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Determination of the second-order ^{1}H NMR parameters for the aromatic protons in 4-fluoroaniline and application to the analysis of the ^{1}H NMR spectra for the aromatic protons in N^4-(4′-fluorophenyl)succinamic acid and in N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid

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ABSTRACT

Four studies of the ^{1}H NMR spectrum for the aromatic protons of 4-fluoroaniline between 1958 and 1974 give three very different solutions to the second-order, AA′BB′X, spectrum. A re-evaluation of the second-order spectrum was done at 300 MHz. Simultaneous simulations of the ^{1}H NMR spectrum and ^{19}F NMR spectrum for 4-fluoroaniline were done using WINDNMR-Pro, and a new set of parameters for the six coupling constants was obtained from the optimized simulations. This new set of parameters was used as a basis to evaluate the AA′BB′X spectrum for the aromatic protons in N^4-(4′-fluorophenyl)succinamic acid and in N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid by simultaneous simulations of the ^{1}H NMR spectrum and ^{19}F NMR spectrum for each using WINDNMR-Pro. Formation of the amide bond results in small, but significant, changes in the values for the set of parameters in both molecules. These results confirm that second-order analyses as an AA′BB′X system are required for derivatives of 4-fluoroaniline, rather than first-order analyses that have been used in previous reports.

1. Introduction

The ^{1}H and ^{19}F NMR spectra for the aromatic protons of 4-fluoroaniline (**1**) form a second-order, AA′BB′X system; the ^{1}H NMR spectrum is the AA′BB′ part of the system and the ^{19}F NMR spectrum is the X part of the system. The amino protons are a broad singlet with no interaction with the aromatic protons or fluoro group. An analysis of the AA′BB′X spectrum was reported, first, at 29.92 MHz (neat) [1]. Subsequently, analyses at 40 MHz (in CCl_4) [2], 60 MHz (neat) [3], and 250 MHz (in $CDCl_3$ in the presence of a lanthanide shift reagent) [4] were reported. When the results from these four analyses are used to simulate the NMR spectrum for the aromatic protons of 4-fluoroaniline at 300 MHz, three very different spectra are obtained. With the significant improvements in NMR instrumentation that have been made since the last reported analysis in 1974, we investigated the ^{1}H NMR spectrum and ^{19}F NMR spectrum for the aromatic protons of 4-fluoroaniline. We needed this information because, in our continuing study of the mechanism of glycosylasparaginase, we synthesized N^4-(4′-fluorophenyl)succinamic acid (**2**) [5,6], and we wished to compare the ^{1}H NMR spectrum for the aromatic protons of 4-fluoroaniline with the ^{1}H NMR spectrum for the aromatic protons in N^4-(4′-fluorophenyl)succinamic acid, which were previously reported simply as two sets of multiplets [5], and as chemical shifts with no coupling constants [6]. We also synthesized N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid (**3**) and report its spectrum. The solvent primarily used for the ^{1}H NMR analysis of N^4-(4′-substituted phenyl)succinamic acids has been Me_2SO-d_6 [7]. But, there is a partial overlap of the residual solvent signal with the signals for the ethylene protons (H2, H3) in several of these molecules. Thus, acetone-d_6 was used as the solvent for this study (but, see Section 3.2). We have retained the original nuclear spin pattern designation in order to simplify the discussion.

2. Materials and methods

4-Fluoroaniline and 2,2-difluorosuccinic acid were purchased from Alfa Aesar, and trifluoroacetic anhydride was purchased from Oakwood Products; the three chemicals were used without further purification. Acetone-d_6 (99.9 atom % ^{2}H), $CDCl_3$ (99.9 atom % ^{2}H), and Me_2SO-d_6 (99.9 atom % ^{2}H) were purchased from Cambridge Isotopes. All other chemicals were at least ACS grade. ^{1}H NMR

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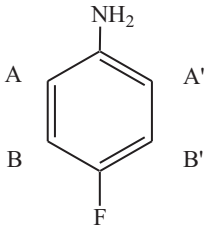
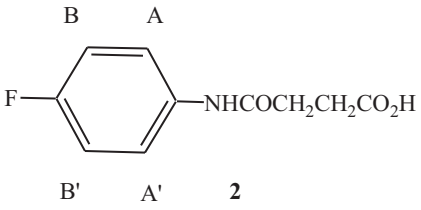
spectra were recorded on a JEOL ECX-300 NMR spectrometer operating at 300.53 MHz in a 5 mm probe at ambient temperature with a 6015 Hz sweep width, 90° pulse angle, and a 65.5k data block; no line-broadening factor was applied to the accumulated FID. Natural abundance ^{13}C NMR spectra were recorded: (1) on a JEOL ECX-300 NMR spectrometer operating at 75.57 MHz in a 5 mm probe at ambient temperature with a 23674 Hz sweep width, 30° pulse angle, and a 32k data block; protons were broad-band decoupled and a line-broadening factor of 2.0 Hz was applied to the accumulated FID, or (2) on a JEOL ECA-500 NMR spectrometer operating at 125.77 MHz in a 5 mm probe at ambient temperature with a 39308 Hz sweep width, 30° pulse angle, and a 65k data block; protons were broad-band decoupled and a line-broadening factor of 2.0 Hz was applied to the accumulated FID. ^{19}F NMR spectra were recorded on a JEOL ECX-300 NMR spectrometer operating at 282.78 MHz in a 5 mm probe at ambient temperature with an 85034 Hz sweep width, 45° pulse angle, and a 131k, 262k, or 524k data block; no line-broadening factor was applied to the accumulated FID. The errors in the measured chemical shifts were ±0.0003 ppm for ^{1}H NMR, ±0.010 or ±0.004 ppm for ^{13}C NMR, and ±0.002, ±0.001, or ±0.0006 ppm for ^{19}F NMR; J values are given in Hz and the errors in the measured coupling constants were ±0.09 for ^{1}H NMR, ±0.72 or ±0.60 for ^{13}C NMR, and ±0.65, ±0.32, or ±0.16 for ^{19}F NMR. Samples were dissolved in acetone-d_6, $CDCl_3$, or Me_2SO-d_6 with TMS as reference for ^{1}H NMR and ^{13}C NMR, and with fluorotrichloromethane as reference for ^{19}F NMR. The ^{1}H NMR and ^{19}F NMR spectra for the aromatic protons were simulated using WINDNMR-Pro (DNMR71.EXE) [8]. Another NMR simulation program, available free of charge, is gNMR [9].



