Acetal Formation from Formylthiophene-2-carboxylic Acids and Recalculation of σ_I and σ_R Substituent Constants of the Acetal Group by ^{13}C NMR Chemical Shifts

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A uv-visible, ^1H and ^{13}C nmr study has been carried out to show that 4-, **1**, and 5-formylthiophene-2-carboxylic acids, **2**, give acetals in methanol. The ms data have confirmed the acetal formation, which has been studied kinetically by the uv technique. The substituent chemical shifts induced on the carboxy carbon atom and on the endocyclic carbon atoms in the acetals formed from **1** and **2** and in the corresponding anions have been used to recalculate σ_I and σ_R values by means of a dual substituent parameter treatment of data.

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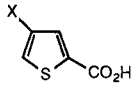
In the course of a ^{13}C nmr study of some 4- and 5-substituted thiophene-2-carboxylic acids perdeuteriomethanol [1] we observed that addition of solvent occurred in carbonyl substituted acids [2]. In fact, the ^{13}C nmr spectra showed a signal at *ca.* 101 ppm due to the sp^3-hybridised carbon atom of the "aldehyde group".

We now report a spectroscopic study of 4-, **1**, and 5-formyl-thiophene-2-carboxylic acids, **2**, showing that these compounds, when dissolved in methanol, easily give the corresponding acetals.



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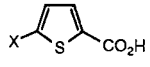


2

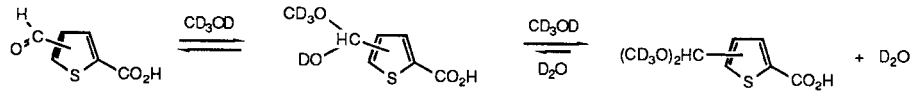
X = CHO

The ^1H nmr spectroscopy appeared a suitable technique for the elucidation of the structural variations observed (see data in Table). A freshly prepared methanolic solution of **1** gave three distinct bands with different areas at δ 9.90, 5.55 and 5.45 relative to the proton bonded at the exocyclic carbon atom of the substituent, X. Spectra recorded at various times showed that peak areas changed and an analysis of the integrated areas indicated that a multistep (consecutive) reaction takes place: the data were interpreted as due to formation of the hemiacetal and the acetal of compound **1** as shown in the Scheme. After *ca.* 7 hours the shape of the integrated areas suggested that in the reaction mixture at least 95% of acetal was present, so indicating a large shift of the equilibrium. The mass spectrum of the residue obtained after distillation of methanol at reduced pressure confirmed that **1** was wholly converted into the corresponding acetal (M^+ 208).

A slower analogous transformation was observed when compound **2** was dissolved in perdeuteriomethanol and the ^1H nmr spectra were determined at various times. The acetal structure of the transformation product was, as above, also confirmed by the mass spectrum (M^+ 208).

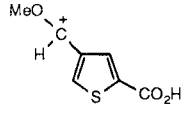
We attempted a kinetic study of the reaction of aldehydes with methanol by calculating the first-order reaction rate constants (*i.e.*, the rate of disappearance of the aldehydes) from the variation of the peak areas with the time but we did not obtain 'linear' kinetics. Since the reactions are acid-catalysed, the behaviour observed depends clearly on the fact that the electronic effects of the formyl, of the hemiacetal and of the acetal groups are different from each other and as a consequence the strength of the acids involved and the hydronium ion concentration change during the course of the reaction. In order to remove this complication the kinetic runs were repeated after addition of some trichloroacetic acid (a suitable strong acid) and the rates of disappearance of the aldehydes were followed by monitoring the carbonyl uv absorption. In this way excellent straight lines were obtained for the first-order pro-

Scheme



1-2 (1-2) **HA** (1-2) **A**

cess. The measured values of kinetic constants for a concentration of hydronium ion equal to unity [3] at 298 K are (0.860 ± 0.020) $M^{-1}s^{-1}$ for **1** and (6.29 ± 0.20) x 10^{-2} $M^{-1}s^{-1}$ for **2**, respectively. Compounds **1** and **2** show a lower reactivity with methanol than benzaldehyde (under the same experimental conditions k 1.74 $M^{-1}s^{-1}$) [4]. In fact, as expected for reactions with carbocationic intermediates, an electron-withdrawing substituent (particularly in a conjugated position) decreases the reaction rates. The different reactivity of **1** and **2** is due to the different stability of alkoxycarbonium ions **3** and **4** formed in the rate-determining step. As a matter of fact, ion **3** is more stable than ion **4**, which contains an electron-withdrawing group in a conjugated position.



