# Thermodynamics of Protonation of Some Five-membered Heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates

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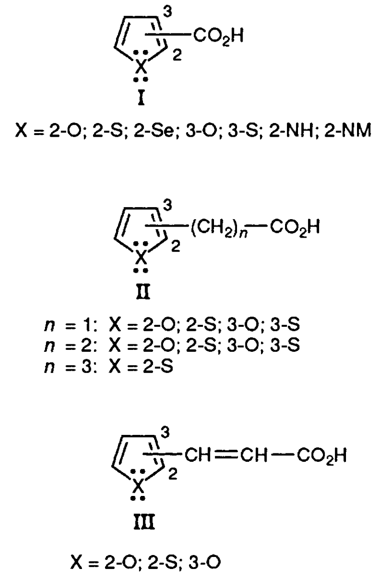
Thermodynamic parameters for the proton complex formation of some five-membered heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates have been determined in aqueous solution at 25 °C and $I = 0.10$ mol dm$^{-3}$ ($KNO_3$) by means of potentiometric and calorimetric measurements. The acidity of heteroarylcarboxylic acids follows the order 2-furoic > 2-thenoic > selenophene-2-carboxylic > 3-furoic > 3-thenoic > pyrrole-2-carboxylic > *N*-methylpyrrole-2-carboxylic. Such a sequence agrees with the different effects of the heteroaryl groups on the carboxylic side chain. A similar trend is observed for the corresponding furyl- and thienyl-alkanoic acids, even though polar effects of heteroatoms on the acidity are less pronounced owing to the presence of the methylenic spacers. The p*K* values of *trans*-heteroarylpropenoic acids turn out to be independent of both the heteroatom and the carboxylic group position. Enthalpic and entropic changes are typical of a 'hard-hard' interaction.

The interest in the side-chain reactivity of five-membered heteroaromatic compounds[1–5] has stimulated a study of the factors contributing to the acidity of the carboxylic side chain. Several p*K* values for the protonation of five-membered heteroarylcarboxylates are available,[6–18] but the majority of them deal with the p*K* values of some substituted furoic,[6] thenoic,[14] selenophene-2-carboxylic,[15] pyrrole-2-carboxylic[16] and tellurophene-2-carboxylic[17] acids, with the aim of testing the reliability of Hammett's equation in these ring systems. These p*K* values have been measured under fairly different experimental conditions, thus rendering the comparison among the diverse terms meaningless. Therefore the knowledge of the p*K* values of a homogeneous series of unsubstituted five-membered heteroarylcarboxylic acids under the same ionic strength and temperature seemed highly desirable. In this connection, we have determined the proton complex formation constants of 19 heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates (Fig. 1) at 25 °C and $I = 0.10$ mol dm$^{-3}$ ($KNO_3$), by potentiometric measurements. The acids have been chosen in order to see the influence of (i) the heteroatom and the position of the carboxylic group (group **I**); (ii) the methylenic spacers (group **II**); and (iii) the spacer rigidity (group **III**).

Usually, the relative strengths of carboxylic acids have been discussed primarily on the basis of their p*K* values; however, since the magnitude of p*K* values results from the relative magnitudes of $\Delta H°$ and $\Delta S°$ values, we have also carried out a calorimetric study, under the same experimental conditions used for the determination of the p*K* values, to dissect the $\Delta G°$ values. To the best of our knowledge $\Delta H°$ and $\Delta S°$ values were determined, by direct calorimetry, only for 2-furoic[11] and pyrrole-2-carboxylic[19] acids. Other thermodynamic data available for 2-furoic and 2-thenoic acids were determined by the van't Hoff equation.[7]

## Experimental

*Chemicals.*—2-Furoic, 2-thenoic, 3-furoic, 3-thenoic, pyrrole-2-carboxylic, *N*-methylpyrrole-2-carboxylic, 2-thienylethanoic, 3-thienylethanoic, 4-(2-thienyl)butanoic, *trans*-3-(2-furyl)propenoic, *trans*-3-(3-furyl)propenoic and *trans*-3-(2-thienyl)propenoic acids were obtained from Aldrich. They were recrystallized from light petroleum (50–70 °C) or aq. ethanol twice before use.



