

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

Nedime DÜRÜST*, Yaşar DÜRÜST and İlknur MERİÇ
*Department of Chemistry, Abant İzzet Baysal University,
TR-14280 Bolu-TURKEY*

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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

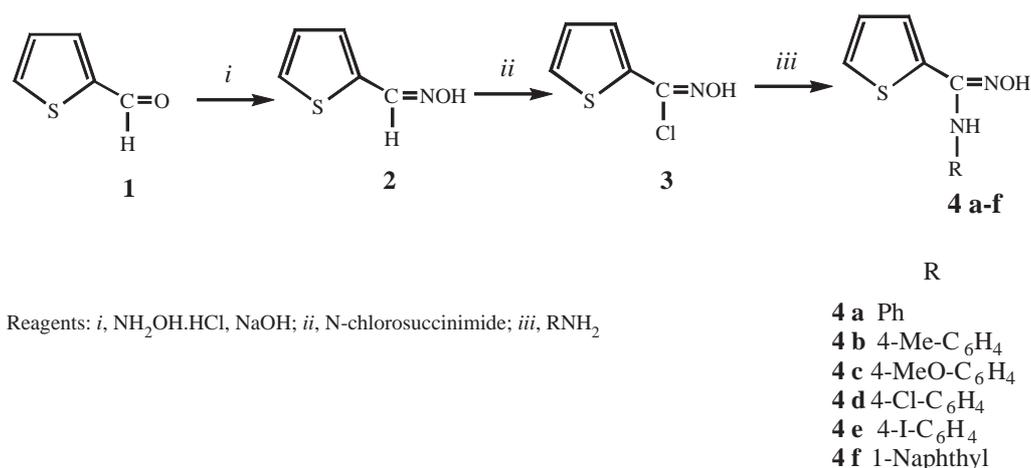
Potentiometric titration in non-aqueous media is a standard method for the determination of the basicity and acidity of various compounds, particularly in organic and pharmaceutical analyses. The reason for using non-aqueous solvents is that many organic compounds of pharmaceutical importance do not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

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-adrenergic³⁻⁹.

As a continuing part of our studies^{10,11} 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.

*Corresponding author



Scheme 1

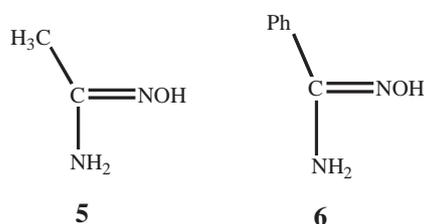


Figure 1

Experimental

IR spectra were recorded on a Shimadzu FTIR-8201 PC spectrometer. ¹H 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; C₅H₅NOS): 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; lit¹². 132-132.5°C, lit¹³.135-136.8°C).

Thiophene-2-hydroximoyl chloride (3; C₅H₄ClNOS): 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, lit¹². 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**; C₁₁H₁₀N₂OS): 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, lit¹³. 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 10⁻³ M in glacial acetic acid. In calculations of the pK_a 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_a 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 ⁻¹ , m.p. (°C); eluant	Yield (%)	NMR (CDCl ₃ +DMSO-d ₆ ; 1:1) δ	MASS m/z (%)
4a	C ₁₁ H ₁₀ N ₂ OS 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 ⁺ , 40), 202 (100), 186 (55), 110 (37), 93 (98), 77 (50)
4b	C ₁₂ H ₁₂ N ₂ OS 3359 (NH), 1629 (C = N), 210-12, lit ¹³ . 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 ₃)	232 (M ⁺ , 87), 215 (85), 200 (60), 186 (15), 117 (30), 107 (100), 91 (58), 77 (54)
4c	C ₁₂ H ₁₂ N ₂ O ₂ 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 ₃)	248 (M ⁺ , 100), 232 (98), 215 (95), 201(12), 187 (20), 123 (51), 108 (65), 92 (13)
4d	C ₁₁ H ₉ ClN ₂ OS 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 ⁺ ,73) 235 (100), 220 (90), 200 (45), 186 (26), 137 (48), 129 (89), 117 (26), 110 (70), 99 (47), 90 (35)
4e	C ₁₁ H ₉ N ₂ OS 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 ⁺ , 65), 328 (50), 312 (35), 219 (65), 200 (100), 184 (28), 111 (44), 91 (42)
4f	C ₁₅ H ₁₂ IN ₂ OS 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 ⁺ , 48), 251 (52), 236 (16)

