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# Acid-Base Equilibria of Some N-Substituted Thiophene-2-Carboxamidoximes in Non-Aqueous Media

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The protonation constants of the amino nitrogens of some N-substituted thiophene-2-carboxamidoximes 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.

**Key Words:** Thiophene, protonation constant, potentiometry,  $pK_a$  values, amidoxime.

## Introduction

Potentiometric titration in non-aqueous 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 non-aqueous 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<sup>1,2</sup>.

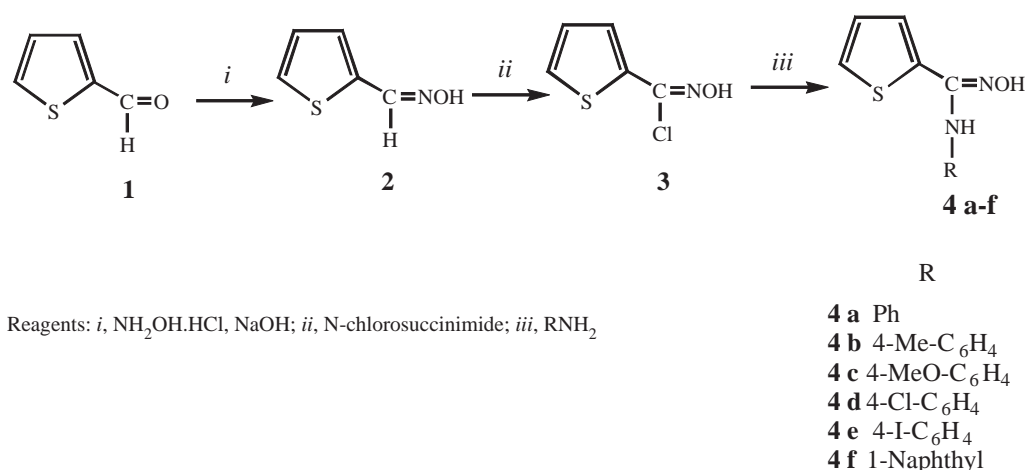
Amidoximes are compounds with both a hydroximino and an amino functionality at the same carbon atom, and are thus closely related to amides, amidines and hydroxamic acids.

Literature searches revealed that a remarkable number of amidoximes have been found to have important biological activities including anti-tuberculostatic, anti-thrombotic and vasodilating, anti-malarial, anti-depressive and alpha-adrenergic<sup>3-9</sup>.

As a continuing part of our studies<sup>10,11</sup> on the acid-base equilibria of the amidoximes and related compounds, we report here the protonation of the amino nitrogens of six N-substituted thiophene-2-carboxamidoximes, of which four are new, (Scheme 1) in acetic acid by potentiometry.

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Scheme 1

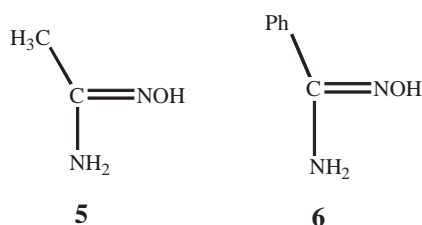


Figure 1

## Experimental

IR spectra were recorded on a Shimadzu FTIR-8201 PC spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker (200 MHz) spectrometer with the solvents noted. Chemical shifts were reported on the scale in ppm relative to TMS as an internal standard. Mass spectra were obtained on a VG spectrometer. Merck Silica Gel (230-400 mesh) and HF254 were used for flash column and thin layer chromatography.

*Thiophene-2-carboxaldehyde oxime (2; C<sub>5</sub>H<sub>5</sub>NOS)*: To a mixture of thiophene-2-carboxaldehyde **1** (5.60 g, 0.05 mol) in water (12.5 ml), ethanol (12.5 ml) and ice (21.5 g) was added hydroxylamine hydrochloride (3.82 g, 0.055 mol). An equivalent amount of 50% NaOH was then added with stirring. The temperature was maintained at 20-25°C by addition of ice. The reaction mixture was stirred for 1 h, extracted with diethyl ether (50 ml), acidified with concentrated HCl to pH 6, and extracted with diethyl ether (2 x 50 ml). The combined ethereal extracts were dried over anhydrous calcium sulfate and evaporated under reduced pressure to give thiophene-2-carboxaldehyde oxime **2** (5.9 g, 93%, m.p. 132-134°C; lit<sup>12</sup>. 132-132.5°C, lit<sup>13</sup>.135-136.8°C).

