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Carboxylic acid ionization constants by ^{19}F NMR spectroscopy

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ABSTRACT: The ^{19}F NMR spectra of 26 simple fluorinated carboxylic acids were measured in aqueous solutions of pH 0.3–10.0. Analysis of the fluorine chemical shift dependence on pH allowed the determination of ionization constants from the titration curves; the values agreed with known pK_a values. The acidity of a fluorinated bilirubin precursor was established using this method. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: ^{19}F NMR; fluorinated carboxylic acids; ionization constants; pK_a

INTRODUCTION

The natural yellow–orange pigment bilirubin is the end product of heme catabolism in mammals.[1] Bilirubin contains two propionic acid groups, and their ionization behavior is implicated in the pigment's hepatic transport, neurotoxicity, formation of gallstones and protein and lipid membrane binding.[2] In a recent investigation of the inter-relationship between altered acidity of synthetic bilirubin analogs and their solution properties, such as stereochemistry, polarity, solubility and excretion, we introduced substituents with a strong electron-withdrawing effect in the vicinity of the carboxylic acid groups.[3,4] Methoxy and methylthio substitution at the α-carbon of each propionic acid of bilirubin was expected to decrease the acid pK_a by 1 unit, but this did not significantly change the pigments' overall properties.[3] In contrast, α-fluoro substitution, which was expected to decrease the pK_a by more than 2 units (CH_3CO_2H, pK_a = 4.76; FCH_2CO_2H, pK_a = 2.58[5]) led to drastically altered properties.[4] Synthetic α,α′-difluoromesobilirubin-XIIIα is polar and water soluble, whereas natural bilirubin is relatively non-polar, lipophilic and completely insoluble in water. Water solubility was attributed to complete ionization of the acid groups at pH ≈ 7. Therefore, we sought to obtain an independent quantitative estimate of acidity of α,α′-difluoromesobilirubin-XIIIα and some of its precursors.

The presence of a fluorine atom, with a nuclear spin I = 1/2, the natural isotopic abundance of 100% and high receptivity (a measure of the ease of detecting a nucleus; ^{19}F is 0.83 of that of protons) offer an opportunity to use ^{19}F NMR spectroscopy for the examination of ionization equilibria. The chemical shift (δ_F) range of a ^{19}F NMR signal is intrinsically very wide, and therefore the fluorine nucleus is an excellent, highly sensitive probe of its environment. This fact was used more than 35 years ago for pK_a determinations of *p*-fluoroacetophenone (C–H acidity) and *p*-fluorobenzamide (N–H acidity),[7] and as recently as 1998 for subtle changes of δ_F arising from solvent-induced isotope shifts due to enrichment of water with H_2 ^{18}O.[8]

The literature provides a number of examples in which ^{19}F NMR spectroscopy was used to study the ionization of protonated amines containing fluorine. Such amines were designed to have pK_as in the physiologically important range (pH 6.5–8.0) and were used in the development and application of NMR indicators for non-invasive and accurate intracellular pH measurement.[9–12] To the best of our knowledge, there have been no systematic reports on titrations of simple carboxylic acids and determination of their pK_as using ^{19}F NMR spectroscopy. In this paper we report on the changes of ^{19}F NMR chemical shifts associated with the ionization of carboxylic acids in the (strongly) acidic pH range, show how such changes can be used to measure their pK_as and apply the method to the pK_a determination of a fluorinated bilirubin precursor (**1**).

RESULTS AND DISCUSSION

A series of carboxylic acids bearing a single fluorine reporter atom on an sp^3-or sp^2-hybridized carbon atom or trifluoromethyl group attached to an aliphatic or aromatic carbon atom were studied. The structures of the acids investigated are shown in Scheme 1.

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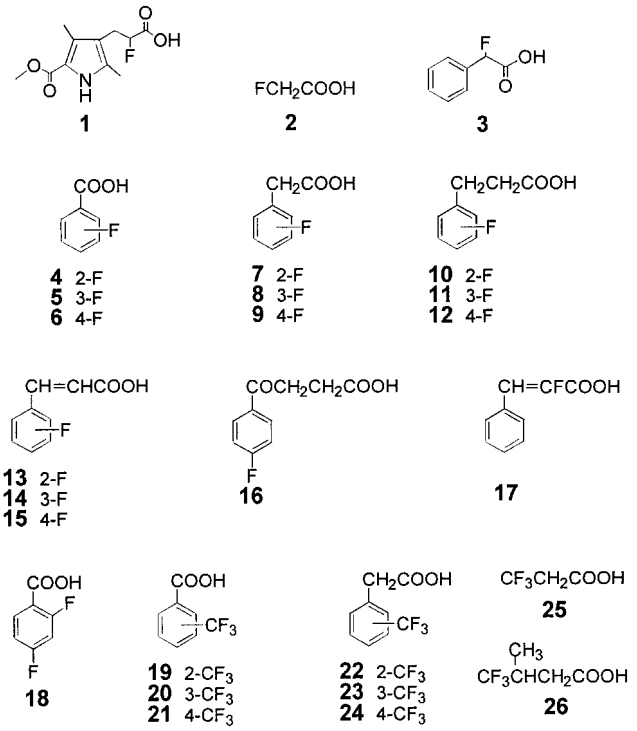