1

2.1. N^4-(4′-Fluorophenyl)succinamic acid (2)

4-Fluoroaniline (5.56 mL, 0.05 mol) and succinic anhydride (5 g, 0.05 mol) were mixed in a flask with benzene:1,4-dioxane (2:1, 60 mL) and stirred at room temperature for 4 days [7,10]. N^4-(4′-Fluorophenyl)succinamic acid precipitated as pale, purple crystals: yield 1.31 g (0.006 mol, 12%); mp 156 °C. ^{1}H NMR (300.53 MHz, acetone-d_6): δ 2.656 (4H, center of AA′BB′, H-2 and H-3), 7.053 (2H, BB′ of AA′BB′X, $J_{BB'}$ = 3.30 Hz, J_{BF} = 8.70 Hz, H-3′ and H-5′), 7.667 (2H, AA′ of AA′BB′X, J_{AB} = 8.90 Hz, $J_{AA'}$ = 2.80 Hz, $J_{AB'}$ = 0.30 Hz, J_{AF} = 5.02 Hz, H-2′ and H-6′), 9.248 (1H, NH), OH not observed [lit. [5] (300 MHz, Me_2SO-d_6): δ 2.50 (4H, m), 7.20 (2H, m), 7.60 (2H, m), 10.00 (1H, s), 12.00 (1H, s); lit. [6] (400 MHz, Me_2SO-d_6): δ 2.51 (H-2), 2.54 (H-3), 7.12 (H-3′ and H-5′), 7.59 (H-2′ and H-6′), 10.00 (NH), 12.13 (OH)]. ^{13}C NMR (75.5 MHz, Me_2SO-d_6): δ 29.309 (C-2), 31.460 (C-3), 115.737 ($^{2}J_{C,F}$ = 21.67 Hz, C-3′ and C-5′), 121.100 ($^{3}J_{C,F}$ = 7.22 Hz, C-2′ and C-6′), 136.225 (C-1′), 158.296 ($^{1}J_{C,F}$ = 239.14 Hz, C-4′), 170.500 (C-4), 174.344 (C-1) [lit. [6] (100 MHz, Me_2SO-d_6): δ 29.28 (C-2), 31.42 (C-3), 115.72 (C-3′ and C-5′), 121.08 (C-2′ and C-6′), 136.21 (C-1′), 158.27 (C-4′), 170.48 (C-4), 174.33 (C-1)]. ^{19}F NMR (282.78 MHz, Me_2SO-d_6): δ −119.755 (X of AA′BB′X, J_{AF} = 5.02 Hz, J_{BF} = 8.70 Hz, F-4′).



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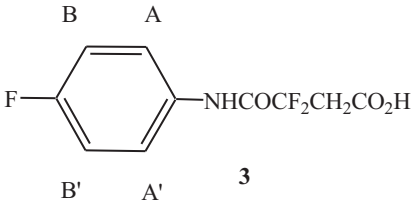
2.2. N^4-(4′-Fluorophenyl)-3,3-difluorosuccinamic acid (3)

2,2-Difluorosuccinic acid (0.100 g, 0.00065 mol) was added to isopropyl acetate (1 mL) [11]. Trifluoroacetic anhydride (0.164 g, 0.108 mL, 0.00078 mol) was added in one portion at room temperature and the mixture was stirred at 60 °C for 2 h to give 2,2-difluorosuccinic anhydride (quantitative) [^{1}H NMR (300.52 MHz, $CDCl_3$): δ 3.38 (2H, t, J_{HF} = 9.6 Hz). ^{19}F NMR (282.78 MHz, $CDCl_3$): δ −105.2 (t, J_{FH} = 9.6 Hz)]. 2,2-Difluorosuccinic anhydride in isopropyl acetate (1 mL) was cooled to 5 °C. A solution of 4-fluoroaniline (0.100 g, 0.0009 mol) in isopropyl acetate (1 mL) was added slowly to the anhydride and stirred for 5 days at 60 °C. Water (5 mL) was added, followed by a saturated solution of sodium carbonate until the pH was 8–9. The organic phase was separated. The aqueous phase was acidified with 5 M HCl to pH 1 and extracted with isopropyl acetate (2 × 10 mL). The organic phase was washed with 2 M HCl (10 mL) and removed under vacuum. A mixture of N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid (97.5%) and N^4-(4′-fluorophenyl)-2,2-difluorosuccinamic acid (2.5%) (determined by ^{1}H NMR and ^{19}F NMR) formed as purple-white crystals: yield 0.072 g (0.00029 mol, 45%). For this study, no attempt was made to separate the isomers. NMR parameters for N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid: ^{1}H NMR (300.52 MHz, acetone-d_6): δ 3.254 (2H, A of A_2X_2, $J_{2,F-3}$ = 14.77 Hz, H-2), 7.025 (2H, BB′ of AA′BB′X, $J_{BB'}$ = 3.10 Hz, J_{BF} = 8.48 Hz, H-3′ and H-5′), 7.667 (2H, AA′ of AA′BB′X, J_{AB} = 8.70 Hz, $J_{AA'}$ = 2.80 Hz, $J_{AB'}$ = 0.30 Hz, J_{AF} = 4.91 Hz, H-2′ and H-6′), 9.806 (1H, s, NH), 11.4 (1H, bs, OH). ^{13}C NMR (125.77 MHz, acetone-d_6): δ 38.842 (t, $^{2}J_{C,F}$ = 25.79 Hz, C-2), 115.336 (d, $^{2}J_{C,F}$ = 23.54 Hz, C-3′ or C-5′), 115.523 (d, $^{2}J_{C,F}$ = 23.54 Hz, C-5′ or C-3′), 115.919 (t, $^{1}J_{C,F}$ = 252.96 Hz, C-3), 122.687 (d, $^{3}J_{C,F}$ = 4.05 Hz, C-2′ or C-6′), 122.719 (d, $^{3}J_{C,F}$ = 4.05 Hz, C-6′ or C-2′), 133.928 (C-1′), 159.756 (d, $^{1}J_{C,F}$ = 242.02 Hz, C-4′), 161.777 (t, $^{2}J_{C,F}$ = 27.89 Hz, C-4), 167.400 (t, $^{3}J_{C,F}$ = 7.95 Hz, C-1). ^{19}F NMR (282.78 MHz, acetone-d_6): δ −104.497 (X of A_2X_2, $^{3}J_{3,H-2}$ = 14.70 Hz, F-3), −118.828 (X of AA′BB′X, J_{AF} = 4.91 Hz, J_{BF} = 8.48 Hz, F-4′). NMR parameters for N^4-(4′-fluorophenyl)-2,2-difluorosuccinamic acid: ^{1}H NMR (300.52 MHz, acetone-d_6): δ 3.443 (2H, A of A_2X_2, $J_{3,F-2}$ = 13.40 Hz, H-3), 7.196 (2H, BB′ of AA′BB′X, H-3′ and H-5′), 7.373 (2H, AA′ of AA′BB′X, H-2′ and H-6′). ^{19}F NMR (282.78 MHz, acetone-d_6): δ −107.364 (X of A_2X_2, $^{3}J_{F,H-3}$ = 13.39 Hz, F-2), −118.835 (X of AA′BB′X, F-4′).