*Thiophene-2-hydroximoyl chloride (3; C<sub>5</sub>H<sub>4</sub>ClNOS)*: To a stirred solution of thiophene-2-carboxaldehyde oxime **2** (1.59 g, 0.0125 mol) in N,N-dimethyl formamide (15 ml) at 25-30°C was added N-chlorosuccinimide in portions over 15 min. The reaction mixture was stirred overnight. The solution was poured into ice water (60 ml) and extracted with diethyl ether (2 x 50 ml), washed with water and dried over anhydrous calcium sulfate and finally evaporated under reduced pressure to give the hydroximoylchloride **3** (yield %; quantitative). m.p.98-101°C, lit<sup>12</sup>. 102°C. The product was used without further purification to obtain the N-substituted thiophene-2-carboxamidoximes **4a-f**.

**General procedure for the synthesis of N-substituted thiophene-2-carboxamidoximes 4a-f**

*N*-phenyl thiophene-2-carboxamidoxime (**4a**; C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S): To a solution of thiophene-2-hydroximoyl chloride **3** (2.0 g, 0.0124 mol) in chloroform (20 ml) was added dropwise freshly distilled aniline (2.30 g, 0.0248 mol) in chloroform with constant stirring at room temperature. The reaction mixture was stirred for 2 days. The precipitate was filtered and the solution was evaporated. The residual solid was subjected to flash column chromatography (eluant: hexane:ethyl acetate; 1:3) to give **4 a** (1.40 g, 51%). m.p. 98-99°C, lit<sup>13</sup>. 91-93°C.

**Potentiometric Titrations**

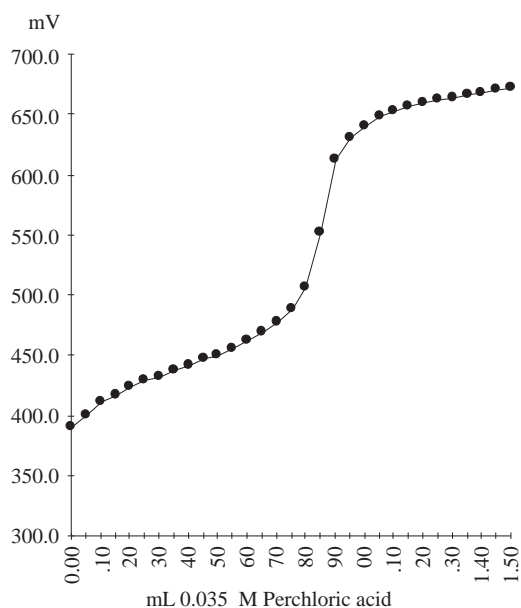
The potentiometric titrations were performed in a 50 ml glass vessel equipped with a combined pH electrode (Ingold), argon inlet and outlet tubes, a magnetic stirrer and titrant inlet. The electrode was modified using saturated KCl solution in anhydrous methanol instead of aqueous KCl solution. The concentration of the titrant solution standardized against diphenylguanidine was 0.035 M in glacial acetic acid. The concentration of the amidoximes **4 a-f**, **5**, **6** was 10<sup>-3</sup> M in glacial acetic acid. In calculations of the pK<sub>a</sub> values, the mV value of the buffer solution was -16 mV and the pH reading was 7. These values were taken as standard. An Orion Model 420 A pH ionmeter was used to measure the cell e.m.f. The temperature was maintained at 25.0 ± 0.1°C.

**Results and Discussion**

The spectroscopic data of six N-substituted thiophene-2-carboxamidoximes **4 a-f**, were given in Table 1. Excellent sigmoid curves were obtained by plotting the potential values recorded against titrant volume (Figure 2). pK<sub>a</sub> values were calculated by making use of the half-neutralization potentials determined from these curves.