Scheme 1

Titration curves of all the fluorinated carboxylic acids **1–26** were constructed by measuring their ^{19}F NMR spectra at 17 different pH values in the range 0.3–10.0 in aqueous solution containing oxalic acid–potassium oxalate. A small amount (5%, v/v) of DMSO-d_6 was added to preserve the solubility over the range of acids selected in Table 1. The limiting fluorine chemical shift values for the free acid and carboxylate anion, their difference $\Delta\delta_F$ and graphically estimated ionization constants are listed in Table 1. The sensitivity values shown in Table 1 are approximated by the ratio $\Delta\delta_F/\Delta$ pH, where ΔpH is a range of ±0.25 units from the pK_a. This range is the steepest part of the titration curve. The maximum ^{19}F NMR chemical shift sensitivity to pH (highest slope) is found, as expected, near the pK_a of the fluorinated carboxylic acid under study. In this pH region there are comparable concentrations of both the acid and its conjugate base present in solution. Here, the ratio of the two species, which interconvert rapidly on the NMR time-scale, and hence the average observed ^{19}F NMR chemical shift are altered dramatically by small pH changes.

In order to explore the feasibility of using ^{19}F NMR to determine carboxylic acid pK_a values, we focused first on fluorinated carboxylic acids of known pK_a, where the pK_a

Table 1. ^{19}F NMR data for carboxylic acids **1–26**

Compound	δ_F(acid)[a]	δ_F(carboxylate)[a]	$\Delta\delta_F$[b]	Sensitivity[c]	pK_a[d]
1	−188.56	−180.91	−7.65	3.82	2.67
2	−228.94	−217.71	−11.23	6.60	2.50
3	−175.13	−164.35	−10.78	5.74	2.33
4	−112.77	−116.82	4.05	1.98	3.31
5	−113.92	−114.76	0.84	0.41	3.68
6	−106.60	−111.03	4.43	2.10	4.01
7	−118.91	−119.08	0.17	0.10	3.96
8	−114.68	−115.16	0.48	0.22	4.02
9	−117.03	−118.42	1.39	0.58	4.14
10	−120.03	−120.17	0.14	0.07	4.62
11	−114.95	−115.19	0.24	0.11	4.59
12	−118.44	−118.99	0.55	0.24	4.55
13	−116.54	−117.78	1.24	0.73	4.08
14	−114.34	−114.68	0.34	0.18	4.12
15	−110.84	−112.86	2.02	1.14	4.21
16	−105.80	−106.31	0.51	0.26	4.44
17	−127.29	−118.91	−8.38	4.81	2.61
18	*o*-F−107.35	−111.84	4.49	2.53	3.29
	p-F−102.68	−108.65	5.97	3.35	3.29
19	−59.53	−59.88	0.35	0.19	2.73
20	−62.86	−62.64	−0.21	0.10	3.90
21	−63.20	−62.74	−0.46	0.22	3.77
22	−60.32	−60.29	−0.03	—	—
23	−62.63	−62.49	−0.14	0.07	4.19
24	−62.48	−62.23	−0.25	0.10	3.99
25	−64.05	−63.79	−0.26	0.15	3.17
26	−73.78	−73.63	−0.15	0.08	4.05

[a] Values reported in δ(ppm) from the chemical shift in Hz and the exact spectrometer frequency of the individual measurement.
[b] $\Delta\delta_F = \delta_F$ (acid) $-\delta_F$ (carboxylate).
[c] $\Delta\delta_F/\Delta$pH.
[d] Determined from the graph of δ_F *vs* pH. The spectra of **1**–**18** were referenced to C_6F_6 at −162.90 ppm and the spectra of **19**–**26** to $CFCl_3$ at 0.00 ppm.

