta_{C=N}$ (ppm), and δ_{NH} (ppm) Values of 3,5-Disubstituted 1,2,4,5-Oxadiazaboroles

entry	R	pK_{BH}^+ (in acetic acid)	$\delta_{C=N}$ (ppm) (in DMSO-d_6 + $CDCl_3$)	δ_{NH} (ppm) (in DMSO-d_6 + $CDCl_3$)
2a	methyl	3.58 ± 0.04	158.28	8.92
2b	phenyl	3.29 ± 0.05	159.88	9.57
2c	*p*-tolyl	3.40 ± 0.05	160.00	9.47
2d	*p*-methoxyphenyl	3.49 ± 0.07	159.60	9.25
2e	*p*-chlorophenyl	3.18 ± 0.12	159.11	9.81
2f	*p*-bromophenyl	3.19 ± 0.09	159.14	9.88
2g	*p*-iodophenyl	3.11 ± 0.04	159.30	9.81
2h	2-aminophenyl[a]		160.03	9.35
2i	*p*-nitrophenyl	2.89 ± 0.05	158.41	10.09
2j	*p*-*N*,*N*-dimethyl-aminophenyl	3.63 ± 0.01	159.98	9.67
2k	2-pyridyl	2.93 ± 0.02	159.55	8.66
2l	3-pyridyl[a]		157.77	10.19
2m	4-pyridyl	3.48 ± 0.02	158.30	10.04
2n	2-thienyl	3.11 ± 0.07	156.04	9.67

[a] Due to the initial protonation of substituents (-NH_2 and pyridyl nitrogen), a good sigmoid curve leading to the determination of the end point could not be obtained.

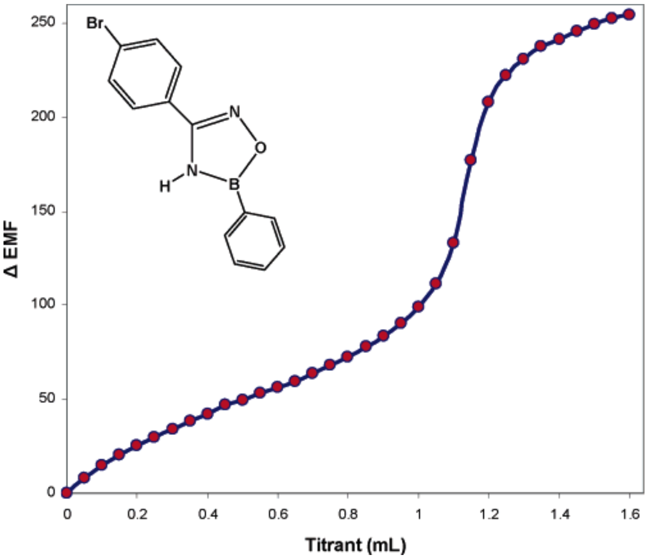
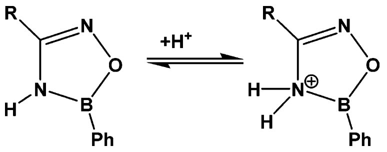


Figure 1. Representative titration curve of mL of titrant vs ΔmV.

Scheme 2



boroles (Scheme 1), were determined potentiometrically in the medium of glacial acetic acid. Results are given in Table 1, and a typical titration curve is shown in Figure 1.

Protonation of the oxadiazaborole heterocycle by an acid will take place on the 4-amino nitrogen that is sp^3-hybridized due to the lone pair of electrons on this nitrogen being more available than the imino one, which is sp^2-hybridized. (Scheme 2). X-ray data of some of the compounds also show the corresponding bond length and bond angle.

pK_{BH}^+ values obtained for the title compounds were correlated with Hammett σ_p constants. In Figure 2, it is clearly seen that electron-releasing substituents (ERG) (i.e., dimethyl amino and methoxy, which have lower Hammett σ constants with higher pK_{BH}^+ values) appeared on the one end of the line and that electron-withdrawing substituents (i.e., halogens, Cl, Br, I, and NO_2, which have higher Hammett σ constants with lower pK_{BH}^+ values) appeared on the other end of the graph. These results are in good accordance with the expected behavior of these groups based on the basicity of amino nitrogen atom of oxadiazaborole ring (atom no. 4 in oxadiazaborole ring numbering). In this regard, when there are ERG groups present on the phenyl ring, there will be an increase in the electron density that may result in resonance delocalization of the lone pairs on the N and O atoms through the aromatic ring and, thus, a higher basicity of these compounds. In the case of EWG groups on the phenyl ring, a reverse effect on pK_{BH}^+ values are observed due to the substantial decrease in the electron density of the amino nitrogen atom of the oxadiazaborole ring through resonance delocalization of the nitrogen lone pair of the ring, that is, basicity of oxadiazaboroles with electron-withdrawing groups on the phenyl ring is decreased depending on the nature of these groups.

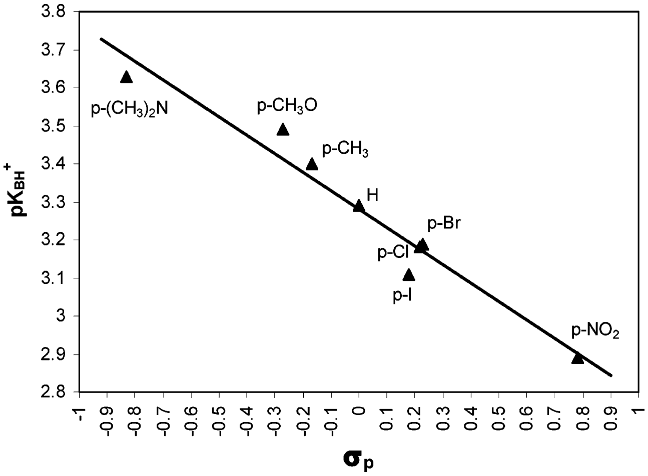


Figure 2. Plot of σ_p constants[20] vs pK_{BH}^+ values.