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3. Results and discussion

3.1. 4-Fluoroaniline

The ^{1}H NMR spectrum at 300 MHz for the aromatic protons and the ^{19}F NMR spectrum at 283 MHz for the fluoro group of

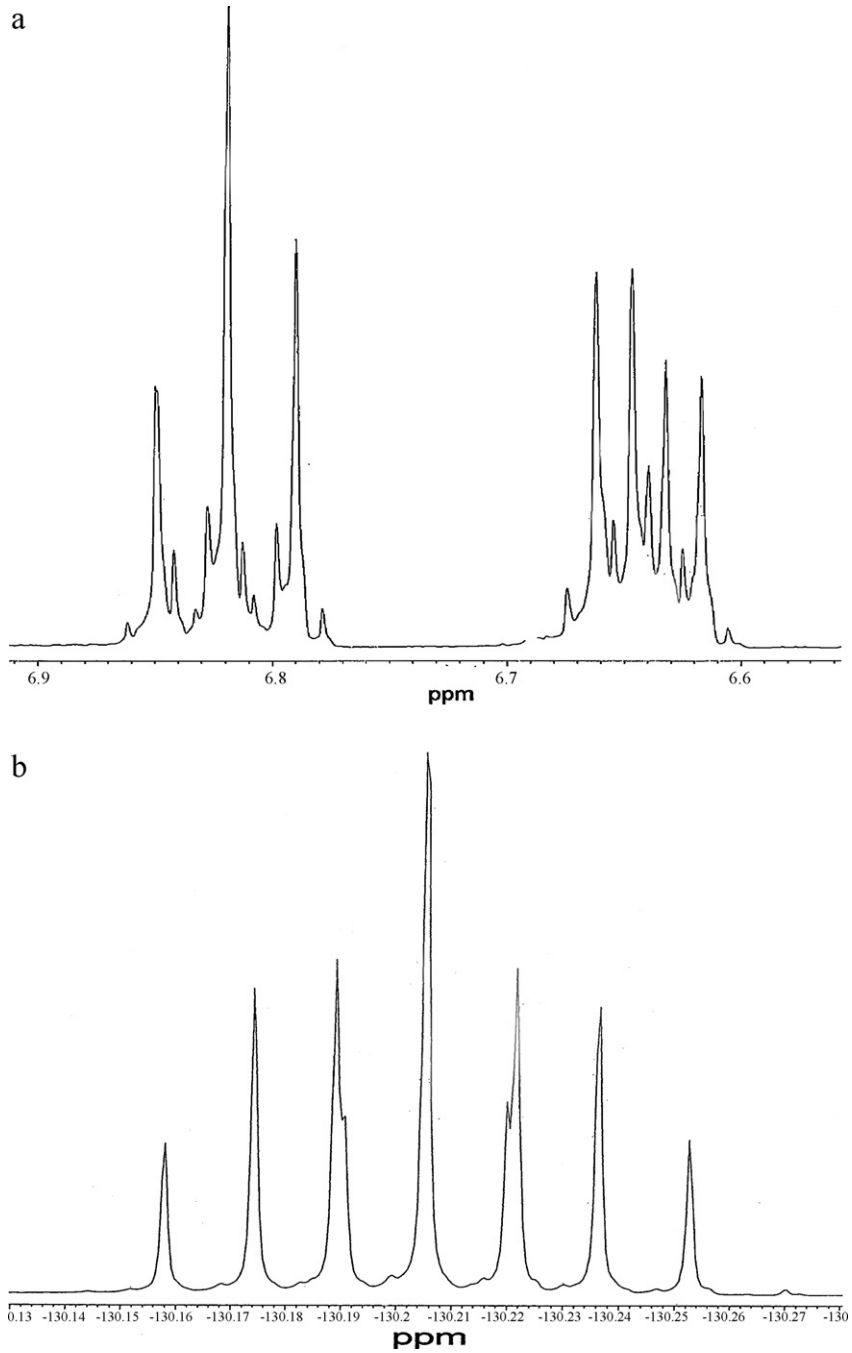

Fig. 1. (a) ^{1}H NMR spectrum for the aromatic protons of 4-fluoroaniline (**1**) in acetone-d_6 (internal standard TMS) at 300.53 MHz; no line-broadening factor was applied. (b) ^{19}F NMR spectrum for the fluoro group of 4-fluoroaniline (**1**) in acetone-d_6 (internal standard CCl_3F) at 282.78 MHz using a 524k data block and 85024 Hz sweep width; no line-broadening factor was applied. The two NMR spectra form a second-order, AA′BB′X, system.