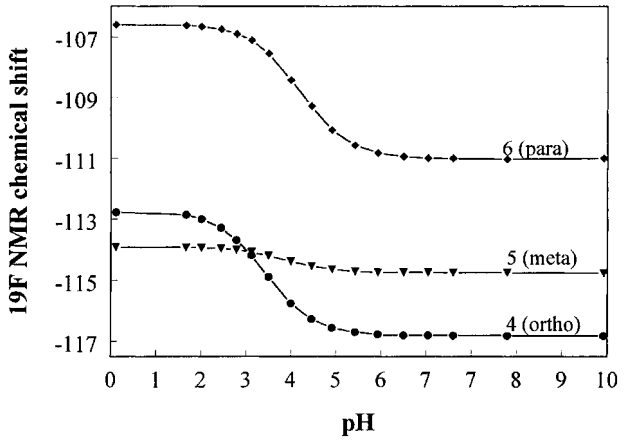

Figure 1. Variation of ^{19}F NMR chemical shift with pH for aqueous solutions of fluorobenzoic acids: ●,4; ▼,5; ◆,6

was determined by classical means. Fluoroacetic acid (**2**, as its sodium salt) was examined first for this purpose. Among all the acids studied, it showed greatest downfield chemical shift change ($\Delta\delta_F = -11.23$ ppm) upon ionization. Plotting δ_F as function of pH showed a typical titration curve, from which one could determine the pK_a by approximate graphical means.

The equilibrium (acidity) constant K_a of an acid HA ionization [Eqn. (1)] is related to the observed chemical shift by Eqn. (2), where X_{HA} is the mole fraction of the non-ionized acid:[13]

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \qquad (1)$$

$$K_a = \frac{[A^-][H_3O^+]}{[HA]}$$

$$\delta_F(\text{observed}) = X_{HA}\delta_F(\text{acid}) + (1 - X_{HA})\,\delta_F(\text{carboxylate}) \qquad (2)$$

$$= \frac{[H_3O^+]\delta_F(\text{acid}) + K_a\delta_F(\text{carboxylate})}{[H_3O^+] + K_a}$$

When $[H_3O^+] = K_a$, the observed δ_F is the average of the limiting δ_F(acid) and δ_F(carboxylate) shifts. The mean δ_F value corresponds to a solution containing equal concentrations of acid and its conjugate base. Consequently, from the graph point coordinate $\delta_F = 1/2$ [δ_F(acid) + δ_F(carboxylate)], the value of pH = pK_a can be determined. For acid **2**, pK_a = 2.50 was found by this approach, in excellent agreement with that in the literature, p$K_a = 2.58 \pm 0.04$.[5,6,14] Alternatively, a sigmoidal curve-fitting program gave pK_a = 2.53, in excellent agreement.

In order to ensure that the presence of the small amount of DMSO-d_6 (5% v/v) used to maintain solution homogeneity did not cause a significant deviation from pK_as determined in its absence, the pK_as of water-soluble acids were re-determined in the absence of DMSO-d_6. The sodium salt of **2** gave pK_a = 2.54 in aqueous oxalate buffer vs 2.53 in the same buffer with 5% (v/v) DMSO-d_6 present.

For additional reference standards to use in calibrating the ^{19}F NMR method to determine carboxylic acid pK_a values, we turned to the three isomeric fluorobenzoic acids. The ^{19}F NMR spectra of 3- and 4-fluorobenzoic acids have previously been measured in acid and base but without a description of their full titration curves.[15] All three isomeric fluorobenzoic acids also showed very good coincidence between ^{19}F NMR-determined and literature pK_as: for *ortho*-isomer **4**, 3.31 *vs* 3.27[14]; for *meta*-isomer **5**, 3.68 *vs* 3.86 ± 0.04;[5,14,16,17] and for *para*-isomer **6**, 4.01 *vs* 4.15 ± 0.005[5,14,17] (see Fig. 1 for titration curves). Sigmoidal curve fitting gave essentially the same pK_a values: **4**, 3.31; **5**, 3.69; and **6**, 3.99. Further comparisons were made between ^{19}F NMR-determined pK_as and literature values, *e.g.* for **20** (although with lower confidence; see below) with an NMR-determined pK_a of 3.90 and potentiometrically measured pK_a = 3.75,[17] and for **26** with an NMR-determined pK_a = 4.05 vs pK_a = 4.15 found for the very similar 4,4,4-trifluorobutanoic acid.[18]

Our conclusion from the comparisons with literature pK_as is that ^{19}F NMR spectroscopy is very well suited for pK_a determination in the (strongly) acidic pH range, much as was shown to be for protonated amines in the physiological pH region.[10–12]

As shown in Figure 1, and found in Table 1, when the fluorine is on a phenyl ring, carboxylic acid ionization causes an *upfield* shift of the ^{19}F resonance. This is consistent with that found in protonated aniline derivatives[10] or imidazoles,[12] where in all cases the fluorine was on a phenyl ring. Hybridization at carbon is not the sole reason for such behavior, because α-fluorocinnamic acid (**17**) exhibited a *downfield* shift, as did **1, 2, 3** and all trifluoromethyl-containing compounds, except **19** (Table 1). Comparison of $\Delta\delta_F$ and sensitivity (Table 1) confirmed earlier observations that a phenyl π-system transmits the polar effects to the fluorine well.[19] Hence the total change in δ_F upon ionization of **4, 5** and **6** is 4.05, 0.84 and 4.43 ppm, respectively (Fig. 1).

