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メタデータ	言語: eng 出版者: 公開日: 2010-03-15 キーワード (Ja): キーワード (En): 作成者: Imoto, Eiji, Motoyama, Ryoza メールアドレス: 所属:
URL	https://doi.org/10.24729/00010924

Studies on the Thiophene Compounds. III. Effects of Substituents on the Dissociation Constants of Thiophenecarboxylic and Thiopheneacetic Acid

By

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(Received February 28, 1954)

Abstract

Acid dissociation constants of substituted thiophenecarboxylic acids and thiopheneacetic acids were determined, and it was shown that the Hammett's law can be applied to thiophene ring even if the effect of the first substituent is considered apparently to be transported to the second substituent merely through the carbon chain of thiophene ring. From these rho-values, combined with what are already known of furan- and benzenecarboxylic acid, it was attempted to explain the effects of hetero atoms in the five membered heteroaromatic rings from the stand point of electronegativity and polarisability.

The interactions of the two substituents, X and Y, attached to thiophene ring have not been examined in detail owing to the following reasons: (A) the alpha-orienting power of ring sulphur atom is very strong, and (B) the relative positions of ortho, meta and para are complicated in the five membered ring.

It is desirable to elucidate the manner of these interactions in order to anticipate the reactions of substituted thiophenes. In this paper, choosing carboxylic group or $-\text{CH}_2\text{COOH}$ group as X and various substituents as Y, the effects of Y to the acid strength were determined. From these results, combined with what are already known about furan-carboxylic, benzoic and phenylacetic acid, it was attempted to explain the effects of the hetero atom in the five membered heteroaromatic compound.

PROCEDURE

The dissociation constants of the acids were determined potentiometrically in water at 25°C. By neglecting the activity coefficient term, the pKa values can be calculated by the following equation;

$$\text{pKa} = \text{pH} - \log \frac{\alpha_t + [\text{H}^+]/[\text{S}]}{1 - \alpha_t - [\text{H}^+]/[\text{S}]}$$

in which α_t is the degree of titration, that is, number of moles of sodium hydroxide added/number of moles of total acid, $[\text{H}^+]$ is the hydrogen ion concentration (mol./l.), and $[\text{S}]$ is the total concentration of acid (mol./l.). The term of $[\text{H}^+]/[\text{S}]$ cannot be neglected because dissociation constants of the samples are in order of $10^{-3} \sim 10^{-4}$. The

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pKa values were determined by averaging the values of pKa calculated from the values of pH determined at several points near half-neutralization.

RESULTS

In Tables 1~10 there are recorded the results of titration of the samples. Fig. 1 shows the relationship between the Hammett's sigma-values and $\log K_a$ thus obtained. In this case, 5- and 4-positions are considered as para and meta to 2-position, respectively. Fig. 1 shows that the Hammett's law can be applied to thiophene ring, even if the effects of the first substituent are considered apparently to be transported to the second substituent merely through the carbon chain of thiophene ring. The rho-values calculated by the method of least square were +1.076 for thiophenecarboxylic acids (5-chloro- and 4-methyl- derivatives were excluded in this calculation) and +0.161 for thiopheneacetic acid, respectively. In Fig. 1, rho-values and the relationships between sigma and $\log K_a$ for benzoic, furan-carboxylic and phenylacetic acid were reproduced from literatures for comparison^{1,2)}.