4-fluoroaniline (**1**) in acetone-d_6 are shown in Fig. 1; the chemical shift for the protons at 2,6 (A,A′) is at δ 6.64 ppm and the chemical shift for the protons at 3,5 (B,B′) is at δ 6.82 ppm. Using the NMR data for each reported analysis (Table 1) [1–4], the second-order, AA′BB′X, ^{1}H NMR spectrum at 300 MHz was simulated using WINDNMR [8], and the results are shown in Fig. 2(a)–(d). There is broad, general agreement between the four analyses with each simulation showing four signals for the A and A′ protons and three signals for the B and B′ protons, but they differ in the details. The first reported analysis at 29.92 MHz by Richards and Schaefer [1] results in a simulation (Fig. 2(a)) with too many lines. The absence of coupling between AA′, AB′, and BB′, *i.e.*, $J_{AA'}$, $J_{AB'}$, and $J_{BB'} \approx 0$, results in simulated spectra (Fig. 2(b) and (d)) that are missing several lines for both the A and B protons. This shows that the analyses by Smith [2] at 60 Hz and by Forchioni and Chachaty [4] at 250 MHz in the presence of a lanthanide shift reagent were incomplete. Interestingly, in an earlier paper by Ernst and Mannschreck [12], the NMR spectrum at 60 MHz of 4-fluoroaniline in $CDCl_3$ in the presence of a lanthanide shift reagent clearly showed several of the missed lines. The analysis by Dischler [3] results in a simulation (Fig. 2(c)) that is very close to the observed spectrum (Fig. 1(a)). The difference between the analyses of Richard and Schaefer [1] and of Dischler [3] is the value for the coupling between the 3 and 5 protons ($J_{BB'}$); Dischler [3] reported a value approximately half that reported by Richards and Schaefer [1] (Table 1). More recent studies of the values for J_{AF} and J_{BF} in

Table 1
Coupling constants (Hz) in the ^{1}H NMR spectrum for the aromatic protons.

J_{AB}	$J_{AA'}$	$J_{AB'}$	$J_{BB'}$	J_{AF}	J_{BF}	Reference
4-Fluoroaniline (literature values)						
8.2	2.5	≈0	6.4	5.1	8.6	[1]
9	–	–	–	5.0	8.1	[2]
8.7	2.7	0.3	3.3	4.7	8.7	[3]
9.2	≈0	≈0	≈0	4.6	8.6	[4]
4-Fluoroaniline (**1**) ($\Delta\nu_{AB}$ = 53.50 Hz)						
8.60	2.70	0.30	3.30	4.62	8.82	This study
N^4-(4′-Fluorophenyl)succinamic acid (**2**) ($\Delta\nu_{AB}$ = 184.68 Hz)						
8.90	2.80	0.30	3.30	5.02	8.70	This study
N^4-(4′-Fluorophenyl)-3,3-difluorosuccinamic acid (**3**) ($\Delta\nu_{AB}$ = 191.90 Hz)						
8.70	2.80	0.30	3.10	4.91	8.48	This study

4-fluoroaniline [13], *N*-substituted 4-fluoroaniline [13], and derivatives of 4-fluoroaniline, for example, *N*-arylpyridinium salts [14] and trimethylammonium salts [14], show that the value of J_{BF} ≈2J_{AF}. Zakrzewska et al. [13] reported values for J_{AF} (4.42 Hz) and J_{BF} (8.71 Hz) in 4-fluoroaniline in $CDCl_3$ at 500 MHz (no full analysis of the ^{1}H NMR spectrum was given).

The set of parameters we used as a basis for our analysis of the AA′BB′X system for 4-fluoroaniline (**1**) in acetone-d_6 was the values from Dischler [3] for J_{AB}, $J_{AA'}$, $J_{AB'}$, and $J_{BB'}$ and the values from Zakrzewska et al. [13] for J_{AF} and J_{BF}. Our approach was to do simultaneous simulations of the ^{1}H NMR spectrum and the ^{19}F NMR spectrum for **1** (Fig. 1) using WINDNMR [8]. The optimized simulations are shown in Fig. 3(a) for the ^{1}H NMR spectrum at 300 MHz and in Fig. 3(b) for the ^{19}F NMR spectrum at 283 MHz. The values for the coupling constants obtained from the optimized simulations are given in Table 1; changes in the values of ±0.05 Hz resulted in simulations that were not as good. From the ^{19}F NMR optimized simulation, the value for J_{AF} was 4.62 Hz and the value for J_{BF} was 8.82 Hz. These values are different from those of Zakrzewska et al. [13], but we believe that these values are more accurate; we were able to resolve the signals (Fig. 1(b)) whereas Zakrzewska et al. [13] did not in their published ^{19}F NMR spectrum, quite possibly due to the line-broadening factor applied. We used no line-broadening factor. Using the values of Zakrzewska et al. [13], the simulation of the ^{19}F NMR spectrum was not correct. The values we obtained for J_{AF} and J_{BF} restricted the variability in the values for J_{AB}, $J_{AA'}$, $J_{AB'}$ and $J_{BB'}$ in the simulation of the ^{1}H NMR spectrum. The values obtained from the optimized simulation of the ^{1}H NMR spectrum (Fig. 3(a)) are in agreement with those of Dischler [3] with the exception of J_{AB} that is slightly smaller. The calculated frequencies and intensities for the 48 lines that make up the simulated ^{1}H NMR spectrum (Fig. 3(a)) are given in Appendix Table A1. The calculated frequencies and intensities for the 16 lines that make up the simulated ^{19}F NMR spectrum (Fig. 3(b)) are given in Appendix Table A2. Of the four analyses [1–4], the values for the coupling constants reported by Dischler [3] more closely simulated the ^{1}H NMR spectrum for the aromatic protons of 4-fluoroaniline in acetone-d_6. However, our optimized values for the second-order, AA′BB′X, NMR spectrum for 4-fluoroaniline given in Table 1 are a new set of parameters that reflects the improvements in NMR instrumentation that have been made. A second-order, AA′BB′X, analysis should be used for 4-fluoroaniline rather than a first-order analysis [15,16].