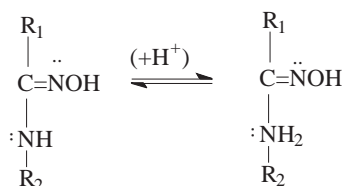
**Table 1.** Spectroscopic data of **4 a-f**.

Entry	Molecular Formula IR (KBr) cm <sup>-1</sup> , m.p. (°C); eluant	Yield (%)	NMR (CDCl <sub>3</sub> +DMSO-d <sub>6</sub> ; 1:1) δ	MASS m/z (%)
<b>4a</b>	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> S 3382 (NH), 1620 (C = N), 98-99; hexane: EtOAc(1:3)	51	8.42 (br.s, 1 H, NOH), 7.56-7.04 (m, 8 H)	218 (M <sup>+</sup> , 40), 202 (100), 186 (55), 110 (37), 93 (98), 77 (50)
<b>4b</b>	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S 3359 (NH), 1629 (C = N), 210-12, lit <sup>13</sup> . 170(d); hexane: EtOAc(1:3)	64	10.04 (br. s, 1 H, NOH), 7.46-6.77 (m, 7 H), 2.65 (s, 3 H, CH <sub>3</sub> )	232 (M <sup>+</sup> , 87), 215 (85), 200 (60), 186 (15), 117 (30), 107 (100), 91 (58), 77 (54)
<b>4c</b>	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> S 3342 (NH), 1632 (C = N), 228-231; hexane: EtOAc(1:3)	59	9.72 (br.s, 1 H, NOH), 7.37-6.62 (m, 7H), 3.74 (s, 3 H, OCH <sub>3</sub> )	248 (M <sup>+</sup> , 100), 232 (98), 215 (95), 201(12), 187 (20), 123 (51), 108 (65), 92 (13)
<b>4d</b>	C <sub>11</sub> H <sub>9</sub> ClN <sub>2</sub> O <sub>2</sub> S 3406 (NH), 1639 (C = N), 206-208; hexane: EtOAc(1:4)	76	10.29 (s, 1 H, NOH), 7.46-6.71 (m, 7 H)	254 (M+2,88), 252(M <sup>+</sup> ,73) 235 (100), 220 (90), 200 (45), 186 (26), 137 (48), 129 (89), 117 (26), 110 (70), 99 (47), 90 (35)
<b>4e</b>	C <sub>11</sub> H <sub>9</sub> N <sub>2</sub> O <sub>2</sub> S 3357 (NH), 1617 (C = N), 222-225; hexane: EtOAc(1:4)	82	10.50 (s, 1 H, NOH), 7.77-6.54 (m, 7 H)	344 (M <sup>+</sup> , 65), 328 (50), 312 (35), 219 (65), 200 (100), 184 (28), 111 (44), 91 (42)
<b>4f</b>	C <sub>15</sub> H <sub>12</sub> IN <sub>2</sub> O <sub>2</sub> S 3355(NH), 1620(C = N), 191-193; hexane: EtOAc(1:3)	43	9.08(br.s, 1 H), 8.33(d, 2 H), 7.87 (d, 2 H), 7.65-7.23(m, 4 H), 6.98 (d, 2 H)	269 (M+1, 100), 268 (M <sup>+</sup> , 48), 251 (52), 236 (16)



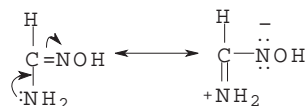
**Figure 2.** Titration curve of **4 a**.

Recently, equilibrium acidities and bond dissociation energies of some aldehyde and ketone oximes in non-aqueous media were reported by Bordwell et al.<sup>14–17</sup>. The basicity of oximes is due to the lone pair of the amino nitrogen (Scheme 2).



**Scheme 2**

As the lone pair of the amino nitrogen atom can be delocalized on to the azomethine  $\pi$  system as shown below<sup>18,19</sup> one may, therefore, expect changes in the basicity of this class of compounds when the substituents both at the azomethine carbon and the amino nitrogen are altered.