In order to examine the ability of fluorine to act as a remote sensor for carboxylic acid ionization, we studied fluorophenylacetic (**7**–**9**) and 3-(fluorophenyl)propionic acids (**10**–**12**) (Figs 2 and 3, respectively). When the fluorine reporter is insulated from the ionizable COOH by one (as in **7**–**9**) or two methylene groups (as in **10**–**12**), the sensitivity is greatly diminished (Table 1). The trend is toward smaller $\Delta\delta_F$ values as the distance between fluorine and carboxyl increases for a given series, *e.g.* in the *para*-isomers. The limit of detection was reached for *o*-fluorophenylacetic acid (**7**) and *o*- (**10**) and *m*-3-(fluorophenyl)propionic acid (**11**), showing $\Delta\delta_F$ = 0.17, 0.14 and 0.24 ppm, respectively. Although the titration

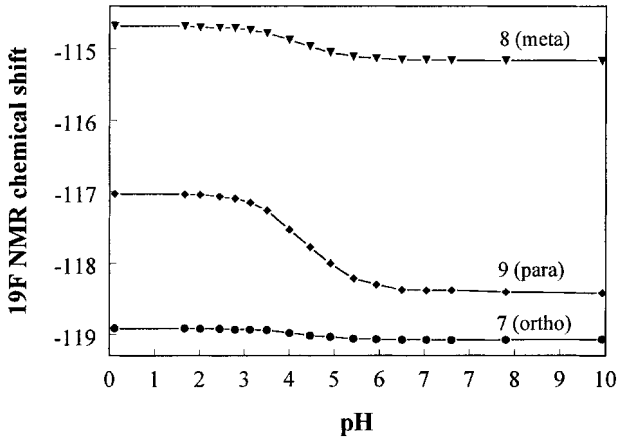

Figure 2. Variation of ^{19}F NMR chemical shift with pH for aqueous solutions of fluorophenylacetic acids: ●,7; ▼,8; ◆,9

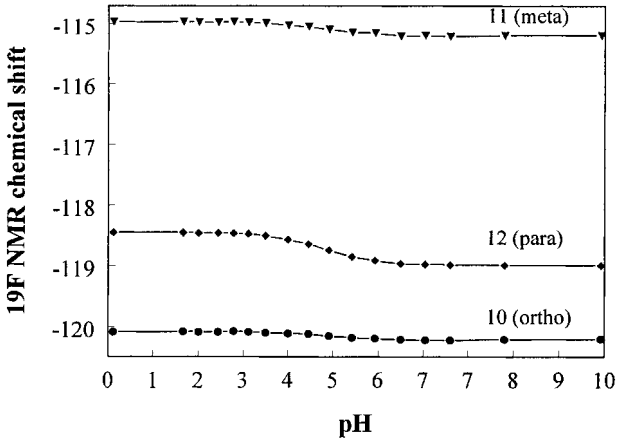

Figure 3. Variation of ^{19}F NMR chemical shift with pH for aqueous solutions of fluorophenylpropionic acids: ●,10; ▼,11; ◆,12

curve can be barely seen in Fig. 3, such small $\Delta\delta_F$ values fall within instrumental and experimental error. Hence $\Delta\delta_F$ values smaller than 0.3 ppm should be considered unreliable for pK_a measurements.

Curiously, the drop in $\Delta\delta_F$ with increasing distance between sensor and ionization center is greater with the *ortho*- and *meta*- isomers than with *para*-isomers and greatest with the *ortho*-isomers. Apparently the number of intervening bonds is not the only factor. In the *o*-fluoro acids **7** and **10**, $\Delta\delta_F$ drops faster than in the *para*-isomers; *e.g.* in **12**, although the fluorine is eight bonds removed from the ionization center, it still senses it well ($\Delta\delta_F$ = 0.55 ppm), whereas in **10**, with a six-bond separation, $\Delta\delta_F$ is only 0.14 ppm (Fig. 2). The influence on pK_a, however, is opposite: *o*-fluoro acids are stronger than *p*-fluoro acids (compare **4** with **6** and **7** with **9**). Fluorine substitution does not exert a significant effect on the acidity of **10–12**. From comparison of the data from **4–12**, it follows that a fluorine at the *para*-position has the best sensitivity.