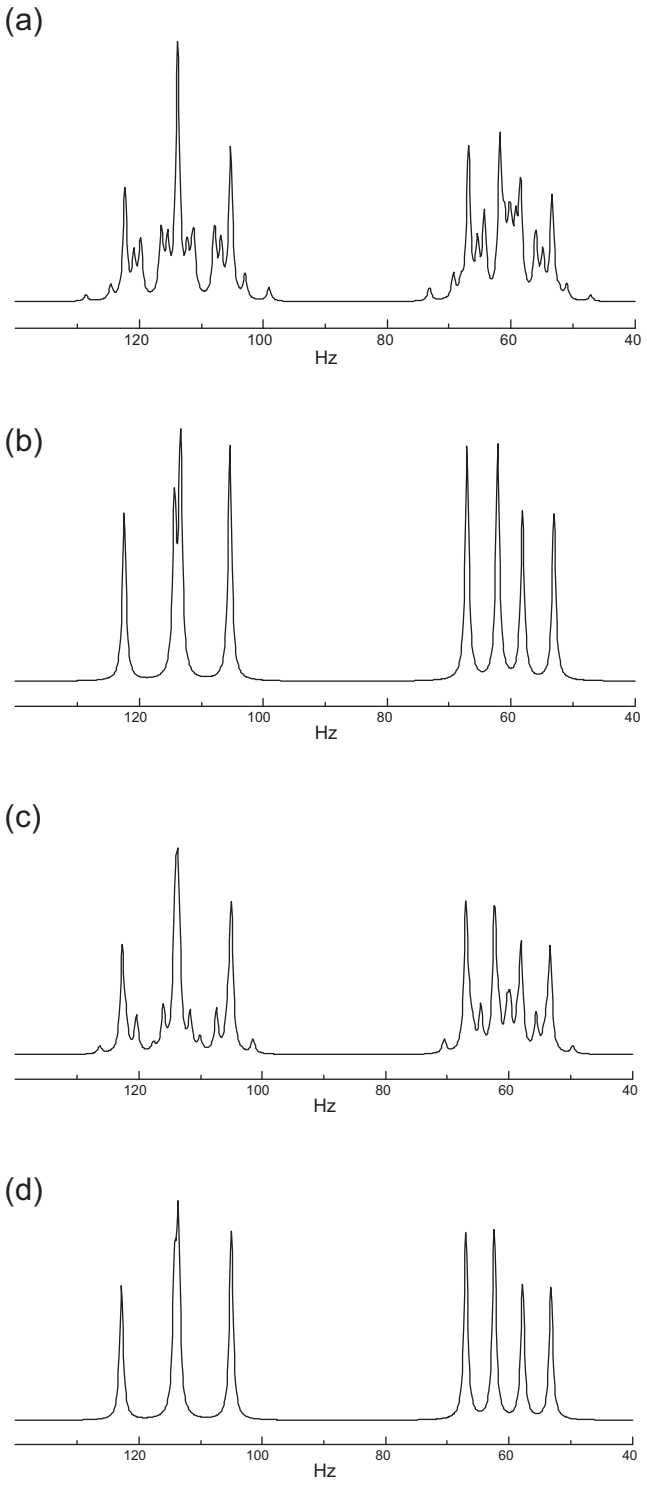

Fig. 2. Simulations of the ^{1}H NMR spectrum for the aromatic protons of 4-fluoroaniline (**1**) at 300 MHz with WINDNMR [8] using the four literature values for the parameters in Table 1: (a) Richards and Schaefer [1], (b) Smith [2], (c) Dischler [3], (d) Forchioni and Chachaty [4]. The parameters reported by Dischler give a simulation that is closest to the NMR spectrum shown in Fig. 1(a).

3.2. N^4-(4′-Fluorophenyl)succinamic acid

N^4-(4′-Fluorophenyl)succinamic acid (**2**) was synthesized by reaction of succinic anhydride with 4-fluoroaniline in a mixture of benzene and 1,4-dioxane (2:1) [7,10]. The ^{1}H NMR chemical shifts are consistent with those reported by Lee et al. [6] and by Ashwell et al. [5]. The ^{1}H NMR spectrum for the ethylene group (H2,H3) is a second-order, AA′BB′, spectrum [17], and will be discussed in detail elsewhere [18]. The ^{13}C NMR spectrum agreed with the chemical shifts for **2** reported by Lee et al. [6], for the methyl ester of **2** [19], and for the aromatic carbons in 4-fluoroacetanilide [20–22]. The coupling constants, $J_{C,F}$, are consistent with those reported for 4-fluoroacetanilide [21]; however, we did not observe coupling between the C1′ and F ($^4J_{C,F}$). The ^{19}F NMR chemical shift