I

X = 2-O; 2-S; 2-Se; 3-O; 3-S; 2-NH; 2-NMe

II

$n$ = 1: X = 2-O; 2-S; 3-O; 3-S
$n$ = 2: X = 2-O; 2-S; 3-O; 3-S
$n$ = 3: X = 2-S

III

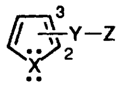
X = 2-O; 2-S; 3-O

**Fig. 1** Five-membered heteroaryl-carboxylic acids **I**, -alkanoic acids **II** and -*trans*-propenoic acids **III**

Selenophene-2-carboxylic acid was prepared by oxidizing selenophene-2-carboxaldehyde with $Ag_2O$; the aldehyde was, in turn, obtained by a Vilsmeyer formylation of selenophene (Aldrich).[20] Overall yield 80%, m.p. 124 °C (aq. ethanol); $\nu_{CO}(CHCl_3)$ 1679 cm$^{-1}$; $\delta_H(CDCl_3)$ 8.34 (5-H, dd, $J_{4,5}$ 5.52, $J_{3,5}$ 1.19), 8.15 (3-H, dd, $J_{3,5}$ 1.19, $J_{3,4}$ 3.93) and 7.40 (4-H, dd, $J_{3,4}$ 3.93, $J_{4,5}$ 5.52).

2-Furyl-, 3-furyl- and 2-thienyl-propanoic acids were prepared by catalytic hydrogenation of the corresponding *trans*-propenoic acids. The appropriate propenoic acid (4 g) was dissolved in 50 cm$^3$ of aq. NaOH (2 g) and Pd/C 10% (0.55 g). Hydrogen was then passed for 4–5 h through the magnetically stirred solution maintained at 55 °C. The solution was then filtered and acidified with 15% HCl (pH 2.5). The propanoic acid was extracted with $Et_2O$ and the organic solution was

**Table 1** Spectroscopic characteristics of furyl- and thienyl-alkanoic acids and of some parent compounds



| | | | δ($CDCl_3$) | | | | | | $M/Z$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| X | Y | Z | 2-H | 3-H | 4-H | 5-H | Y | $\nu_{C=O}/cm^{-1}$ | $M^+$ | Base peak |
| O | 2-$CH_2$ | $CO_2H$ | — | 6.35 | 6.26 | 7.38 | 3.74 | 1720.7 | 126 | 81[a] |
| S | 2-$CH_2$ | $CO_2H$ | — | 6.98 | 6.98 | 7.24 | 3.89 | 1717.3 | 142 | 97[b] |
| O | 3-$CH_2$ | $CO_2H$ | 7.40 | — | 6.40 | 7.40 | 3.53 | 1716.7 | 126 | 81[a] |
| S | 3-$CH_2$ | $CO_2H$ | 7.18 | — | 7.05 | 7.31 | 3.70 | 1714.7 | 142 | 97[b] |
| O | 2-$CH_2CH_2$ | $CO_2H$ | — | 6.05 | 6.29 | 7.32 | 2.99/2.72 | 1714.2 | 140 | 81[a] |
| S | 2-$CH_2CH_2$ | $CO_2H$ | — | 6.85 | 6.93 | 7.14 | 3.18/2.76 | 1712.8 | 156 | 97[b] |
| O | 3-$CH_2CH_2$ | $CO_2H$ | 7.27 | — | 6.29 | 7.36 | 2.78/2.63 | 1713.5 | 140 | 81[a] |
| S | 3-$CH_2CH_2$ | $CO_2H$ | 7.00 | — | 6.96 | 7.25 | 2.99/2.70 | 1712.8 | 156 | 97[b] |
| S | 2-$CH_2CH_2CH_2$ | $CO_2H$ | — | 6.80 | 6.92 | 7.13 | 2.90/2.42/2.02 | 1710.3 | 170 | 97[b] |
| O | 2-$CH_2$ | Cl | — | 8.25 | 6.25 | 7.30 | 4.48 | — | 116 | 81[a] |
| O | 3-$CH_2$ | Cl | 7.41 | — | 6.46 | 7.46 | 4.49 | — | 116 | 81[a] |
| S | 3-$CH_2CH_2$ | Cl | 7.08 | — | 6.99 | 7.29 | 3.72/3.11 | — | 146 | 97[b] |
| O | 2-$CH_2$ | CN | — | 6.34 | 6.37 | 7.41 | 3.78 | — | 107 | 52[c] |
| O | 3-$CH_2$ | CN | 7.44 | — | 6.40 | 7.46 | 3.52 | — | 107 | 52[c] |
| S | 3-$CH_2CH_2$ | CN | 7.04 | — | 6.95 | 7.25 | 3.00/2.61 | — | 137 | 97[b] |