Fluorine detection of ionization is much more effective when the phenyl ring is conjugated with rather than insulated from the carboxyl group, as in cinnamic acids **13–15** *vs* the corresponding hydrocinnamic (phenylpropionic) acids **10–12** (Table 1). For example, $\Delta\delta_F$ = 2.03 ppm for **15** is much larger than $\Delta\delta_F$ = 0.55 ppm for the saturated acid **12**. Fluorine substitution on the phenyl ring of **13–15** increases their acidity *vs* that of the parent cinnamic acid (pK_a = 4.44).[14]

2,4-Difluorobenzoic acid (**18**) offered the opportunity to follow simultaneously two different fluorine NMR signals. The *para*-fluorine of **18** exhibited a larger chemical shift change ($\Delta\delta_F$ = 5.97 ppm) and greater sensitivity than those of the *ortho*-fluorine ($\Delta\delta_F$ = 4.48 ppm). It was comforting to note that analysis of the titration curves from either fluorine signal provided an identical pK_a value (3.29). Interestingly, the presence of the *para*-fluorine did not decrease the pK_a of **18** below that of *o*-fluorobenzoic acid (**4**), pK_a = 3.31.

In an attempt to lower the NMR detection threshold by increasing the number of identical fluorines per molecule, the spectra of trifluoromethyl-containing acids **19–26** were measured. However, the CF_3 substituent proved less effective than a directly attached fluorine, *cf*. monofluoro *p*-fluorobenzoic acid **6** ($\Delta\delta_F$ = 4.43 ppm) or even **9** ($\Delta\delta_F$ = 1.39 ppm) with the corresponding *p*-trifluoromethylbenzoic acid **21** ($\Delta\delta_F$ = −0.46 ppm). The reason for such diminished sensitivity of the trifluoromethyl probe is not clear but might be rooted in the inherently narrower ^{19}F chemical shift dispersion range (−55 to −65 ppm) in RCF_3 compounds over a wide range of R groups, *i.e.* even if R = OR′ the range is the same.[20,21] In contrast, one fluorine atom on a secondary aliphatic carbon has chemical shift dispersion range of −160 to −230 ppm, and in ArF it is −100 to −200 ppm. Thus, the last case with a wide dispersion might be expected to be the most responsive to subtle changes in the nature of Ar, while CF_3 would be intrinsically insensitive to changes.

The ^{19}F NMR spectra of pyrrolepropionic acid **1** measured at various pH are presented in Fig. 4. This α-fluorinated acid showed a favorable downfield chemical shift change $\Delta\delta_F$ = −7.65 ppm upon ionization, and a sensitivity of 3.82 ppm per pH unit near the pK_a. From Fig. 4 it can be seen that not only does the chemical shift change with pH, but so does the splitting pattern of the fluorine multiplet. The titration curve of **1**, displayed in Fig. 5, had an inflection point at pH 2.67 corresponding to its pK_a. This ^{19}F NMR-determined pK_a of **1** is very close to those of fluoroacetic acid (**2**) ($\Delta\delta_F$ = −11.23 ppm, pK_a = 2.50) and α-fluorocinnamic acid (**17**) ($\Delta\delta_F$ = −8.38 ppm, pK_a = 2.61). Only α-fluorophenylacetic acid (**3**) is a stronger acid ($\Delta\delta_F$ = −10.78 ppm, pK_a = 2.33). Hence the decrease in pK_a due to a single fluorine alpha to the carboxylic acid group is ∼2 pK units, an estimate in

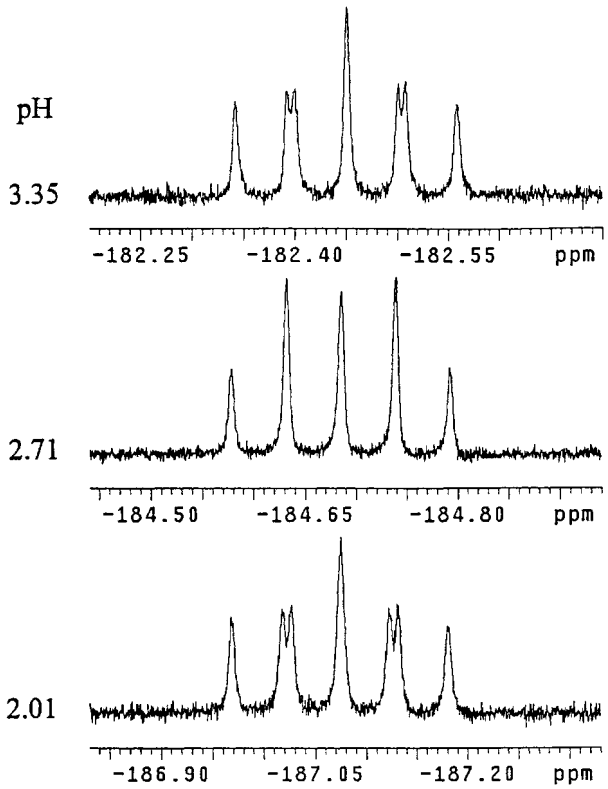

Figure 4. Changes of ^{19}F NMR chemical shift and $^{19}F^{1}H$ coupling pattern of α-fluoro(pyrrole)propionic acid **(1)** with pH

