^{1}H Nuclear Magnetic Resonance Spectra of Some 3- and 5-Substituted Thiophen-2-carboxamides †

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The ^{1}H n.m.r. spectra of some 3- and 5-substituted thiophen-2-carboxamides in $CDCl_3$ are reported. 3-Substituted thiophen-2-carboxamides show intramolecular hydrogen bonding between the N–H proton and the 3-substituent and also an intermolecular hydrogen bond, except for the 3-methyl derivative, which exhibits only intermolecular hydrogen bonding. 5-Substituted thiophen-2-carboxamides exhibit intermolecular hydrogen bonding. The chemical shifts for the 4-protons of 3-substituted thiophen-2-carboxamides correlate with σ_p (r = 0.962; ρ = 1.39). Correlation for the 4-protons of the 5-substituted amides is poor.

The activation energies of rotation of the 3-substituted amides are higher than those of the corresponding 5-substituted derivatives. For 5-substituted amides the activation energies of rotation depend on the electronic nature of the substituents, and $\Delta G^\ddagger (T_c)/\sigma_p^+$ shows a linear relationship (r = 0.954; ρ = 1.77).

Our interest in the amide group arises from its presence in polypeptides, and the fact that the partial double bond character of the N–C amide bond permits rotational isomerism about this bond.[1–3]

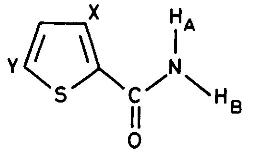
In the course of our research on the application of linear free energy relationships to five-membered ring derivatives we have shown that *ortho*-correlations can be obtained.[4–10] Moreover, we have studied recently the protonation of some heterocyclic carboxamides.[11–13] Here we report the ^{1}H n.m.r. spectra of some 3- and 5-substituted thiophen-2-carboxamides (1) in $CDCl_3$ solution.

In these amides hindered rotation about thienyl–CO and C–N bonds is considered. That 2-thienylcarbonyl compounds exist exclusively in the *s-trans* conformation is supported by n.m.r. studies,[14–17] *X*-ray analysis,[14,18] and dipole moment measurements.[18–20] The aim of this work was to investigate the effect of a substituent in the 3- or 5-position of the thiophen ring on the rotational barrier about the C–N bond.

Results and Discussion

The two hydrogen atoms of the amino group in the amides (1) give separate peaks which coalesce on raising the temperature (Table). The values of the chemical shifts have been measured at different concentrations, below the coalescence temperature, and extrapolated to infinite dilution.

3-Substituted thiophen-2-carboxamides, except the 3-methyl derivative, show the N–H$_A$ signal to be concentration-independent and at low field; that of N–H$_B$ is concentration-dependent and at higher field (Table). The low field shift of N–H$_A$ in the 3-substituted amides indicates that these protons are involved in intramolecular hydrogen bonding with the 3-substituent.[21,22] In the case of N–H$_B$ intermolecular hydrogen bonding occurs, with self-association of the amides (1) and formation of a cyclic dimer.[3] 3-Methylthiophen-2-carboxamide shows the N–H$_A$ signal at higher field and concentration-independent; that of N–H$_B$ is concentration-dependent and at lower field, as a result of the carbonyl group anisotropic effect,[2] indicating that it is involved in intermolecular hydrogen bonding with self-association in a cyclic dimer.



(1)

X = OMe, SMe, Me, F, Br, or I, Y = H
X = H, Y = OMe, SMe, Me, Cl, or Br

5-Substituted thiophen-2-carboxamides exhibit intermolecular hydrogen bonding: they show the two N–H signals to be concentration-dependent, with that of N–H$_B$ at lower field owing to the carbonyl group anisotropic effect.