[a] Pyrylium ion. [b] Thiopyrylium ion. [c] $C_4H_4^+$.

dehydrated with anhydrous $Na_2SO_4$ and filtered. The product obtained after evaporation of $Et_2O$ was crystallized from light petroleum (30–50 °C): 3-(2-furyl)propanoic acid, yield 65%, m.p. 57 °C;[21,22] 3-(3-furyl)propanoic acid, yield 75%, m.p. 66–67 °C;[23] and 3-(2-thienyl)propanoic acid, yield 75%, m.p. 50 °C.[24,25]

2-Furylethanoic, 3-furylethanoic and 3-(2-thienyl)propanoic acids were prepared by alkaline hydrolysis of the corresponding nitriles,[26] which were obtained from the chlorides, that were, in turn, prepared from the 2-furyl-, 3-furyl- and 2-thienyl-methanol (Aldrich). The alcohols (10–15 g) were dissolved in a solution containing anhydrous $Et_2O$ (25 $cm^3$) and pyridine (10 $cm^3$). After cooling (−10 °C), thionyl chloride (10–15 g) was slowly added. The ether solution was evaporated and the residue was distilled under reduced pressure: 2-furylchloromethane, yield 60%, b.p. 23 °C (0.3 mmHg);[27] 3-furylchloromethane, yield 60%, b.p. 20 °C (0.3 mmHg);[28,29] 3-thienylchloroethane, yield 90%, b.p. 80 °C (1 mmHg).[30] The chlorides (5–7 g) together with KCN (5 g) were dissolved in dimethylsulfoxide (40 $cm^3$) and refluxed for 3 h. The reaction mixture was poured into cold water, extracted with $Et_2O$, dehydrated with anhydrous $Na_2SO_4$, filtered off and evaporated. The residue was then distilled under reduced pressure: 2-furylethanenitrile, yield 50%, b.p. 37 °C (0.4 mmHg);[27] 3-furylethanenitrile, yield 60%, b.p. 46 °C (0.4 mmHg);[28,29] 3-thienylpropanenitrile, yield 60%, b.p. 74–75 °C (0.5 mmHg).[31] The nitriles (4–5 g) were dissolved in 50 $cm^3$ of aq. KOH (6–7 g) and refluxed for 4–5 h. The reaction mixture was decolourised with carbon, filtered and cooled to 0 °C. An $Et_2O$ solution (100 $cm^3$), containing $H_2O$ (10 $cm^3$) and $H_2SO_4$ (96%, 8 g), was then added. The organic layer was separated, dehydrated and evaporated to dryness. The residue was crystallized from light petroleum (50–70 °C): 2-furylethanoic acid, yield 95%, m.p. 71–73 °C;[32] 3-furylethanoic acid, yield 95%, m.p. 66–69 °C;[28,33] 3-(3-thienyl)propanoic acid, yield 70%, m.p. 60–62 °C.[23] The $^1H$ NMR data in $CDCl_3$, CO stretching frequencies in $CHCl_3$ and some mass spectra data of the above chlorides, nitriles and carboxylic acids are reported in Table 1.

*Potentiometric Measurements.*—The potentiometric measurements were carried out by means of four fully automated sets of apparatus. These made use of Metrohm equipment (meter, E 654; combined glass electrode, EA 125) and were controlled by two IBM PCs. All measurements were carried out at 25.0 ± 0.1 °C using thermostatted cells. The solutions were magnetically stirred and kept in an atmosphere of $CO_2$- and $O_2$-free nitrogen, which was bubbled through 0.10 mol $dm^{-3}$ $KNO_3$ solutions. The ionic strength was maintained at 0.10 mol $dm^{-3}$ ($KNO_3$). Values of $E°$, $E_j$, and Nernstian slope of the electrode system were determined by titrating $HNO_3$ with $CO_2$-free KOH standard solutions. To avoid systematic errors and check for reproducibility, experiments were run simultaneously in at least two of the four different sets of potentiometric apparatus. Experimental details for the potentiometric measurements are given in Table 2.