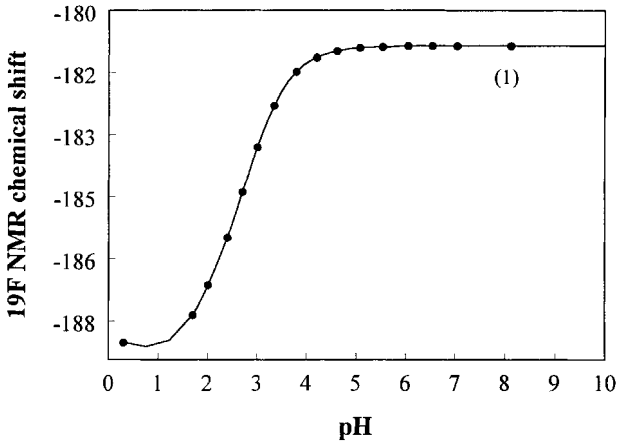

Figure 5. Variation of ^{19}F NMR chemical shift with pH for aqueous solutions of α-fluoro(pyrrole)propionic acid (**1**)

good agreement with literature data on the effect of one strongly electronegative fluorine substituent. The pK_a of **1** provides suggestive evidence that the acidity of the bilirubin synthesized from **1**[4] would also show a corresponding increase (~100-fold), and this doubtless contributes to its peculiar properties, such as its aqueous solubility.

Further work is in progress (P. B. Karadakov, University of Surrey, UK) to understand the observed ^{19}F NMR chemical shifts and $\Delta\delta_F$ by applying *ab initio* calculations.

CONCLUSIONS

The fluorine nucleus appears to be an excellent probe for monitoring by NMR ionization equilibria in acidic aqueous medium. Its wide chemical shift dispersion range allows accurate pK_a determinations for a variety of carboxylic acids. The method defines the expected high acidity of a fluorinated bilirubin precursor to be pK_a = 2.67.

EXPERIMENTAL

The ^{19}F NMR spectra were acquired at 25 ± 1 °C on a Varian Unity Plus spectrometer at 470.254 MHz in 5 mm tubes, and were referenced against external standards: hexafluorobenzene (5 ± 0.02 mM in $CHCl_3$) at δ − 162.90 ppm or $CFCl_3$ (10 ± 0.05 mM in $CHCl_3$) at δ 0.00 ppm, with shifts upfield from $CFCl_3$ being negative.[20] Typical experimental parameters were flip angle 55°, interpulse delay 3 s, collecting 128 transients, and spectral width 35 kHz using 70K data points. Each FID was zero filled to 262K and multiplied with an exponential function (line broadening 0.1 Hz) prior to Fourier transformation to give a 0.27 Hz digital resolution. Proton decoupling was not applied and consistently the chemical shift of a selected prominent line was followed. pH measurements were made using an Orion Model 811 pH meter with an Orion Model 91-02 combination electrode calibrated twice for the range 0.3–10.0 at pH 4.00, 7.41 and 10.00. Potassium tetraoxalate buffers (50 mM)[14] were used throughout, the pH being adjusted with HCl or KOH. The pH values reported in Table 1 refer to those of freshly prepared aqueous oxalic acid–oxalate containing solutions before dissolving the fluorinated acid. A stock solution of the each acid **1–26** (concentration 40 ± 1 mM) was prepared in DMSO-d_6. A 100 µl aliquot was diluted to a volume of 2 ml at each pH of the oxalate buffer, giving a total fluorinated acid concentration of 2.00 ± 0.05 mM and 5% (v/v) DMSO-d_6 in the NMR samples. The pH values of the NMR solutions were then rechecked and showed only small changes of 0.03–0.25 pH units, with larger variations occurring with the more acidic compounds. These findings are consistent with previous studies that showed that very low concentrations of DMSO exert only a very small effect on buffer pH.[22]

The small amount of added DMSO-d_6 served as an internal NMR deuterium lock and was used to maintain solution homogeneity. Whereas a number of the acids (*e.g.* **2, 4, 5** and **25**) used in this work are soluble in the

oxalate buffer over the entire pH range, others were not. When the measurements were repeated on soluble acids in the absence of DMSO-d_6, the same pK_as were measured as in the presence of DMSO-d_6.