In 3-substituted thiophen-2-carboxamides the chemical shifts of 4-H and 5-H are influenced by the substituents. A plot of $\delta_{4\text{-H}}$ against σ_p gives a linear relationship ($\delta_{4\text{-H}} = 7.09 + 1.39\sigma_p$; $r = 0.962$). Correlation with σ_p is better than that with σ_p^+ and the ρ value is similar to that found for benzamides,[23] acetanilides, and phenylureas.[24] No correlation is shown by the 5-H, N–H$_A$, and N–H$_B$ signals. For 5-substituted thiophen-2-carboxamides the chemical shifts of 3-H and 4-H are influenced by the substituents. A plot of $\delta_{4\text{-H}}$ against σ_p gives a poor linear relationship ($\delta_{4\text{-H}} = 6.78 + 1.18\sigma_p$; $r = 0.814$). No correlation was found for 3-H, N–H$_A$, and N–H$_B$.

The existence of partial C–N double bond character in amides results in rotational barriers about this bond, which are intermediate between those for a pure single bond and a pure double bond. The magnitudes of these barriers have been calculated by the Gutowsky–Holm method,[25] and the values are reported in the Table.

In the 3-substituted amides the lowest activation energies for rotation are found for the 3-methyl and 3-methylthio compounds. 3-Methoxythiophen-2-carboxamide shows the highest value, owing to the strong hydrogen bond between the oxygen atom of the methoxy group and N–H$_A$.[26,27] The activation energies for rotation for the 3-substituted amides give no correlation with σ_p, σ^*, or E_s.

For 5-substituted thiophen-2-carboxamides the activation energies for rotation depend on the electronic nature of the substituents. Although the activation energies for rotation are not referred to the same temperature but are calculated at the

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Chemical shifts (p.p.m.) for N–H, 3-H, 4-H, and 5-H, coupling constants of ring protons, coalescence temperatures, and energy of rotation about C–N bond of 3- and 5-substituted thiophen-2-carboxamides (1) in $CDCl_3$

Substituent	N–H_A	N–H_B	3-H	4-H	5-H	Others	$J_{3,4}$/Hz	$J_{4,5}$/Hz	T_c/K [a]	$\Delta G^‡$ [b] kcal mol^{-1}
Y = H										
X = OMe	7.04	5.74		6.72 (d)	7.27 (d)	3.91		5.9	318	15.2
SMe	7.75	6.16		7.02 (d)	7.40 (d)	2.52		5.2	262	12.3
Me	5.94	6.25		6.82 (d)	7.18 (d)	2.48		4.8	258	13.0
F	6.37	5.94		7.32 (d)	6.77 (d)			5.8	290	14.4
Br	6.85	6.17		7.38 (d)	6.95 (d)			5.6	298	14.6
I	6.87	5.87		7.31 (d)	7.04 (d)			5.0	285	13.7
X = H										
Y = OMe	6.00	6.12	7.20 (d)	6.21 (d)		3.93	4.0		218	11.3
SMe	6.06	6.19	7.40 (d)	6.93 (d)		2.63	3.9		228	11.8
Me	6.10	6.35	7.40 (d)	6.80 (d)		2.46	3.6		252	12.7
Cl	5.71	5.93	7.35 (d)	6.95 (d)			4.4		254	12.9
Br	5.75	5.95	7.30 (d)	7.02 (d)			4.2		256	13.1

±1 K. [b] ±0.1 kcal mol^{-1}.

coalescence temperature, a plot of $\Delta G^‡(T_c)$ of 5-substituted amides against σ_p^+ shows a linear relationship [$\Delta G^‡(T_c) = 12.87 + 1.77\sigma_p^+$; $r = 0.954$]; the 2- and 5-positions are considered as *para*-like and for these σ_p^+ values are used. The correlation with σ_p^+ shows that significant conjugation between the 5-substituents and the amide carbonyl group occurs, as found for *NN*-dimethylbenzamides.[27,28]

The activation energies for rotation of 3-substituted amides are higher than those of the corresponding 5-substituted derivatives owing to the intramolecular hydrogen bonding between the 3-substituent and N–H_A. The 3- and 5-methylthiophen-2-carboxamides, where no intramolecular hydrogen bond is formed, show almost the same values of the activation energies for rotation.

Experimental

All amides are known and have been reported elsewhere.[7,29] ^{1}H N.m.r. spectra were recorded at 80 MHz with a Bruker WP-80 FT spectrometer equipped with variable temperature accessories. Temperatures are considered to be accurate to ±1 °C. All spectra were calibrated against Me_4Si as internal standard.

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