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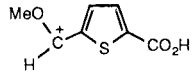

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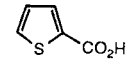
An analysis by uv spectroscopy of methanolic solutions of **1** and **2** performed at various times gave the following results. Freshly prepared solutions showed λ (nm) 232 (m) 247 (sh) with ε 17300 and 9500 for compound **1** and λ (nm) 285 (m) with ε 13900 for compound **2** [5]. After some hours or days, respectively, the spectra of the solutions gave the following different values: λ (nm) 245 (m) and 263 (sh) with ε 8300 and 5000 for compound **1** and λ (nm) 254 (m) and 263 (sh) with ε 12600 and 11400 for compound **2**. These spectroscopic shifts seem to indicate a reduced conjugation between X-substituent and the heterocyclic ring according to the change of hybridisation of the carbon atom of X.

Also the ^{13}C nmr spectra of acids **1** and **2** in perdeuteriomethanol revealed the transformation of the X-substituent. In order to measure the chemical shift values of compounds **1** and **2** in the acetal form we accumulated the scans only after the complete transformation. The chemical shift values of acetals of acids **1** and **2**, and of the anions $\mathbf{1}^-$ and $\mathbf{2}^-$ together with those of thiophene-2-carboxylic acid (**5**) are collected in the Table.



5

The substituent chemical shifts (SCSs) induced on the carboxy carbon atom in acetals formed from compounds **1** and **2** compared with those of the series previously examined [1] indicate that the acetal group produces a substituent effect similar to that exerted by alkyl or electron-donating (OMe and SMe) groups [1].

On the other hand, the acetal group is a substituent for

Table

^{13}C [a] and ^1H NMR Chemical Shifts (in ppm) Relative to TMS in Perdeuteriomethanol

^{13}C Chemical Shifts

Compound	C(2)	C(3)	C(4)	C(5)	CO_2H or CO_2^-	$CH(OCD_3)_2$
1A	136.04 (0.35)	133.41 (−1.17)	142.58 (13.69)	131.43 (−2.39)	165.11 (−0.23)	101.18
1^-A	145.25 (0.49)	129.69 (−1.10)	141.46 (13.45)	127.65 (−2.22)	169.97 (−0.37)	101.64
2A	135.71 (0.02)	134.30 (−0.28)	127.23 (−1.66)	150.67 (16.85)	165.34 (0.00)	101.11
2^-A	145.04 (0.28)	130.26 (−0.53)	126.54 (−1.47)	146.19 (16.32)	170.11 (−0.23)	101.59
5 [b]	135.69	134.58	128.89	133.82	165.34	
5^- [b]	144.76	130.79	128.01	129.87	170.34	

^1H Chemical Shifts

Compound	C(3)-H	C(4)-H	C(5)-H	CHO	$CH(OD)(OCD_3)$	$CH(OCD_3)_2$
1	8.10 (s)		8.60 (s)	9.90 (s)		
1HA	7.70 (s)		7.80 (s)		5.55 (s)	
1A	7.70 (s) [c]		7.70 (s) [c]			5.45 (s)
2	7.90 (s) [c]	7.90 (s) [c]		10.10 (s)		
2HA	7.70 (d) [d]	7.10 (d) [d]			5.75 (s)	
2A	7.70 (d) [d]	7.10 (d) [d]				5.65 (s)

[a] In parentheses the SCSs relative to the unsubstituted [**5** or $\mathbf{5}^-$] have been reported. [b] Data from ref [1]. [c] Two coincident protons. [d] $J_{C(3)\text{-}H,C(4)\text{-}H}$ = 4 Hz.

which the literature substituent constant values are scattered [6,7] (σ_I 0.18 and −0.02, σ_R 0.00 and −0.03). In order to recalculate the σ_I and σ_R values for this group we fitted the SCSs data collected for acetals of 4- and 5-formylthiophene-2-carboxylic acids and the corresponding anions in perdeuteriomethanol to the dual substituent parameter (DSP) linear free energy relationships (l.f.e.r.s) previously obtained for 4- and 5-substituted thiophene-2-carboxylic acid and the corresponding anions [1]. In several cases, in fact, σ-values have been determined by regression. The values obtained are of different reliability depending on the number of data and on their precision but anyway they represent the best method to weight the substituent effect.

The statistical method used to compute substituent constant values is that recommeded by Wold and Sjostrom [8]. In fact, at some moment in time, statistical values will be more precise than a remeasured value of a single series because the accumulation of data from several series is faster than a decrease of the error of measurement in a single series. Recently [9] σ_I and σ_R values for deuterium atom have been computed by the same statistical analysis using ^{13}C nmr data.

The substituent constants σ_I and σ_R for the acetal group have been calculated by quantitative statistical analysis using equation 1 [10].

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R + i \qquad (1)$$

The DSP l.f.e.r.s used by us [1] to separate inductive and resonance contributions of substituent effects on ^{13}C nmr chemical shifts can be accordingly used for our purpose. A correlation based on 8 individual carbon shifts relative to the most significant correlations ($R > 0.95$) obtained previously [1] gave the following results: $\sigma_I = 0.10 \pm 0.01$ and $\sigma_R = -0.13 \pm 0.01$, with a good multiple correlation coefficient ($R = 0.998$). It must be noticed that the σ_R value derived by this analysis is a hybrid out of the different $\sigma_{I,R}$ scales [11,12] currently used to establish the highest fit correlations between substituents and SCS data, changing the scale even for different carbon atoms in a single compound. Anyway, not too different results were obtained when the parameters σ_I and σ_R were deduced from correlations performed with homogeneous scales.