^{1}H NMR spectra (at 500.6 MHz) and ^{13}C NMR spectra (at 125.9 MHz) were measured in $CDCl_3$ and referenced to the residual $CHCl_3$ ^{1}H signal at 7.26 ppm and the $CDCl_3$ ^{13}C signal at 77.00 ppm.

Commercial fluorinated acids **2** (as sodium salt), **3, 4, 5, 6, 8, 19, 20, 21** and **23** were obtained from Aldrich, **7, 9, 17, 22** and **24** from Acros, **13, 15, 18, 25** and **26** from Oakwood Products and **14** and **16** from Lancaster. The syntheses of **1, 10, 11** and **12** are described below.

3-(2,4-Dimethyl-5-methoxycarbonyl-1*H*-pyrrol-3-yl)-2-fluoropropionic acid (1). A mixture of the corresponding dimethyl ester[4] (257 mg, 1 mmol), 6 ml of methanol and 1.25 ml (1.25 mmol) of 1 M aqueous sodium hydroxide was stirred at room temperature for 24 h. The methanol was evaporated under vacuum. The residue was dissolved in 10 ml of 0.2 M sodium hydroxide, extracted with diethyl ether (10 ml) and the aqueous layer was acidified with 10% hydrochloric acid. The solution was concentrated under vacuum to ~3 ml and the precipitated semi-solid product was recrystallized from methanol–water to afford 104 mg (43%) of acid **1**, m.p. 186–187 °C. ^{1}H NMR [$CDCl_3$ + 20% (v/v) DMSO-d_6], δ 1.75 (3H, s), 1.79 (3H, s), 2.44 (1H, m), 2.54 (1H, m), 3.34 (3H, s), 4.37 (1H, ddd, $^2J_{FH}$ = 49.6 Hz, $^3J_{HH}$ = 7.9, 4.0 Hz), 10.14 (1H, s), 12.35 (1H, br s) ppm; ^{13}C NMR [$CDCl_3$ + 20% (v/v) DMSO- d_6], δ 9.57, 10.22, 26.39 (d, $^2J_{FC}$ = 21.9 Hz), 49.46, 88.07 (d, $^1J_{FC}$ = 184.0 Hz), 113.81 (d, $^3J_{FC}$ = 2.1 Hz), 115.40, 126.26, 131.14, 160.69, 170.24 (d, $^2J_{FC}$ = 23.8 Hz) ppm.

Alkylation of dimethyl malonate with fluorobenzyl chlorides. *General procedure.* To a solution of freshly prepared from sodium under N_2 solution of sodium methoxide (0.1 mol) in 50 ml of anhydrous methanol was added 0.1 mol of dimethyl malonate in 10 ml of methanol over 10 min through a septum. After 10 min of stirring the corresponding fluorobenzylchloride (0.05 mol) was added neat over 15 min and the mixture was refluxed for 5 h. After cooling, half of the solvent was evaporated under vacuum and the residue was diluted with 50 ml of water and acidified with 5% hydrochloric acid. The product was extracted with diethyl ether (3 × 50 ml). The combined extracts were washed with water (3 × 30 ml), dried (anhydrous $MgSO_4$) and filtered and, after removing the solvent, the product was distilled under vacuum.

Methyl 3-(2-Fluorophenyl)-2-methoxycarbonylpropionate. Obtained in 67% yield, b.p. 127–128 °C (1 mmHg). ^{1}H NMR, δ 3.25 (2H, d, J = 7.8 Hz), 3.70 (6H, s), 3.75 (1H, t, J = 7.8 Hz), 6.98–7.07 (2H, m), 7.17–7.23 (2H, m) ppm; ^{13}C NMR, δ 28.21, 51.43, 52.13, 114.96 (d, $^2J_{FC}$ = 21.8 Hz), 123.80 (d, $^4J_{FC}$ = 3.4 Hz), 124.25 (d, $^2J_{FC}$ = 15.1 Hz), 128.48 (d, $^3J_{FC}$ = 8.2 Hz), 130.97 (d, $^3J_{FC}$ = 4.3 Hz), 160.88 (d, $^1J_{FC}$ = 246.4 Hz), 168.65 ppm.

Methyl 3-(3-Fluorophenyl)-2-methoxycarbonylpropionate. Obtained in 65% yield, b.p. 126–128 °C (1 mmHg). ^{1}H-NMR, δ 3.21 (2H, d, J = 7.8 Hz), 3.66 (1H, t, J = 7.8 Hz), 3.71 (6H, s), 6.83–6.94 (3H, m, $^3J_{FH}$ = 9.4, 7.8 Hz), 7.13–7.22 (1H, m) ppm; ^{13}C NMR, δ 34.11, 52.32, 53.00, 113.50 (d, $^2J_{FC}$ = 21.1 Hz), 115.45 (d, $^2J_{FC}$ = 21.3 Hz), 124.24 (d, $^4J_{FC}$ = 2.3 Hz), 129.83 (d, $^3J_{FC}$ = 8.4 Hz), 140.06 (d, $^3J_{FC}$ = 7.4 Hz), 162.53 (d, $^1J_{FC}$ = 245.7 Hz), 168.71 ppm.