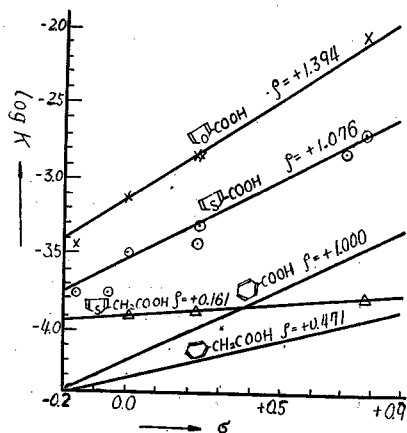


Fig. 1. $\log K_a - \sigma$

Table 1. Result of the titration of 0.0642 g. of 2-thiophenecarboxylic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
2.000	3.38	0.3894	4.17	9.634	3.50
2.568	3.57	0.5000	2.69	9.528	3.49
3.000	3.68	0.5841	2.09	9.452	3.49
3.496	3.84	0.6806	1.44	9.364	3.48

average pKa=3.49, $K_a=3.24 \times 10^{-4}$.

Table 2. Result of the titration of 0.1032 g. of 5-bromo-2-thiophenecarboxylic acid in 100 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
1.500	3.17	0.2937	6.76	4.907	3.29
2.000	3.29	0.3915	5.13	4.883	3.30
2.554	3.43	0.5000	3.72	4.857	3.30
3.000	3.56	0.5873	2.75	4.835	3.30
3.500	3.73	0.6852	1.86	4.812	3.31
4.000	3.93	0.7831	1.17	4.789	3.31

average pKa=3.30, $K_a=5.01 \times 10^{-4}$.

Table 3. Result of the titration of 0.0808 g. of 5-chloro-2-thiophene-carboxylic acid in 100 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
1.500	3.25	0.2943	5.62	4.895	3.41
2.000	3.38	0.3924	4.17	4.871	3.42
2.548	3.52	0.5000	3.02	4.845	3.41
3.000	3.64	0.5887	2.29	4.824	3.40

average pKa=3.41, $K_a=3.89 \times 10^{-4}$

Table 4. Result of the titration of 0.0715 g. of 4-methyl-2-thiophene-carboxylic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
1.500	3.44	0.2908	3.63	9.766	3.75
2.000	3.61	0.3878	2.45	9.673	3.76
2.579	3.80	0.5000	1.58	9.566	3.77
3.000	3.92	0.5816	1.20	9.490	3.75

average pKa=3.76, $K_a=1.74 \times 10^{-4}$

Table 5. Result of the titration of 0.0769 g. of 5-methyl-2-thiophene-carboxylic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
2.000	3.52	0.3606	3.02	10.40	3.72
2.773	3.79	0.5000	1.62	10.25	3.76
3.200	3.93	0.5770	1.17	10.16	3.77
4.000	4.22	0.7213	0.60	10.01	3.79

average pKa=3.76, $K_a=1.74 \times 10^{-4}$

Table 6. Result of the titration of 0.0862 g. of 4-nitro-2-thiophenecarboxylic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	[Total acid] $\times 10^3$ mol./l.	pKa
2.554	3.00	0.5000	10.0	9.467	2.81
3.000	3.12	0.5880	7.59	9.386	2.81

average pKa=2.81, $K_a=1.55 \times 10^{-3}$

Table 7. Result of the titration of 0.0827 g. of 5-nitro-2-thiophenecarboxylic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	$[Total\ acid] \times 10^3$ mol./l.	pKa
0.500	2.53	0.1022	29.5	9.451	2.68
1.500	2.70	0.3065	20.0	9.268	2.68
2.447	2.91	0.5000	12.3	9.100	2.67
3.000	3.08	0.6130	8.32	9.005	2.70

average pKa=2.68, $K_a=2.09 \times 10^{-3}$

Table 8. Result of the titration of 0.0716 g. of 2-thiopheneacetic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	$[Total\ acid] \times 10^3$ mol./l.	pKa
1.500	3.56	0.2905	2.75	9.779	3.89
2.000	3.72	0.3873	1.91	9.685	3.88
2.582	3.92	0.5000	1.20	9.577	3.90
3.500	4.23	0.6778	0.589	9.413	3.89

average pKa=3.89, $K_a=1.29 \times 10^{-4}$

Table 9. Result of the titration of 0.0917 g. of 5-chloro-2-thiopheneacetic acid in 50 ml. of water with 0.09753 N NaOH.

NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	$[Total\ acid] \times 10^3$ mol./l.	pKa
2.000	3.71	0.3757	1.95	9.985	3.89
2.622	3.86	0.5000	1.38	9.866	3.88
3.000	4.01	0.5636	0.977	9.796	3.88
4.000	4.41	0.7514	0.389	9.615	3.92
5.000	5.10	0.9393	0.0794	9.440	3.90

average pKa=3.89, $K_a=1.29 \times 10^{-4}$

Table 10. Result of the titration of 0.0921 g. of 5-acetyl-2-thiopheneacetic acid in 50 ml. of water with 0.09753 N NaOH.

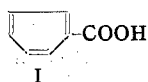
NaOH ml.	pH	α_t	$[H^+] \times 10^4$ mol./l.	$[Total\ acid] \times 10^3$ mol./l.	pKa
1.500	3.45	0.2926	3.55	9.709	3.76
2.000	3.61	0.3901	2.45	9.615	3.76
2.563	3.79	0.5000	1.62	9.512	3.76
4.000	4.34	0.7801	0.457	9.259	3.76
4.500	4.63	0.7877	0.234	9.174	3.76

average pKa=3.76, $K_a=1.74 \times 10^{-4}$

DISCUSSION

1. Acid strength of non-substituted acids.

For the discussion of the results, it is appropriate to begin with the comparison of acid strength of nonsubstituted acids, that is benzoic, furancarboxylic and thiophene-carboxylic acid. In these acids, π -electrons tend to flow out to carboxyl group from aromatic ring due to the strong electron attracting power of the former. To compare the relative ease with which this outflow of π -electrons from aromatic ring takes place, one $-\text{C}=\text{C}-$ group of benzene ring is considered to correspond to a hetero atom. That is, benzoic acid is compared with heterocyclic compounds as indicated by the formula I.



Then, independently of the basis of computation, the values of electronegativities increase in the sequence $\text{O} > \text{S} > \text{C}=\text{C}$ ³⁾ and the polarisabilities are in the order of $\text{O} < \text{S} < \text{C}=\text{C}$. Consequently, the relative ease of outflow of π -electrons must be in the order of $\text{O} < \text{S} < \text{C}=\text{C}$. The electrometric shift of carbonyl group which renders positive charge to the carbon atom of the carboxyl group is hindered by the outflow of electrons from aromatic ring, that is, the dissociation of proton is hindered. It is evident from the above consideration that the acid dissociation constant increases in the sequence benzoic < thiophenecarboxylic < furancarboxylic acid.

2. The interpretation of the rho-values when the carboxyl groups are conjugated with the aromatic rings.

It is convenient to begin with the 2-thiophenecarboxylic acid, whose 5-position is occupied by a $-\text{M}$ substituent. In such case, π -electrons tend to pass from the second substituent to thiophene ring. Such an inflow of π -electrons is accepted by ring carbon atoms and sulphur atom. This results in a decrease of $\delta+$ on sulphur atom produced by the heteroaromatic resonance, and in an increase of $\delta-$ on each ring carbon atom. As a result, $\delta+$ on the carbon atom of carboxyl group tends to decrease through the 2-carbon atom, and the acidic dissociation of proton is impeded. Moreover, the decrease of $\delta+$ on sulphur atom results in a decrease of its F effect which lowers the acid strength further. The $+\text{M}$ substituents effect conversely. Therefore, the value of rho takes + sign.