In a recent study, we determined the stoichiometric protonation constants of these compounds in ethanol-water mixture by potentiometry<sup>10</sup>. In this study, we report the synthesis and characterization of some N-substituted thiophene carboxamidoximes and the  $\text{pK}_a$  values for the protonation equilibria of the amino nitrogens of **4 a-f**, **5** and **6** in acetic acid.

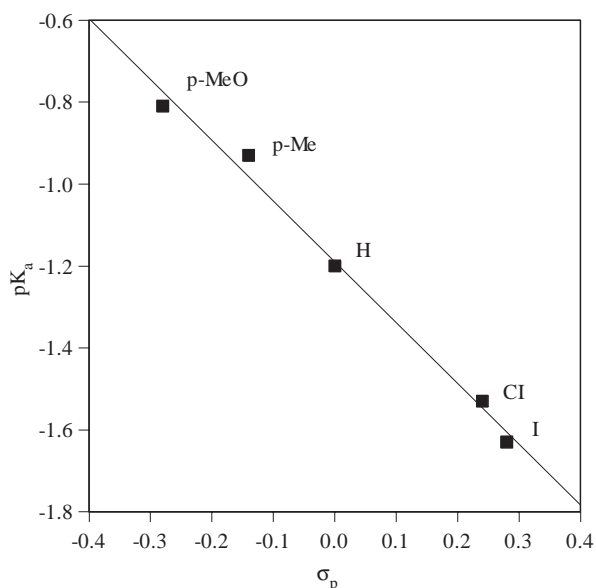
The  $\text{pK}_a$  values and half-neutralization potentials (HNP) are given in Table 2. A typical titration curve for **1** is presented in Figure 2.

**Table 2.**  $pK_a$  and half-neutralization values of **4 a-f**, **5**, **6**.

	HNP(mV)	$pK_a$
<b>4 a</b>	468	-1.20
<b>4 b</b>	452	-0.93
<b>4 c</b>	445	-0.81
<b>4 d</b>	487	-1.53
<b>4 e</b>	493	-1.63
<b>4 f</b>	467	-1.18
<b>5</b>	417	-0.17
<b>6</b>	410	-0.21

The acetamidoxime **5**<sup>19</sup> with no substituent on the amino nitrogen atom has a  $pK_a$  value of -0.17 compared with -0.21 for benzamidoxime **6**.<sup>20</sup> Accordingly, we may expect that these values would be higher than the amidoximes with a substituent on the amino nitrogen atom. The lone pair on the amino nitrogen atom without a substituent will readily attach to a proton. The  $pK_a$  value of acetamidoxime **5** is somewhat higher than that of benzamidoxime **6** since the methyl group has an electron-donating effect while a phenyl group will withdraw electrons.

When substitution occurs on the amino nitrogen, there is a remarkable decrease in the  $pK_a$  values of amidoximes. Thus, the  $pK_a$  value of **4 a** is lower than that of **4 b**. This difference is due to the electron-releasing methyl substituent on the phenyl ring in **4 b**. The  $pK_a$  value of **4 c** with a stronger electron-donating methoxy substituent is higher than those of both **4 a** and **4 b**. The compound **4 f**, with a naphthyl group on the amino nitrogen atom has a  $pK_a$  value of -1.18, very close to that of **4 a**. This is as expected since phenyl and naphthyl rings show similar effects on the basis of their resonance structures. The  $pK_a$  values of compounds **4 d** and **4 e**, having chlorine and iodine atoms on the phenyl ring, are the lowest: -1.63 for **4 e** and -1.53 for **4 d**. The lower  $pK_a$  values of the amidoximes containing chlorine and iodine atoms can be explained by predominating inductive effects of halogens over resonance delocalization through the benzene ring.  $pK_a$  values were also correlated with appropriate Hammett  $\sigma_p$  constants<sup>21</sup> (Figure 3).

**Figure 3.** Hammett plot of the  $pK_a$  values vs. sigma constants.

In conclusion, six N-substituted amidoximes bearing a thiophene ring were synthesized and the potentiometric study of these compounds has shown that the basicity order of the amino nitrogen is in accordance with the electronic and mesomeric properties of the substituents on the benzene ring of the substituents on the amino nitrogen.

## Acknowledgement

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