Methyl 3-(4-Fluorophenyl)-2-methoxycarbonylpropionate. Obtained in 70% yield, b.p. 125–127 °C (1 mmHg). ^{1}H NMR, δ 3.19 (2H, d, J = 7.8 Hz), 3.63 (1H, t, J = 7.8 Hz), 3.70 (6H, s), 6.96 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{FH}$ = 8.7 Hz), 7.15 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{FH}$ = 5.4 Hz) ppm; ^{13}C NMR, δ 33.72, 52.36, 53.43, 115.17 (d, $^2J_{FC}$ = 21.4 Hz), 130.16 (d, $^3J_{FC}$ = 7.9 Hz), 133.23 (d, $^4J_{FC}$ = 2.9 Hz), 161.56 (d, $^1J_{FC}$ = 244.7 Hz), 168.86 ppm.

Fluorohydrocinnamic acids. *General procedure.* A solution of 2.40 g (10 mmol) of the foregoing dimethyl ester in 20 ml of methanol was mixed with a solution of 2.00 g (50 mmol) of sodium hydroxide in 10 ml of water and the mixture was refluxed for 3 h. The methanol was evaporated under vacuum and the residue was acidified with concentrated hydrochloric acid. Sodium chloride (~ 5 g) was added and the diacid was extracted with diethyl ether (5–6 × 25 ml). The residue, after evaporation of the diethyl ether, was heated on an oil-bath at 145–150 °C for 1 h. After cooling, the crude monoacid was purified by radical chromatography on silica gel (eluent 1.5–2% methanol in dichloromethane) followed by recrystallization from dichloromethane–hexane.

3-(2-Fluorophenyl)propionic acid (10). Obtained in 90% yield, m.p. 76–77 °C. ^{1}H NMR, δ 2.70 (2H, t, J = 7.7 Hz), 2.99 (2H, t, J = 7.7 Hz), 7.00–7.11 (2H, m), 7.18–7.27 (2H, m), 11.98 (1H, br s) ppm; ^{13}C NMR, δ 24.21 (d, $^3J_{FC}$ = 2.2 Hz), 34.12, 115.30 (d, $^2J_{FC}$ = 21.8 Hz), 124.07 (d, $^4J_{FC}$ = 3.4 Hz), 126.90 (d, $^2J_{FC}$ = 15.6 Hz), 128.20 (d, $^3J_{FC}$ = 8.1 Hz), 130.54 (d, $^3J_{FC}$ = 4.6 Hz), 161.10 (d, $^1J_{FC}$ = 245.3 Hz), 179.38 (d, $^5J_{FC}$ = 3.0 Hz) ppm.

3-(3-Fluorophenyl)propionic acid (11). Obtained in 85% yield, m.p. 44–45 °C. ^{1}H NMR, δ 2.69 (2H, t, J = 7.6 Hz), 2.96 (2H, t, J = 7.6 Hz), 6.88–7.03 (3H, m, $^3J_{FH}$ = 9.0, 7.7 Hz), 7.21–7.30 (1H, m), 11.96 (1H, br s) ppm; ^{13}C NMR, δ 30.15, 35.25, 113.29 (d, $^2J_{FC}$ = 21.0 Hz), 115.18 (d, $^2J_{FC}$ = 21.2 Hz), 123.89 (d, $^4J_{FC}$ = 1.7 Hz), 129.97 (d, $^3J_{FC}$ = 8.3 Hz), 142.56 (d, $^3J_{FC}$ = 7.3 Hz), 162.85 (d, $^1J_{FC}$ = 245.7 Hz), 179.28 ppm.

3-(4-Fluorophenyl)propionic acid (12). Obtained in 86% yield, m.p. 86–87 °C. ^{1}H NMR, δ 2.67 (2H, t, J = 7.6 Hz), 2.93 (2H, t, J = 7.6 Hz), 6.98 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{FH}$ = 8.7 Hz), 7.16 (2H, dd $^3J_{HH}$ = 8.7 Hz, $^4J_{FH}$ = 5.5 Hz), 11.69 (1H, br s) ppm; ^{13}C NMR, δ 29.66, 35.70, 115.28 (d, $^2J_{FC}$ = 21.4 Hz), 129.67 (d, $^3J_{FC}$ = 7.9 Hz), 135.68 (d, $^4J_{FC}$ = 3.2 Hz), 161.47 (d, $^1J_{FC}$ = 244.3 Hz), 179.45 ppm.

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