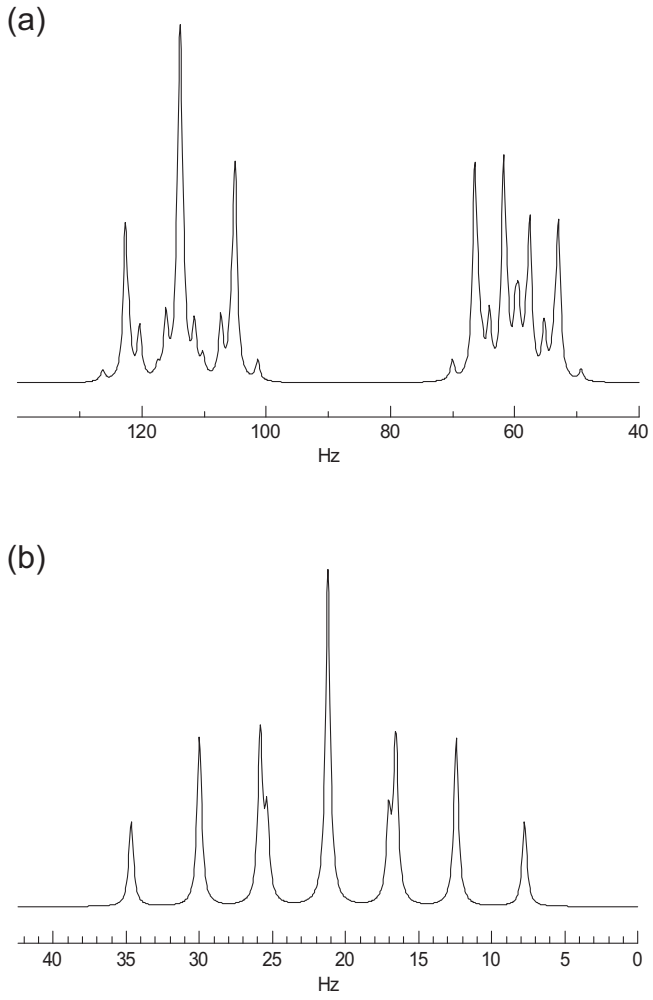

Fig. 3. (a) Optimized simulation of the ^{1}H NMR spectrum for 4-fluoroaniline (**1**) (Fig. 1(a)) using WINDNMR [8]. (b) Optimized simulation of the ^{19}F NMR spectrum for 4-fluoroaniline (**1**) (Fig. 1(b)) using WINDNMR [8]. The values obtained for the six coupling constants from the simultaneous simulations of these two NMR spectra are given in Table 1 and are a new set of values for the parameters for this second-order, AA′BB′X, system.

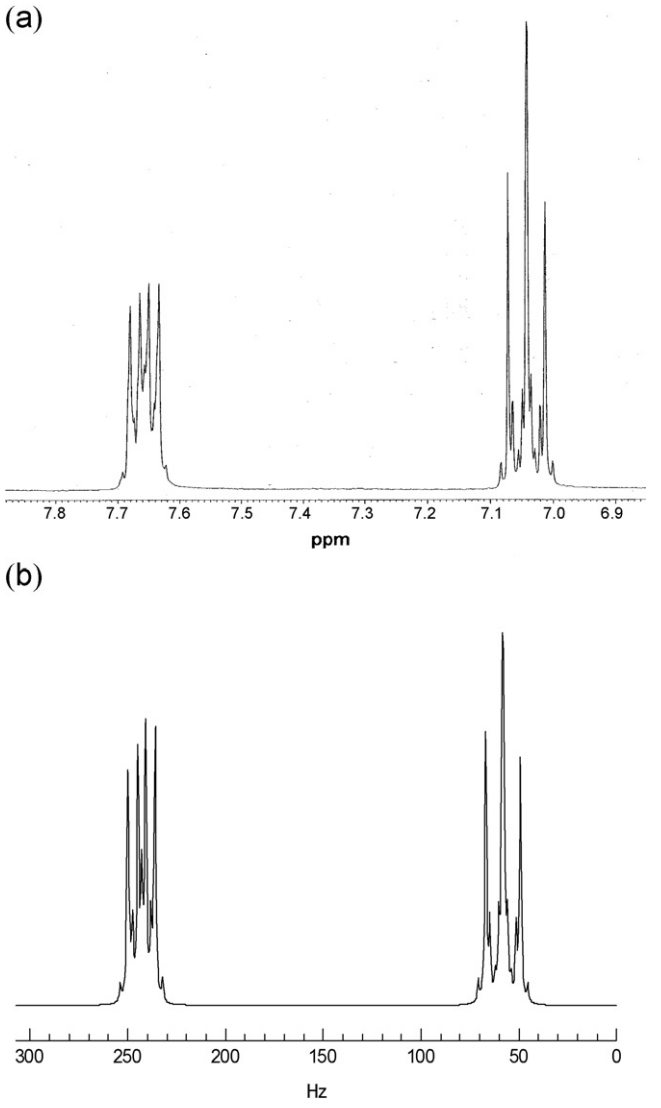

Fig. 4. (a) ^{1}H NMR spectrum for the aromatic protons of N^4-(4′-fluorophenyl)succinamic acid (**2**) in acetone-d_6 at 300.53 MHz; no line-broadening factor was applied. (b) Optimized simulation of the spectrum in (a) at 300 MHz using WINDNMR [8]. From the simultaneous simulations of the ^{1}H NMR spectrum shown in (a) and the ^{19}F NMR spectrum (not shown) the values for the six coupling constants are given in Table 1. The values for the coupling constants change upon formation of the amide bond.

(−118.03 ppm) agreed with the reported value for 4-fluoroacetanilide [21].