*Calorimetric Measurements.*—The calorimetric measurements were performed at 25.000 ± 0.001 °C using a Tronac 450 isoperibolic calorimeter, equipped with a 25 $cm^3$ titration Dewar. Solutions of the ligand at pH *ca.* 5–6 were titrated with standard $HNO_3$, to minimize water formation, according to a procedure already described.[34] Details of the calorimetric experiments are given in Table 3. The titration data, corrected for all non-chemical energy terms, determined in separate experiments, were refined simultaneously to obtain the final $\Delta H°$ values.

*Calculations.*—Calculations concerning the calibration of the electrode system ($E°$, slope and $E_j$), were performed by the least-squares computer program ACBA,[35] that refines the parameters of an acid–base titration by using a non-linear least-squares method minimizing the function $U = \Sigma(V_{\text{exptl},i} - V_{\text{calc},i})$ where $V_i$ is the volume of the titrant added at the $i$th point. The potentiometric data concerning ligand purities and protonation constants were handled both by ACBA[35] and SUPERQUAD,[36] that refines the error square sum based on measured electrode potentials. The enthalpies of formation were computed by means of the least-squares computer program DOEC,[37] which minimizes the function $U = \Sigma(Q_{\text{calc},i} - Q_{\text{exptl},i})^2$, where $Q_i$ is the heat of reaction at the $i$-th point. Other details were as previously described.[38]

*Spectroscopic Measurements.*—The IR spectra were recorded in $CHCl_3$ solutions using a Perkin–Elmer 1600 FT IR spectrophotometer. The $^1H$ NMR spectra were obtained in $CDCl_3$ solutions by a Varian Gemini 300 spectrometer, using

**Table 2** Experimental conditions for the potentiometric measurements of protonation in five-membered heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates in aqueous solution at 25 °C; $I = 0.10$ mol dm$^{-3}$ ($KNO_3$)

| No. | Ligand (Acid) | $C^0_L$/mmol dm$^{-3}$ | Titrant (KOH)/mmol dm$^{-3}$ | pH | No. of points |
|---|---|---|---|---|---|
| 1 | 2-Furoic | 4.7–4.9 | 84.4–99.4 | 2.5–5.5 | 211 |
| 2 | 2-Thenoic | 4.0–7.0 | 85.2–99.7 | 2.6–5.2 | 271 |
| 3 | Selenophene-2-carboxylic | 1.5–7.8 | 99.3–100.2 | 2.8–4.4 | 119 |
| 4 | 3-Furoic | 5.0–8.0 | 84.4–99.1 | 2.5–5.0 | 100 |
| 5 | 3-Thenoic | 5.5–6.5 | 86.0–99.7 | 2.5–6.5 | 182 |
| 6 | Pyrrole-2-carboxylic | 4.0–5.3 | 84.4–99.4 | 2.5–6.0 | 184 |
| 7 | *N*-Methylpyrrole-2-carboxylic | 2.5–5.5 | 84.4–99.4 | 2.5–5.8 | 165 |
| 8 | 2-Furylethanoic | 6.0–6.4 | 99.7 | 2.8–4.5 | 110 |
| 9 | 2-Thienylethanoic | 5.0–5.5 | 99.4–99.7 | 3.2–4.9 | 159 |
| 10 | 3-Furylethanoic | 5.8–6.9 | 99.7–100.2 | 2.8–4.5 | 105 |
| 11 | 3-Thienylethanoic | 5.0–5.5 | 85.2–99.7 | 2.5–5.6 | 164 |
| 12 | 3-(2-Furyl)propanoic | 5.1–5.3 | 100.0–100.7 | 3.4–5.0 | 67 |
| 13 | 3-(2-Thienyl)propanoic | 5.1–5.8 | 99.7–100.1 | 2.9–5.4 | 114 |
| 14 | 3-(3-Furyl)propanoic | 5.5–6.5 | 100.7 | 3.0–5.3 | 133 |
| 15 | 3-(3-Thienyl)propanoic | 4.8–5.6 | 99.7 | 2.9–5.5 | 139 |
| 16 | 4-(2-Thienyl)butanoic | 2.6–5.4 | 100.0–100.1 | 3.6–5.0 | 61 |
| 17 | *trans*-3-(2-Furyl)propenoic | 1.5–3.0 | 84.4–99.1 | 2.7–5.2 | 211 |
| 18 | *trans*-3-(2-Thienyl)propenoic | 2.2–3.3 | 85.8–100.3 | 3.6–5.1 | 194 |
| 19 | *trans*-3-(3-Furyl)propenoic | 4.7–5.8 | 99.7–100.2 | 2.8–5.3 | 95 |