Now, the specific behaviors of the different rings to the inflow of π -electrons from a $-\text{M}$ substituent should be considered. In case of furan ring, even if the $-\text{M}$ substituent is the same, much more π -electrons pass to the ring owing to the strong electronegativity of ring oxygen atom. This accumulation of π -electrons in furan ring reduces its aromaticity and must be canceled by the outflow to carboxyl group. In case of thiophene ring, as the electronegativity of sulphur is not so strong as oxygen, this accumulation as well as the tendency of outflow to carboxyl group is smaller than in the case of furan ring. As a result, the effects of $-\text{M}$ substituents to the acid strength are greater with furan ring. On the other hand, in case of $+\text{M}$ substituents, as furan ring resist against the outflow of π -electrons, this mesomerism must be resulted in the outflow of π -electrons from carboxyl group. With thiophene ring, according to the smaller electronegativity and greater polarisability of sulphur atom, the tendency of outflow of π -electrons from carboxyl group is covered with the outflow from the ring as compared with furan ring. As a result,

also in this case, the effects of substituents are smaller with thiophene ring. By the similar consideration, it is recognized that the effects of substituents are much smaller with benzene ring. In conclusion, the rho-value increases in the sequence furan > thiophene > benzene.

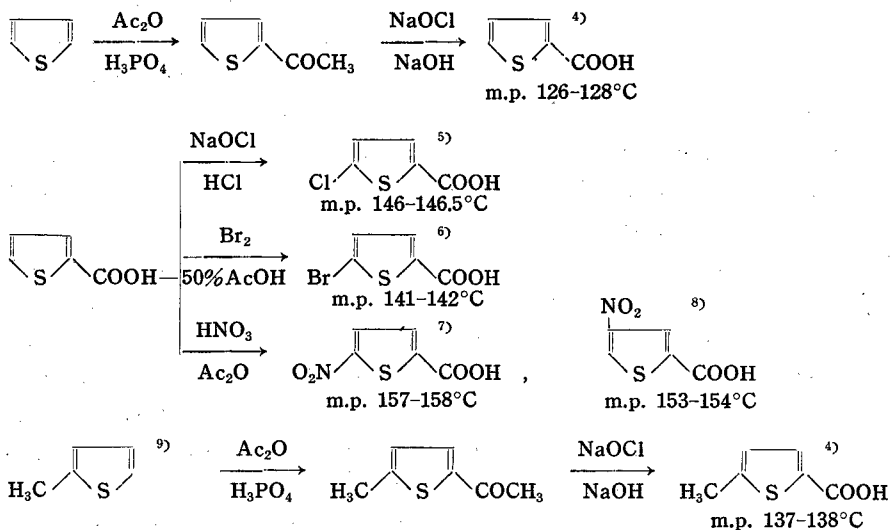
3. The interpretation of the rho-values when the carboxyl groups are not conjugated with the aromatic rings.