The ^{1}H NMR spectrum at 300 MHz for the aromatic protons of **2** in acetone-d_6 is shown in Fig. 4(a); it is readily apparent this is a second-order, AA′BB′X, system. Interestingly, formation of the amide bond results in a mirror image of the spectrum for 4-fluoroaniline. The 2′,6′ protons shift from δ 6.64 ppm to δ 7.67 ppm while the 3′,5′ protons at δ 6.82 ppm shift to δ 7.05 ppm. Similar observations have been reported for other derivatives of 4-fluoroaniline, for example, 4-fluoroacetanilide [23,24], N-fluorophenyl-1,8-naphthalimide [25], N-arylpyridinium salts [14], and trimethylammonium salts [14], as well as 4-fluoroaniline in the presence of a lanthanide shift reagent [12]. As for 4-fluoroaniline, simultaneous simulations of the ^{1}H NMR spectrum (Fig. 4(a)) and ^{19}F NMR spectrum (not shown) for **2** were done with WINDNMR [8] using the new set of parameters for 4-fluoroaniline (Table 1) as the basis set. The optimized simulation for the ^{1}H NMR spectrum is shown in Fig. 4(b) and the values obtained for the coupling constants from the optimized simulations are given in Table 1. Upon formation of the amide bond, the values for several of the coupling constants change; this is not surprising as the same phenomenon occurs in other 4′-substituted phenyl anilides [7]. The most significant changes occur in the values for J_{AB} (increases), J_{AF} (increases), and J_{BF} (decreases).

The ^{1}H NMR spectrum for the aromatic protons of **2** at 300 MHz was previously reported simply as two sets of multiplets, a first-order analysis [δ 7.20 (m, 2H), 7.60 (m, 2H)] [5], and at 400 MHz as simply chemical shifts [δ 7.12 (H-3′,5′), 7.59 (H-2′,6′)] [6]. The ^{1}H NMR spectrum for the aromatic protons of other derivatives of 4-fluoroaniline have been described by a first-order analysis: methyl N^4-(4′-fluorophenyl)succinamate [19], 4-fluoroacetanilide [20–24,26–28], N-fluorophenyl-1,8-naphthalimide [25], 5-*N*-(*N*-4′-fluorophenylacetamide)-10,20-diphenylporphyrin [29], and *N*-(4-fluorophenyl)-5-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide [30]. The ^{1}H NMR spectrum for the aromatic protons of **2** (Fig. 4(a)) shows that, upon formation of the amide bond, the spectrum for 4′-fluorophenyl group does not change from a second-order, AA′BB′X, spectrum to a first-order spectrum.

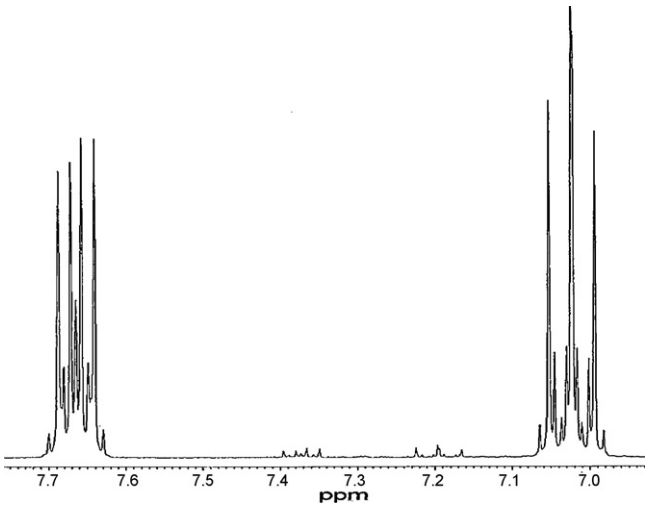

Fig. 5. ^{1}H NMR spectrum for the aromatic protons of N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid (**3**) in acetone-d_6. The signals at δ 7.20 and 7.37 ppm are signals for the aromatic protons of the small amount (2.5%) of N^4-(4′-fluorophenyl)-2,2-difluorosuccinamic acid formed in the reaction of 2,2-difluorosuccinic anhydride and 4-fluoroaniline, and shows that nucleophilic attack does not necessarily occur at the more electrophilic carbon. From the simultaneous simulations of this ^{1}H NMR spectrum and the ^{19}F NMR spectrum (not shown) the values for the six coupling constants for **3** are given in Table 1. The difluoromethylene affects the magnitudes of the values for several of the coupling constants, but does not affect the chemical shifts for the aromatic protons.

Although the solvent primarily used for the ^{1}H NMR analysis of N^4-(4′-fluorophenyl)succinamic acid, and *N*-4′-fluorophenyl anilides in general, has been Me_2SO-d_6, acetone-d_6 was the solvent used in this study because of a partial overlap of the residual solvent signal in Me_2SO-d_6 with the signals for the ethylene group (H2,H3) in several N^4-(4′-substituted phenyl)succinamic acids [7]. However, we investigated the solvent effect [31] on the ^{1}H NMR spectrum for the aromatic protons in **2** in Me_2SO-d_6 (not shown). The chemical shift for the 2′,6′ protons was shifted upfield approx. 0.08 ppm (δ 7.67 ppm in acetone-d_6 to δ 7.59 ppm in Me_2SO-d_6) while the chemical shift for the 3′,5′ protons was downfield approx. 0.07 ppm (δ 7.05 ppm in acetone-d_6 to δ 7.12 ppm in Me_2SO-d_6). Switching solvents resulted in small changes in the line spacings and intensities in the splitting patterns as expected for a second-order spin system, but the values for the six coupling constants obtained from the optimized simulations were the same in the two solvents for the aromatic protons of N^4-(4′-fluorophenyl)succinamic acid.

