Investigations on *N,N*-Dialkylbenzamides by NMR Spectroscopy

5†—Analysis of Static and Dynamic Proton NMR Spectra of 2-Fluoro- and 2,6-Difluoro-*N,N*-dimethyl- and *N,N*-Diethylbenzamides

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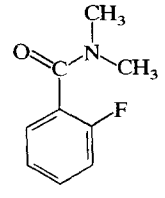
The analysis of static and dynamic proton NMR spectra of 2-fluoro- and 2,6-difluoro-*N,N*-dimethyl- and *N,N*-diethyl-benzamides at various temperatures has been carried out. The conformations of the compounds have been deduced on the basis of long-range through-space proton–fluorine couplings. Free energies of activation of amide rotation have been determined for all compounds, and of carbonyl-ring rotation for one compound.

INTRODUCTION

In the series of ring-substituted *N,N*-dialkylbenzamides the fluoro compounds are a particularly interesting case, because they exhibit long-range spin–spin coupling between alkyl protons and fluorine occupying *ortho*-positions in the ring.[2,3] This coupling causes substantial complication in the analysis of the spectra; however, it provides an additional unique source of information concerning the conformations of the compounds. Continuing our NMR investigations on benzamides,[1,4–6] we report and discuss the results of the detailed analysis of variable-temperature NMR spectra of 2-fluoro-*N,N*-dimethylbenzamide (**1**), 2-fluoro-*N,N*-diethylbenzamide (**2**), 2,6-difluoro-*N,N*-dimethylbenzamide (**3**) and 2,6-difluoro-*N,N*-diethylbenzamide (**4**).



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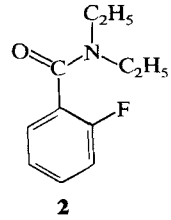

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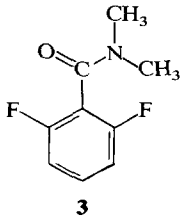

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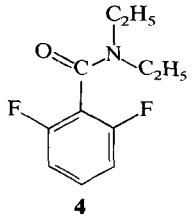

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EXPERIMENTAL

Syntheses

Compounds **1–4** were prepared in a standard manner by the reaction of a toluene solution of the corresponding acid chloride with an aqueous solution of dimethyl- or diethyl-amine, respectively. 2,6-Difluorobenzoic acid, the starting material for **3** and **4**, was obtained from 2,6-dinitrotoluene according to a modified procedure from Lock.[7] This consisted in direct oxidation of 2,6-difluorobenzyl bromide to the acid with $KMnO_4$ (yield 64%). The resulting amides were purified by distillation. The purity of the compounds was checked by TLC and NMR spectroscopy. The boiling points of **1** and **2** have been given previously;[1] for **3** b.p. = 88 °C/0.6 Torr and for **4** b.p. = 96 °C/0.6 Torr.

NMR Spectra

NMR spectra were recorded for 0.5 M solutions of **1–4** in CD_3CN. Five-millimetre NMR tubes were carefully degassed and sealed. FT ^1H NMR spectra were recorded on a Varian XL100 spectrometer at 100 MHz. At least eight scans per spectrum were accumulated and the final digitization density was greater than three points per half-height line width for the static spectra and at least six points per hertz for the dynamic spectra. The technique of temperature determination (accuracy 0.3 K) has been described elsewhere.[8]

For the analysis of the static NMR spectra the DAVINS[9] computer program and for the dynamic spectra the DNMR5[10] program were used. The calculations were performed on a CDC Cyber 175 computer in the Leibniz Rechenzentrum, Munich. Chemical

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Table 1. Spectral parameters[a] of the aromatic region of the spectra of compounds 1–4

Compd.	δ_3	δ_4	δ_5	δ_6	$J(23)$	$J(24)$	$J(25)$
1	7.1685(1)	7.4456(1)	7.2433(1)	7.3325(1)	9.97(1)	5.50(1)	0.13(1)
2	7.1675(1)	7.4305(1)	7.2350(1)	7.3010(1)	9.83(1)	5.52(1)	0.11(1)
3	7.0551(1)	7.4594(1)	7.0551(1)	—	8.87(1)	6.64(1)	−1.07(1)
4	7.0492(1)	7.4447(1)	7.0492(1)	—	8.78(1)	6.65(1)	−1.07(1)

Compd.	$J(26)$	$J(34)$	$J(35)$	$J(36)$	$J(45)$	$J(46)$	$J(56)$	$W_{1/2}$
1	6.93(1)	8.42(1)	1.04(1)	0.40(1)	7.49(1)	1.80(1)	7.63(1)	0.18(1)
2	6.93(1)	8.42(1)	1.05(1)	0.39(1)	7.49(1)	1.80(1)	7.61(1)	0.19(1)
3	3.82(1)	8.52(1)	0.88(1)	−1.07(1)	8.52(1)	6.64(1)	8.87(1)	0.18(1)
4	3.96(1)	8.52(1)	0.88(1)	−1.07(1)	8.52(1)	6.65(1)	8.78(1)	0.19(1)

[a] Chemical shifts are given in ppm from TMS and coupling constants and line widths in Hz. The standard deviations in parentheses refer to the last digit listed.

shifts were determined by first referring the results from the analysis (which were relative to a suitable chosen zero) to the middle signal of the quintet of the proton of the deuteriated solvent, and then adding the chemical shift of the solvent relative to TMS.