**Table 3** Experimental conditions for the calorimetric measurements of protonation in five-membered heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates in aqueous solution at 25 °C; $I = 0.10$ mol dm$^{-3}$ ($KNO_3$)

| No. | Ligand (Acid) | $C^0_L$/mmol dm$^{-3}$ | Titrant ($HNO_3$)/mmol dm$^{-3}$ | pH | No. of points |
|---|---|---|---|---|---|
| 1 | 2-Furoic | 8.5–9.5 | 400.0 | 3.1–4.7 | 280 |
| 2 | 2-Thenoic | 9.0–10.0 | 400.0 | 2.5–5.2 | 119 |
| 3 | Selenophene-2-carboxylic | 4.7–5.5 | 201.4 | 2.5–5.2 | 20 |
| 4 | 3-Furoic | 8.0–10.0 | 400.0 | 2.7–5.9 | 75 |
| 5 | 3-Thenoic | 8.5–9.5 | 400.0 | 2.5–6.5 | 67 |
| 6 | Pyrrole-2-carboxylic | 2.0–13.0 | 400.0 | 2.5–6.0 | 159 |
| 7 | *N*-Methylpyrrole-2-carboxylic | 9.0–9.9 | 400.0 | 2.5–6.0 | 147 |
| 8 | 2-Furylethanoic | 7.0–8.0 | 201.4 | 2.6–5.0 | 20 |
| 9 | 2-Thienylethanoic | 9.0–10.5 | 400.0 | 3.2–5.8 | 62 |
| 10 | 3-Furylethanoic | 7.6–9.8 | 201.4–400.0 | 2.6–5.4 | 193 |
| 11 | 3-Thienylethanoic | 9.5–10.5 | 400.0 | 2.5–5.6 | 60 |
| 12 | 3-(2-Furyl)propanoic | 7.5–8.5 | 201.4 | 2.4–5.2 | 22 |
| 13 | 3-(2-Thienyl)propanoic | 7.0–8.0 | 806.5 | 2.5–4.0 | 25 |
| 14 | 3-(3-Furyl)propanoic | 7.0–8.0 | 201.4 | 2.5–5.2 | 20 |
| 15 | 3-(3-Thienyl)propanoic | 6.5–7.5 | 201.4 | 2.5–5.5 | 26 |
| 16 | 4-(2-Thienyl)butanoic | 4.9–5.4 | 201.4 | 2.5–5.5 | 21 |
| 17 | *trans*-3-(2-Furyl)propenoic | 7.0–10.0 | 402.1 | 3.7–6.2 | 160 |
| 18 | *trans*-3-(2-Thienyl)propenoic | 2.4–2.6 | 400.0 | 3.6–5.1 | 44 |
| 19 | *trans*-3-(3-Furyl)propenoic | 8.0–9.0 | 806.5 | 2.5–4.5 | 40 |

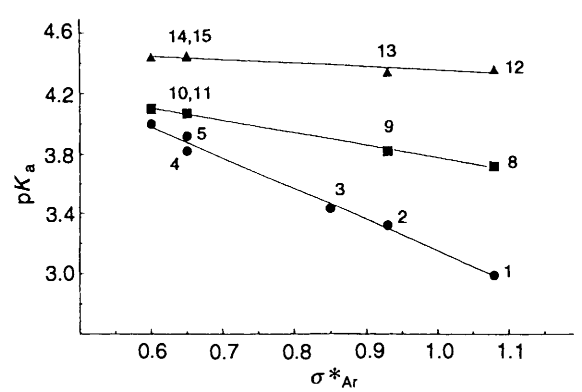


Fig. 2 Plots of p$K_a$ values of heteroaryl-carboxylic (●), -ethanoic (■) and propanoic (▲) acids *versus* the $\sigma^*$ constants of heteroaromatic rings. Key for numbers is that of Table 4. The p$K_a$ values of the corresponding benzene derivatives ($\sigma^*_{phenyl} = 0.60$)[41] are taken from refs. 42 and 43.