3.3. N^4-(4′-Fluorophenyl)-3,3-difluorosuccinamic acid

N^4-(4′-Fluorophenyl)-3,3-difluorosuccinamic acid (**3**) was synthesized by reaction of 2,2-difluorosuccinic anhydride (prepared by reaction of 2,2-difluorosuccinic acid with trifluoroacetic anhydride) with 4-fluoroaniline [11]. It was expected that the electrophilicity of the carbonyl carbon adjacent to the difluoromethylene group would give N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid as the only product as has been observed for other reactions [7,11]. However, interestingly, a very small percentage of N^4-(4′-fluorophenyl)-2,2-difluorosuccinamic acid (2.5%) was formed in the reaction as shown in the ^{1}H NMR spectrum for the aromatic protons (Fig. 5), as well as the methylene protons (not shown). In N^4-(4′-fluorophenyl)-2,2-difluorosuccinamic acid, the chemical shift for the 2′,6′ protons is δ 7.37 ppm and the chemical shift for the 3′,5′ protons is δ 7.20 ppm. In N^4-(4′-fluorophenyl)-3,3-difluorosuccinamic acid (**3**), the chemical shift for the 2′,6′ protons is δ 7.67 ppm and the chemical shift for the 3′,5′ protons is δ 7.03 ppm, which are nearly identical to the chemical shifts for the same protons in **2** (above), so the difluoromethylene group adjacent to the amide bond has no effect on the chemical shifts for the aromatic protons. The ^{19}F NMR spectrum for the aromatic fluorine and difluoromethylene group (not shown) also showed signals for the mixture of products. Only **3** was observed in the ^{13}C NMR spectrum due to signal to noise limitations. The chemical shifts and $J_{C,F}$ coupling constants for the aromatic carbons were consistent with **2** (above) and with values reported for 4-fluoroacetanilide [20–22], including the two sets of signals for C2′,6′ and C3′,5′ as reported by Kajihara et al. [20]. Coupling of the carbons to the fluoro groups was observed for the 4 aliphatic difluorosuccinamic acid carbons that were consistent with the values for carbon–fluorine coupling.

As for 4-fluoroaniline, simultaneous simulations of the second-order, AA′BB′X system in the ^{1}H NMR spectrum (Fig. 5) and ^{19}F NMR spectrum (not shown) for **3** were done with WINDNMR [8] using the new set of parameters for 4-fluoroaniline (Table 1) as the basis set. The values obtained for the coupling constants from the optimized simulations (not shown) are given in Table 1. As was true for **2**, the values for several of the coupling constants change upon formation of the amide bond. Importantly, the presence of the difluoromethylene group affects the magnitudes for the values for four of the coupling constants compared to **2**. It is particularly interesting that the coupling constants decrease in value. These results indicate that, in amide derivatives of 4-fluoroaniline from other fluoro acids, such as tetrafluorosuccinic acid, trifluoroacetic acid, etc., the fluoro groups affect the magnitudes of the coupling constants in the AA′BB′X spectrum for the aromatic protons.

4. Conclusions

A new set of parameters was obtained for the second-order, AA′BB′X, NMR spectrum for 4-fluoroaniline by simultaneous simulation of the ^{1}H and ^{19}F NMR spectra using WINDNMR. The NMR spectrum for the aromatic protons of 4′-fluoroanilides is second-order, AA′BB′X; simultaneous simulation of the ^{1}H and ^{19}F NMR spectra gave optimized values for the coupling constants that change upon formation of a carboxamide bond. The values for the coupling contants are the same in acetone-d_6 and in Me_2SO-d_6, although there are small changes in the chemical shifts for the protons in the two solvents; small changes occur in the line spacings and intensities in the splitting patterns in the NMR spectrum as expected for a second-order system.

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Appendix A

See Tables A1 and A2.

Table A1
Calculated frequencies and intensities for the optimized simulation of the ^{1}H NMR spectrum for 4-fluoroaniline at 300.53 MHz using the new set of parameters in Table 1 ($\Delta\nu_{AB}$ = 53.50 Hz).

Line	Frequency[a]	Intensity
1	121.71	2.32
2	66.40	2.32
3	114.35	2.32
4	122.67	2.32
5	70.00	1.69
6	122.70	1.69
7	59.85	1.69
8	113.92	1.69
9	61.76	0.78
10	57.54	0.78
11	65.86	0.78
12	126.31	0.78
13	66.48	1.68
14	116.16	1.68
15	122.08	1.68
16	66.46	1.68
17	105.56	0.77
18	113.88	0.77
19	113.91	0.77
20	65.34	0.77
21	55.21	0.31
22	53.91	0.31
23	110.22	0.31
24	57.52	0.31
25	52.90	1.23
26	61.22	1.23
27	113.74	1.23
28	113.76	1.23
29	58.14	2.35
30	61.84	2.35
31	117.50	2.35
32	107.37	2.35
33	64.06	1.45
34	120.37	1.45
35	113.29	1.45
36	61.81	1.45
37	104.96	0.91
38	53.49	0.91
39	52.87	0.91
40	113.81	0.91
41	104.94	0.31
42	49.28	0.31
43	101.44	0.31
44	57.50	0.31
45	59.41	1.43
46	111.57	1.43
47	105.02	1.43
48	52.86	1.43

[a] The chemical shift (in Hz) from TMS may be obtained by adding 1935.02 Hz to the frequency.

Table A2
Calculated frequencies and intensities for the optimized simulation of the ^{19}F NMR spectrum for 4-fluoroaniline at 282.78 MHz using the new set of parameters in Table 1.

Line	Frequency[a]	Intensity
1	34.64	1.00
2	30.00	1.00
3	25.86	1.00
4	25.85	1.00
5	30.00	1.00
6	21.21	1.00
7	21.20	1.00
8	17.06	1.00
9	25.36	1.00
10	21.21	1.00
11	21.21	1.00
12	12.41	1.00
13	16.55	1.00
14	16.57	1.00
15	12.41	1.00
16	7.77	1.00

[a] The chemical shift (in Hz) from fluorotrichloromethane may be obtained by adding −36840.63 Hz to the frequency.

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