RESULTS AND DISCUSSION

The ^{1}H NMR spectra of **1–4** show a complicated pattern for the aromatic protons, which is independent of temperature and well separated from the remaining part of the spectrum. The analysis of this region of the spectrum, treated as an ABCDX spin system for **1** and **2**, and as an ABB'XX' spin system for **3** and **4** (where X and X' denote fluorine) with the DAVINS program is a trivial task. The results of these calculations are given in Table 1. The determined line widths can serve as a measure of the quality of the spectra. Excellent agreement between the experimental and theoretical spectra proves that the neglect of long-range spin–spin couplings between aliphatic and aromatic protons is fully justified.

The aliphatic regions of the spectra of **1–4** are temperature dependent, since they are affected by various internal rotation processes. Rotations of methyl and methylene groups around C—N and C—C single bonds are, of course, rapid on the NMR time scale over the whole range of accessible temperatures.[11,12]

At room temperature, amide rotation around the (CO)—N bond is restricted for **1–4**, and geminal alkyls give well separated multiplets. The rotation around the Ar—(CO) single bond has no influence on the spectra of **1** and **3** because of symmetry reasons. The methyl regions of the spectra of these compounds taken at room temperature were analysed as A_3B_3X and $A_3B_3X_2$ systems, respectively. The results of these calculations are presented in Table 2.

An additional test calculation with the assumption that $J(AB) = 0$ showed that the remaining parameters are virtually unaffected by this assumption. The neglect of the $J(BX)$ coupling gave slightly more pronounced effects. The fact that the $J(BX)$ coupling constants are very small is in accord with expectation,[13–15] if one takes into account that the methyl protons are removed from fluorine by six bonds and that the low-field methyl signal (B) belongs to the methyl group in the *Z*-configuration.[2,16] The spin–spin coupling between *ortho*-fluorines and *E*-methyl protons results from a through-space mechanism, rather than a through-bond mechanism, and its magnitude could be used as a measure of the through-space distance between coupled nuclei.[2,13–15] It explains, in an obvious manner, the difference in the magnitude of the couplings between the fluorines and the *Z*- and *E*-methyl groups. Comparison of the magnitudes of $J(AX)$ in **1** and **3** gives information about the conformational preference in **1**. The equilibrium conformation of **1** and **3** is a result of the delicate interplay of steric repulsive forces, interactions between charges centred mainly on heteroatoms and of the tendency of maximalization of conjugation of the *p* and π electron systems.

One can expect four energy minima for the carbonyl-ring rotation. These minima are equivalent in the case of **3** because of symmetry reasons. The $J(AX)$ coupling constants depend in this case only on the twist angle between the aromatic ring plane and the amide moiety, and equal the arithmetic average of the coupling constants between the methyl protons and the fluorines in the 2- and 6-positions. Taking into account that through-space coupling constants decrease rapidly with increasing distance between coupled nuclei,[14] one can expect that the coupling constant between the methyl protons and the more distant fluorine should be close to zero. Therefore, the other coupling constant should be of the order of 1.3 Hz, i.e. twice as large as the observed average value of $J(AX)$. In **1** there are two pairs of equivalent energy minima during the carbonyl-ring rotation. It is expected that twist angles in these minima will be similar to those in **3**. This expectation is supported by the observed similar values of $\Delta\delta_{AB}$ in the spectra of **1**

Table 2. Spectral parameters[a,b] for compounds 1 and 3, aliphatic region, at 26 °C

Compd.	δ_A	δ_B	$^6J(AX)$	$^6J(BX)$	$^4J(AB)$	$W_{1/2}$
1	2.8449(1)	3.0286(1)	1.20(1)	0.16(1)	0.09(1)	0.40(1)
3	2.8774(1)	3.0544(1)	0.64(1)	0.08(1)	0.01(3)	0.33(1)

[a] See Table 1.
[b] A, the *E*-methyl protons (upfield multiplet); B, the *Z*-methyl protons (low-field singlet).