$Me_4Si$ as internal standard. Mass spectra were obtained by a Finnigan MAT 80 spectrometer at 70 eV.

## Results and Discussion

The protonation constants of heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates, as well as $\Delta G^\circ$, $\Delta H^\circ$ and $\Delta S^\circ$ values, are listed in Table 4. The p$K$ values of 2-furoic and 2-thenoic acids are virtually coincident with those of literature measured in the same experimental conditions.[10,39] No comparison is possible for the remaining ligands because of either lack of data or non-homogeneous experimental conditions. The log $K$ values cover a fairly wide range (2.99–4.54) to allow reliable correlations. The acidity of carboxylic acids 1–5 (Table 4) follows the order 2-furoic > 2-thenoic > selenophene-2-carboxylic > 3-furoic > 3-thenoic, as predicted on the basis of electronegativities and the position of the heteroatoms. Such a sequence agrees with the polarity of the heteroaryl ring systems, expressed by Taft's $\sigma^*$ constants[3,40] (Fig. 2). The log $K$ values of ligands 6 and 7 are consistent with the predominance of electron-releasing effects of 2-pyrrolyl and *N*-methyl-2-pyrrolyl groups, as supported by the C=O bond stretching frequency of the carboxylic group (1672 cm$^{-1}$), which is lower than that of 2-furoic and 2-thenoic acids (1699 and 1682 cm$^{-1}$, respectively).

A similar acidity trend is also found for the ligands 8–16,

**Table 4** Equilibrium constants (log *K*) and thermodynamic parameters for protonation of five-membered heteroaryl-carboxylates, -alkanoates and -*trans*-propenoates in aqueous solution at 25 °C; $I$ = 0.10 mol dm$^{-3}$ ($KNO_3$). The values in parentheses represent three times the standard deviation.

| No. | Ligand (Acid) | log $K$ | $-\Delta G°$/kcal mol$^{-1}$ | $\Delta H°$/kcal mol$^{-1}$ | $\Delta S°$/cal mol$^{-1}$ K$^{-1}$ |
|---|---|---|---|---|---|
| 1 | 2-Furoic | 2.99(1) | 4.08(1) | 1.02(3) | 17.1(1) |
| 2 | 2-Thenoic | 3.32(1) | 4.53(1) | 0.45(3) | 16.7(1) |
| 3 | Selenophene-2-carboxylic | 3.43(1) | 4.68(1) | 0.25(1) | 16.5(3) |
| 4 | 3-Furoic | 3.82(1) | 5.21(1) | −0.03(2) | 17.4(1) |
| 5 | 3-Thenoic | 3.92(3) | 5.34(4) | −0.10(2) | 17.6(1) |
| 6 | Pyrrole-2-carboxylic | 4.22(1) | 5.75(1) | −0.66(2) | 17.1(1) |
| 7 | *N*-Methylpyrrole-2-carboxylic | 4.51(1) | 6.14(1) | −0.49(2) | 19.0(1) |
| 8 | 2-Furylethanoic | 3.72(1) | 5.08(1) | 0.62(1) | 19.1(2) |
| 9 | 2-Thienylethanoic | 3.82(1) | 5.21(1) | 0.45(1) | 19.0(2) |
| 10 | 3-Furylethanoic | 4.07(1) | 5.54(1) | 0.43(1) | 20.0(1) |
| 11 | 3-Thienylethanoic | 4.07(1) | 5.55(1) | 0.52(1) | 20.4(1) |
| 12 | 3-(2-Furyl)propanoic | 4.36(1) | 5.94(1) | 0.25(1) | 20.8(1) |
| 13 | 3-(2-Thienyl)propanoic | 4.34(1) | 5.92(1) | 0.25(1) | 20.7(1) |
| 14 | 3-(3-Furyl)propanoic | 4.44(1) | 6.05(1) | 0.33(1) | 21.4(2) |
| 15 | 3-(3-Thienyl)propanoic | 4.45(1) | 6.07(1) | 0.45(1) | 21.9(2) |
| 16 | 4-(2-Thienyl)butanoic | 4.54(1) | 6.19(2) | 0.18(1) | 21.4(1) |
| 17 | *trans*-3-(2-Furyl)propenoic | 4.29(1) | 5.84(1) | −0.76(2) | 17.1(1) |
| 18 | *trans*-3-(2-Thienyl)propenoic | 4.25(1) | 5.80(1) | −0.77(1) | 16.9(2) |
| 19 | *trans*-3-(3-Furyl)propenoic | 4.31(1) | 5.87(1) | −0.70(2) | 17.4(1) |