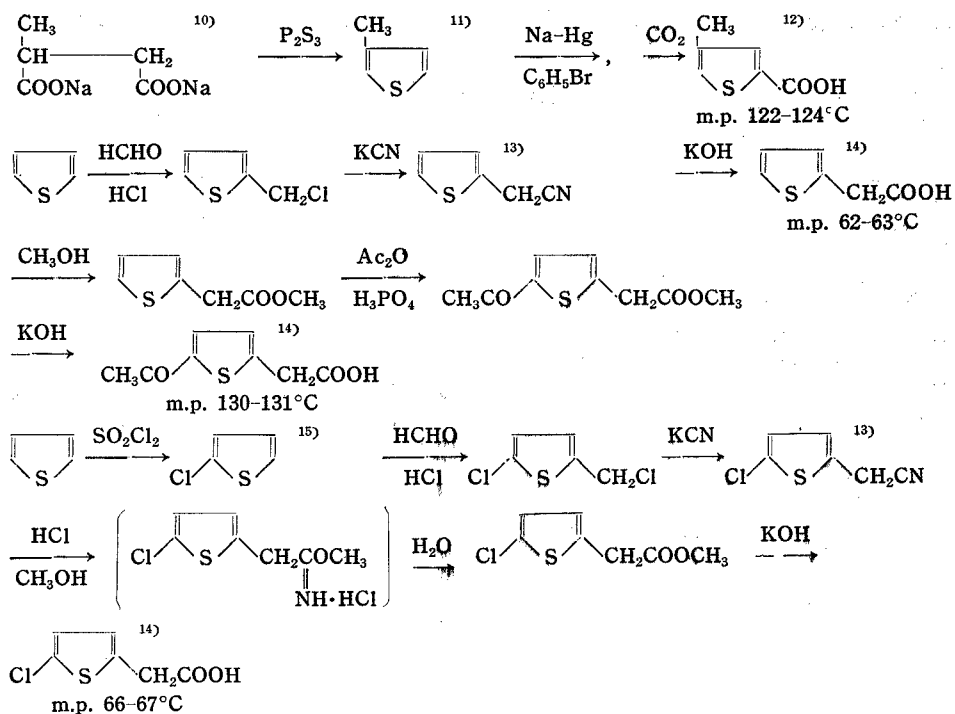
It was seen in the previous section that the mode of giving and taking of π -electrons between the substituents and rings is affected remarkably by the electron withdrawing power of ring hetero atoms. When the carboxyl groups are conjugated with ring, it suffers this effect directly, resulting in the greater rho-values of heterocyclic compounds. However, when the carboxyl groups are separated from the aromatic rings by a methylene group, as in the case of thiopheneacetic acid, there is no polarisability effect but that is brought about through inductive mechanism. That is, in this case, there is only a transmission of a change induced by substituents in electronic charges on alpha-carbon atom through I effect. Now, an inflow of π -electrons into a ring from a $-M$ substituent can be accommodated by a hetero atom. In case of $+M$ substituent, a hetero atom hinders an outflow of π -electrons from a ring. All the above effects reduce the change in electronic charge on alpha-carbon atom, and these effects can be considered to increase in the sequence furan > thiophene > benzene ring from the stand point of electronegativities and polarisabilities. As a result, in this case, the effects of substituents should decrease in the sequence of furan < thiophene < benzene ring, although no data can be obtained with furan acetic acid in the present situation.

EXPERIMENTAL

All melting points are uncorrected.

Materials. The carboxylic acids used were prepared as follows,





These carboxylic acids were purified by repeated recrystallizations to show the constant melting points as indicated above.

Determination of dissociation constants. *Conductance Water.* The conductance water was prepared with ion exchange resins (Dow Chem. Co.) by the mixed bed system, and reserved in a pyrex glass bottle. *0.1N Sodium Hydroxide Solution.* Metallic sodium was dissolved in conductance water and reserved in a pyrex glass bottle protected from carbon dioxide with soda-lime tube. The solution was siphoned into a micro-buret (graduated in 0.01 ml.) suspended over the bath as required. *pH Meter.* Glass electrode pH meter combined with saturated carmel electrode was made after Okuda and Maruyama using 1A7GT valve¹⁶⁾. It was calibrated in the same conditions of titration against standard buffer solutions of pH 1.20, 3.15, 5.12, 6.12 and 6.90. Its pH-mV curve was obtained by the method of least square. The accuracy was ± 0.02 pH. The pH meter was occasionally checked up by titrating pure benzoic acid, revealing always satisfactory results. *Determination of pKa values.* A sample of about 0.0005 mole was taken in 200 ml. pyrex glass beaker and weighed accurately. Fifty ml. of conductance water was pipetted into the beaker and the sample was dissolved. In case of 5-bromo- and 5-chlorothiophene-carboxylic acid, 100 ml. of water was used because of their low solubility. Then the beaker was placed in constant-temperature bath of $25.00 \pm 0.05^\circ\text{C}$. When the temperature equilibrium was obtained, appropriate amounts of sodium hydroxide solution were added successively and pH values were measured at each addition. At half-neutralization point, accurately the calculated amount of sodium hydroxide solution was added.

Acknowledgement. The authors wish to thank Socony-Vacuum Laboratories for supplying thiophene.

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