The σ_I value derived in this work well compares with the estimated literature value (σ_I 0.18) [5] and with that reported for the group $CH(OH)_2$ (σ_I 0.22) by Grob and Schlageter [13] in their study of dissociation of 4-substituted quinuclidinium perchlorates in water. On the other hand, σ_I 0.05 ÷ 0.1 values were reported for CH_2OR substituents [14]; the substitution of one hydrogen atom with the methoxy group in the acetal group scarcely affects the value found with our analysis.

It is usually accepted that the σ_R values of alkyls arise from their hyperconjugative effect which is dependent on the number of the hydrogen atoms bonded to the carbon atom of the substituent. Accordingly we have calculated a resonance constant for the acetal group (σ_R −0.13 ± 0.01) which falls among the lowest values reported for the methyl group (σ_R −0.11 ÷ −0.25). The value calculated by us is in the range of low resonance substituents as also shown by one of the literature values (σ_R = −0.03) [7].

EXPERIMENTAL

Spectroscopic Measurements.

The ^1H or ^{13}C nmr spectra were recorded on Varian 60A and FT80A spectrometers, respectively, in perdeuteriomethanol solutions with TMS as internal standard (data in Table). Experimental conditions for ^{13}C nmr spectra are reported in ref [1]. The uv-visible spectra were run on a Beckman DU-6 spectrophotometer.

Mass spectra were run on a Jeol-JMS-01SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and accelerating voltage of 10 KV.

Kinetic Measurements.

The kinetics were followed spectrophotometrically in methanol at 25 ± 0.1° in a thermostatted compartment. The concentration of the solutions of the compounds **1** and **2** was *ca.* 1.70 x 10^{-4} *M* while that of trichloroacetic acid ranged from 1 x 10^{-3} to 4 x 10^{-3} *M*. The apparent kinetic constants increase with increasing trichloroacetic acid concentration: the values reported in the text have been obtained by extrapolation at $[H^+]$ 1 *M*. Optical density measurements were made by monitoring the disappearance of the carbonyl uv absorption at the maximum [λ (nm) 232 and 285 for **1** and **2**, respectively].

Synthesis and Purification of Compounds.

Methanol was purified as previously described [14]. 4-, **1** and 5-formylthiophene-2-carboxylic acids, **2**, were prepared as reported in the reference quoted in [5].

Acknowledgements.

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REFERENCES AND NOTES

[1] R. Noto, L. Lamartina, C. Arnone and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 689 (1987).

[2] *para*-Formylfluorobenzene seems to show a simlilar behaviour. In fact, for this compound Taft and co-workers reported [see R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963)] that a fast reaction occurs in methanol, but they did not offer any interpretation of this. We suggest that the reaction involved could be the hemiacetal formation.

[3] Under the experimental conditions used the equilibrium of formation of **1-2**, **A** is largely shifted towards right. Moreover in the discussion of the results we only report a comparison among kinetic data measured at unity concentration of hydronium ion.

[4] T. S. Davis, P. D. Feil, D. G. Kubler and D. J. Wells, Jr., *J. Org. Chem.*, **40**, 1478 (1975) and references therein.

[5] The uv and visible spectra of compounds **1** and **2** in ethanol have been reported by Gronowitz [see S. Gronowitz, A. Biezais and B. Mathiasson, *Arkiv Kemi*, **21**, 256 (1963)] who found λ (nm) 233 (m) and 250 (sh) with ε 23000 and 8900 for **1** and λ (nm) 281 (m) with ε 13600 for **2**.

[6] O. Exner in "Correlation Analysis in Chemistry", N. B. Chapman and J. Shorter, eds, Plenum Press, New York and London, 1978, chapter 10.

[7] W. A. Sheppard, *Tetrahedron*, **27**, 945 (1971).
[8] S. Wold and M. Sjostrom, *CAOC Newsletter*, **2**, 26 (1981).
[9] H. Kunzer and S. Berger, *J. Am. Chem. Soc.*, **107**, 2804 (1985).
[10] As a matter of fact we used an "unconstrained" version (1) of the Taft equation, which allows one to estimate the standard deviations of the regression parameters (in this case the substituent constants). The true Taft equation [see S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973)] is:

$$SCS = \rho_I\sigma_I + \rho_R\sigma_R \qquad (2)$$

[11] See references quoted in 7.
[12] In principle the substituent considered is not able to give different σ_R values, therefore the use of different σ_R scales is allowed.
[13] C. A. Grob and M. G. Schlageter, *Helv. Chim. Acta*, **59**, 264 (1976).
[14] A. Weissberger, "Techniques of Organic Chemistry", 2nd Ed, Vol. 7, Interscience, New York, 1963, p 334.