(0.184 ppm) and of **3** (0.177 ppm), since this quantity is governed mainly by the twist angle.[4,16] The values of $J(AX) = 1.2$ Hz at room temperature and 1.3 Hz at −37 °C suggest that the conformation with the methyl group closer to fluorine is strongly preferred for **1**. Such a preference can also be predicted if one considers coulombic interaction between fluorine, being the centre of negative charge, and the amide moiety.

The larger line width determined in the methyl region of the spectrum (0.40 Hz) than in the aromatic region (0.18 Hz) in the case of **1** can be attributed, at least in part, to dynamic effects. However, in the case of **3**, which exhibits a much higher coalescence temperature, the observed difference of 0.15 Hz in line widths must be due to relaxation effects.

The spectra of **2** and **4** measured at room temperature consist of two slightly overlapping ethyl patterns, showing no further fine splitting but with different apparent line widths in every multiplet. We also failed to see the expected fine splitting in the ^{19}F NMR spectra, under conditions of noise decoupling from the aromatic protons. The appropriate splitting appeared in the ^{19}F spectra of **1** and **3**, although the apparent coupling constants were slightly decreased owing to off-resonance decoupling effects. However, in the spectra of the ethyl compounds under identical experimental conditions, we obtained only broadened singlets. The lack of the expected triplet splittings is certainly due to additional splittings of the signal caused by remaining long-range couplings.

Strictly the ethyl regions of the proton spectra of **2** and **4** are parts of 11 and 12 spin systems, respectively, of the type A_3B_3CDEFX and $A_3B_3CC'DD'XX'$ when assuming restricted carbonyl-ring rotation, or of the type $A_3B_3CC'DD'X$ and $A_3B_3CC'DD'X_2$ in the case of fast rotation. Certainly some of the long-range spin–spin couplings are ineffective, and can be neglected in the analysis. In spite of this, the analysis of such large spin systems by the DAVINS program, although possible, would in practice require very long computing times. Moreover, in view of the simplicity of the experimental spectra, one would expect strong correlations between some parameters, and there is no chance of obtaining reliable results by brute force methods.

We decided to perform several calculations in order to prove which of the long-range couplings differ substantially from zero, and to estimate their values. In the calculations we exploited the fact that carbonyl-ring rotation is fast at room temperature (see below). Moreover, from the long-range couplings between protons belonging to different ethyl groups we neglected all but the inter-methylene couplings. We also assumed that the natural line width in all multiplets is identical. In several runs we also made simplifying assumptions neglecting methylene–methylene coupling, or fluorine–*Z*-ethyl proton coupling, or both. All these assumptions allow us to apply simplified model spin systems in the calculations. In the first series of calculations (A) we treated the spectra as the superposition of two A_3B_2X or $A_3B_2X_2$ spin systems, respectively. In the second series (B), analysing the methyl region of the spectra of **2** and **4**, we adopted as a model spin system $A_3B_3C_2X$ and $A_3B_3C_2X_2$, respectively, assuming $J(AB) = 0$ and ν_C equals the mean value of the chemical shifts of the methylene protons. In the third series of calculations (C), analysing the methylene part of the spectrum, we adopted as model spin systems $A_3B_2C_2X$ and $A_3B_2C_2X_2$, respectively, assuming for ν_A the mean value of the chemical shifts of the methyl protons. Parameters ν_X in all calculations, ν_C and $J(CX)$ in calculations (B) and ν_A and $J(AX)$ in calculations (C) have not been optimized.

The results of these calculations (see Table 3) can be summarized as follows. (i) In spite of the lack of fine splitting in the experimental spectra, the long-range couplings between fluorines and protons of the *E*-ethyl group are pronounced. The values obtained for these constants are practically independent of the type of calculation. (ii) Coupling constants between methylene groups influence the spectrum, since calculations of type (A) gave too narrow and too intense lines in the methylene regions of the theoretical spectra. (iii) The best fit between experimental and theoretical spectra was obtained when the coupling constant between fluorine and the *Z*-methylene protons was also treated as a variable parameter.

Based on the fact that spin–spin couplings between fluorine and the *E*-methylene group are practically identical for **2** and **4**, we concluded that there is no conformational preference with respect to rotation around the ring-carbonyl bond. The difference in conformational preferences in **1** and **2** can be attributed to the difference in the steric requirements of methyl and ethyl groups.

The four-bond spin–spin coupling between protons α to nitrogen in *N,N*-dialkylamides is usually negligible (see, however, Refs 12 and 17). The non-zero value of this coupling shown for **2** and **4** may have consequences in the analysis of dynamic spectra in the case of low exchange rates.[18]

The relatively high value of the line width obtained for **2** is certainly caused by dynamic effects. The line width for **4** is slightly larger than for **3** (see Tables 2 and 3), which is probably the result of unresolved spin–spin couplings.