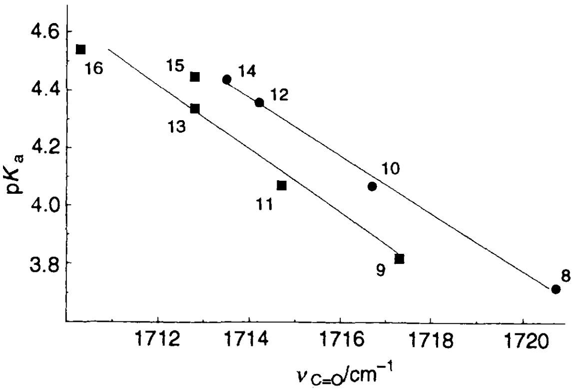


**Fig. 3** Plots of p$K_a$ values of furyl- (●) and thienyl-alkanoic (■) acids *versus* the IR frequency of C=O stretching in the carboxylic group. Key for numbers is that of Table 4.

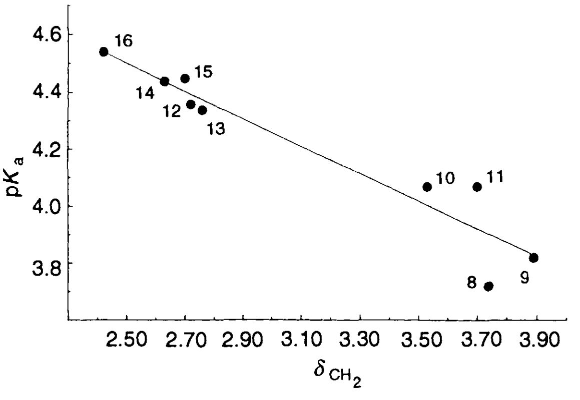


**Fig. 4** Plot of p$K_a$ values of heteroarylalkanoic acids *versus* the chemical shift of $CH_2$ protons bonded to carboxylic group. Key for numbers is that of Table 4.

where the presence of a saturated spacer renders possible the transmission of polar effects only, by chain induction from the heterocycles. Fig. 2 shows that also for these ligands the p*K*s correlate linearly with $\sigma^*$ values of heterocycles. The slopes of the three straight lines markedly decrease (in absolute value) on going from the ligands with no spacer ($\rho^* = -1.98$) to the ones with a single ($\rho^* = -0.82$) or two ($\rho^* = -0.22$) methylenic spacers; data for benzene derivatives have also been included in this diagram. Additional evidence for the predominance of polar effects is provided by the correlations of the p*K* values with IR C=O stretching frequencies (Fig. 3) and $^1$H NMR chemical shifts of the methylenic protons adjacent to the carboxylic group (Fig. 4).

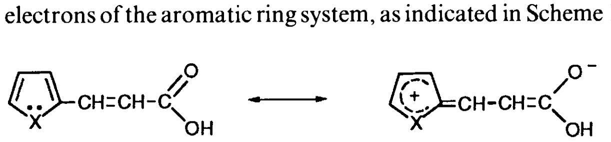
No significant differences were found within the *trans*-propenoic acids (17–19), which all have the same acidity as the analogous benzene derivative, *i.e.* cinnamic acid (p*K* = 4.27),[44] for reasons that will be discussed below.

The enthalpic and entropic changes (Table 4) are typical of a 'hard–hard' interaction,[45] for which a negligible enthalpic and a favourable entropic contribution are expected. In fact for the reaction between a 'hard' donor and a 'hard' acceptor, strong bonds between these and the water molecules of their hydration sphere have first to be broken. This requires energy which is not completely regained by formation of the predominantly electrostatic proton to carboxylate oxygen bond. Thus, the net reaction tends to be endothermic. On the other hand, the liberation of the water molecules of the hydration shells implies a large entropic gain, which constitutes the driving force of the reaction between hard particles. Accordingly, for instance, the protonation of ethanoate at 25 °C results in a $\Delta H°$ value of −0.19 kcal mol$^{-1}$ and a $\Delta S°$ value of 20.2 cal mol$^{-1}$ deg$^{-1}$.[46]