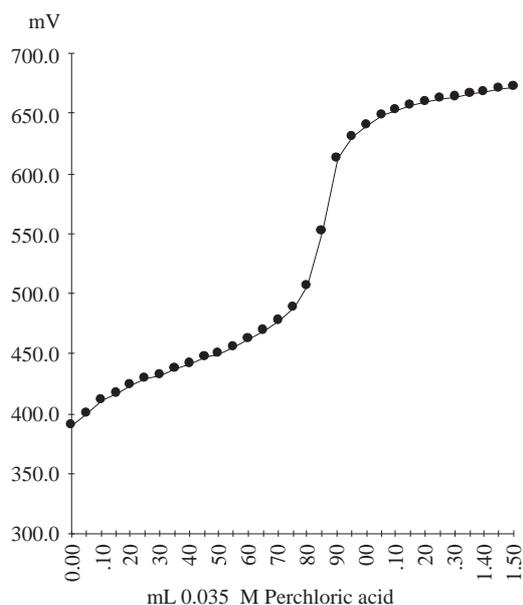
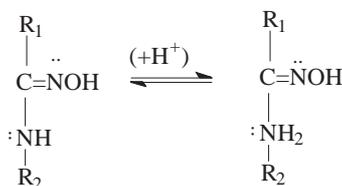


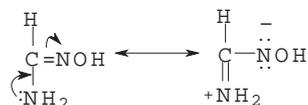
Figure 2. Titration curve of **4 a**.

Recently, equilibrium acidities and bond dissociation energies of some aldehyde and ketone oximes in non-aqueous media were reported by Bordwell et al.^{14–17}. 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 π system as shown below^{18,19} 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 potentiometry¹⁰. In this study, we report the synthesis and characterization of some N-substituted thiophene carboxamidoximes and the pK_a values for the protonation equilibria of the amino nitrogens of **4 a-f**, **5** and **6** in acetic acid.

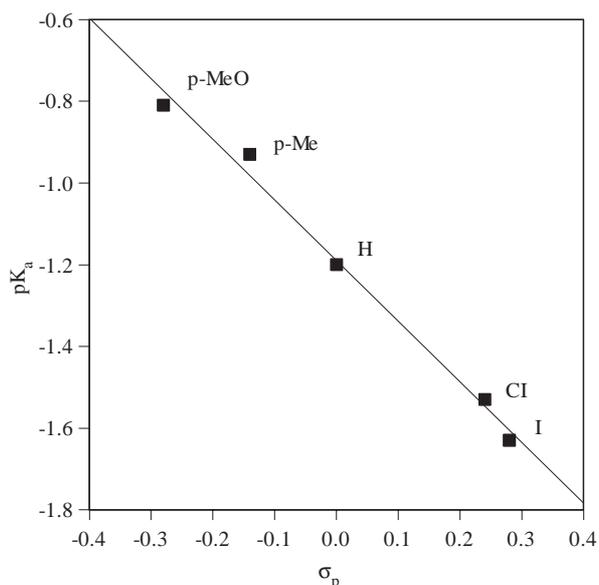
The pK_a values and half-neutralization potentials (HNP) are given in Table 2. A typical titration curve for **1** is presented in Figure 2.

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

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

The acetamidoxime **5**¹⁹ with no substituent on the amino nitrogen atom has a pK_a value of -0.17 compared with -0.21 for benzamidoxime **6**.²⁰ 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 σ_p constants²¹ (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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