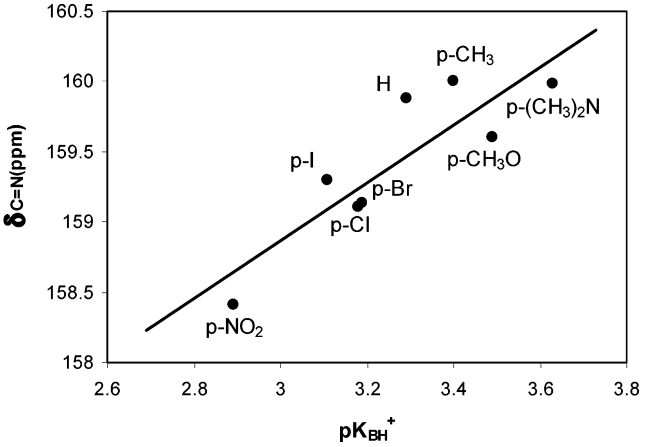


Figure 3. Plot of pK_{BH}^+ versus $\delta_{C=N}$ (ppm).

On the other hand, a correlation between ^{13}C NMR chemical shifts of imino carbons (atom no. 3) of oxadiazaboroles and pK_{BH}^+ values were accomplished, that is, the higher the pK_{BH}^+ values, the higher carbon chemical shifts (Figure 3).

Also, a linear correlation was found between Hammett σ constants and ^{13}C NMR chemical shifts of imino carbons (Figure 4). In addition, the chemical shift positions of NH protons of the oxadiazaborole ring and Hammett σ constants are correlated (Figure 5). The graph accounts for the higher NH chemical shifts while a strongly electron-withdrawing substituent like NO_2 on the phenyl ring is present at the 3-position of the heterocycle. A lower δ value (NH chemical shift) was observed when an

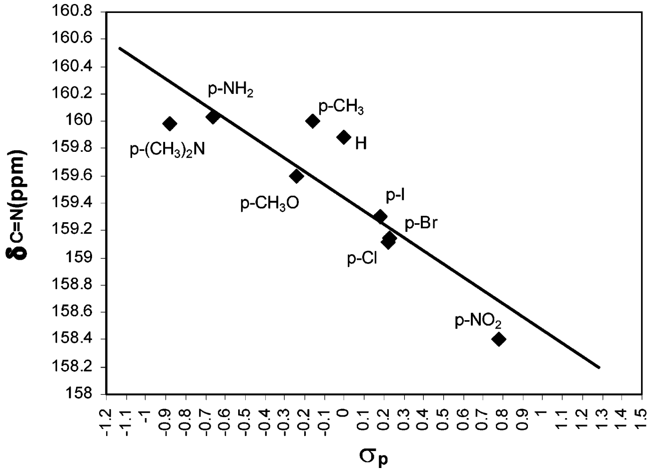


Figure 4. Plot of Hammett σ_p constants[20] vs $\delta_{C=N}$ (ppm).

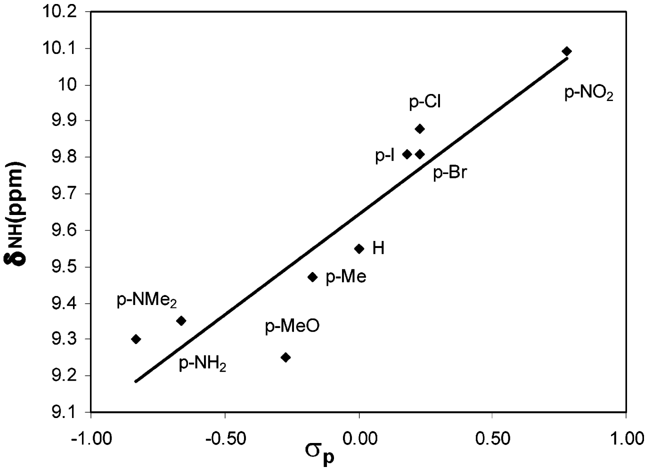


Figure 5. Plot of Hammett σ_p constants vs δ_{NH} (ppm).

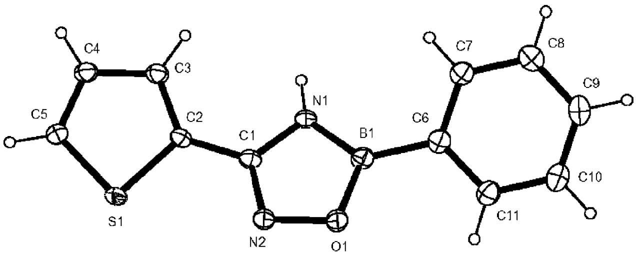


Figure 6. X-ray crystal structure of **2n**.

electron-releasing substituent such as a dimethylamino existed on the phenyl ring (see Figure 6). These results are theoretically expected trends in NMR shifts for NH protons adjacent to electron-withdrawing and electron-releasing groups.

Conclusions

In this work, the basicity constants (pK_{BH^+}) of 1,2,4,5-oxadiazaboroles were determined potentiometrically in acetic acid medium, and the correlations between these values and Hammett σ constants were established. The results were interpreted based on the electronic-mesomeric properties of the existing groups on the phenyl ring at the 3-position of the title oxygen-, nitrogen-, and boron-containing five-membered non-aromatic heterocycles.

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Supporting Information Available:

Experimental procedures, physical, and spectral data for the compounds **2a**−**n** and crystallographic data for **2n.** This information is available free of charge via the Internet at http: //pubs.acs.org.

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