The $\Delta S°$ values for the protonation of 2-furoate, 2-thenoate and selenophene-2-carboxylate anions are essentially the same. The different acidities of the three ligands result from a different enthalpic contribution, which becomes less unfavourable on going from 2-furoic to selenophene-2-carboxylic acid, thus supporting the idea that the different electronegativity of the heteroatom is the predominant factor. In fact, the more endothermic contribution, concerning the protonation of 2-furoate, is to be ascribed to the presence of the more electronegative oxygen heteroatom, which renders the carboxylate negative charge 'less available' for protonation than is in 2-thenoate or in selenophene-2-carboxylate. This interpretation is strengthened by the $\Delta H°$ and $\Delta S°$ values pertinent to 3-furoic and 3-thenoic acid; in fact, in this case, the larger distance of the electronegative heteroatoms from the protonation site exerts a less pronounced influence on the negative charge, thus leading to $\Delta H°$ values of comparable magnitude. The lower acidity of the two pyrrolic derivatives, if compared to the furan, thiophene and selenophene analogues, mainly arises from differences in the enthalpic contributions. The presence in the pyrrolic derivatives of electron-releasing effects causes the charge of the carboxylate group to be 'more available' than it is in the furan, thiophene and selenophene derivatives, thus resulting in favourable $\Delta H°$ contributions. If one compares the two pyrrolic derivatives with one another, it cannot be excluded that the more favourable enthalpic contribution of pyrrole-2-carboxylic acid ($-0.66$ *vs.* $-0.49$ kcal mol$^{-1}$*) is due to the presence, in the unmethylated compound, of a hydrogen bond between the OH of the carboxylic group and the nitrogen of the pyrrole ring.

The data concerning the furyl- and thienyl-alkanoic acids (8–16) show that also in these cases the different acidities are to be ascribed to different enthalpic contributions, arising from the different electronegativity of the heteroatoms. The differences tend to disappear as the distance of the heteroatom from the basic centre increases. When the spacer becomes large enough to minimize the influence of the heterocyclic ring [*e.g.* 4-(2-thienyl)butanoic acid], the thermodynamic parameters tend to those of ethanoic acid.[46]

The acidity of *trans*-furyl- and -thienyl-propenoic acids (17–19) is independent of both the position of the carboxylic group and the type of heteroatom. The lesser entropic contribution shown by the propenoic derivatives, with respect to the propanoic ones, may be ascribed to the possible delocalization of π electrons of the aromatic ring system, as indicated in Scheme 1.



**Scheme 1**

The contribution of resonance polar forms renders the propenoic acids more rigid than the analogous propanoic acids, where such a delocalization cannot take place. The lower entropic contributions observed for the propenoic derivatives are consistent with this interpretation. Moreover, the stabilization of the acidic forms of the propenoic systems is also consistent with the more favourable enthalpic differences.

It is noteworthy that these acids (17–19) have thermodynamic parameters significantly different from those of the analogous saturated acids (12–14), though having roughly the same p*K* values. p*K* values of the same magnitude originate from substantially different enthalpic and entropic contributions. In fact, whilst the protonation of propenoates is enthalpically more favoured [$\Delta(\Delta H^\circ)$ *ca.* 1 kcal mol$^{-1}$] than that of the corresponding propanoate derivatives, the protonation of the latter ones is entropically more favoured [$\Delta(T\Delta S^\circ)$ *ca.* 1 kcal mol$^{-1}$].

This clearly shows that a discussion of data based on log *K* differences only may lead to erroneous conclusions, if one wants to single out the structural and/or electronic factors determining these differences. In fact log *K*s, which result from the combination of both enthalpy and entropy values, may 'conceal' subtle differences.[47]

It must also be stressed that a direct calorimetric determination of the enthalpy of reaction is to be preferred to an evaluation that makes use of van't Hoff's equation. For instance, the first complexation step of $UO_2^{2+}$ with the fluoride ion, determined by the van't Hoff equation, turned out to be exothermic.[48] A reinvestigation of the same system, by direct calorimetry, demonstrated that the reaction is instead endothermic and can correctly be classified as a classical 'hard–hard' interaction.[45]

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* 1 cal = 4.184 J.

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