Among the investigated compounds, only the spectra of **2** show pronounced changes on lowering the temperature. The methylene protons of the *Z*-ethyl group, which give the low-field multiplet, become anisochronous and the quartet observed at room temperature splits into a complicated multiplet. These

Table 3. Spectral parameters[a,b,c] for compounds 2 and 4, aliphatic region, at 26 °C

Compd.	δ_A	δ_B	δ_C	δ_D	$W_{1/2}$
2	1.0165(1)	1.1869(1)	3.1629(1)	3.5023(1)	0.70(1)
4	1.0365(1)	1.1915(1)	3.1936(1)	3.5264(1)	0.39(1)

Compd.	^3J(AC)	^7J(AX)	^6J(CX)	^3J(BD)	^6J(DX)	^4J(CD)
2	7.13(1)	0.47(1)	0.70(2)	7.12(1)	0.22(7)	0.35(2)
4	7.15(1)	0.45(1)	0.66(1)	7.13(1)	0.26(2)	0.24(2)

[a] See Table 1.
[b] A_3C_2, the *E*-ethyl protons (upfield multiplets); B_3D_2, the *Z*-ethyl protons (low-field multiplets).
[c] Coupling constants which are not specified are assumed to be zero.

changes are not accompanied by any visible changes in the respective methyl triplet, since the two vicinal coupling constants are equal. The signals of the *E*-ethyl group are not affected in this temperature range. Such phenomena observed for 2-substituted *N,N*-diethylbenzamides were proved to be due to the restricted rotation around the ring-carbonyl bond.[19,20] Even at the lowest temperature accessible in CD_3CN, the lines are still broadened. The detailed analysis of the *Z*-methylene signal of the static spectrum at the low exchange limit was, therefore, not possible.

The analysis of the dynamic spectra was performed in two steps. First, the methyl region of the spectrum was analysed using calculations of type (B), treating the spectrum as being static. Then, the *Z*-methylene region of the spectrum was analysed by the DNMR5 program as the BC part of exchanging spin systems $A_3BCX \rightleftharpoons A_3CBX$. In this calculation the line width was not optimized, and its value was assumed to be greater by 0.20 Hz than that obtained in the first step of the analysis. This correction was added to compensate for the neglected long-range couplings. This is, of course, an approximate analysis. However, the errors introduced can be assumed to be negligible if only the free energy of activation is reported: $\Delta G^{\neq} = 51.1\ kJ\ mol^{-1}$. This value is based on the spectrum at −45 °C. This barrier can be compared with that of 2-chloro *N,N* diethylbenzamide ($\Delta G^{\neq} = 62.3\ kJ\ mol^{-1}$).[21] The difference is certainly due to the difference in the volume of the ring substituent.

For **1–4** one observes dynamic phenomena above ambient temperature due to amide rotation, which finally causes signal averaging of the protons of the geminal *N*-alkyl groups. The full analysis of the dynamic spectra of **1** and **3** is feasible using the standard version of DNMR5. The spectra of **1** were analysed on the basis of the correct spin system $A_3B_3X \rightleftharpoons B_3A_3X$, while for **3** the methyl signals were treated as A and B parts of exchanging systems $A_3X_2 \rightleftharpoons B_3X_2$ without introducing measurable errors. In the case of **2** and **4** the analysis is not so trivial, and an unsimplified treatment is not possible. To overcome the introduction of errors by neglecting one or more coupling constants through the simplification of the spin system, we decided to analyse only the methyl parts of the spectra, as A and B parts of $A_3C_2X \rightleftharpoons B_3C_2X$ and $A_3C_2X_2 \rightleftharpoons B_3C_2X_2$ systems, respectively, undergoing non-mutual exchange.

The determined free energies of activation of the amide rotation for **1–4** are shown in Table 4. Their values agree with trends known from the literature.[1,5,22] The differences between the barriers determined for methyl and ethyl compounds can be explained on assuming that the increase of the bulk of the *N*-substituents sterically destabilizes the ethyl compound, and that in the case of the monofluoro compound (**2**) destabilization is stronger in the ground state of rotation, whereas in the case of the difluoro compound (**4**) destabilization is more pronounced in the transition state of the rotation.

Table 4. Free energies of activation, $\Delta G^{\neq}$, for amide rotation in dialkylbenzamides

	N,N-Dimethylbenzamides		*N,N*-Diethylbenzamides	
Ring substituent	$\Delta G^{\neq}$(kJ mol^{-1})	T(K)	$\Delta G^{\neq}$(kJ mol^{-1})	T(K)
H[5]	65.2	291	62.9	291
2-Fluoro	75.5	353	74.5	353
2,6-Difluoro	84.1	367	86.4	367
2,6-Dichloro[6]	92.1	418	99.5	418

CONCLUSIONS

In compounds **1–4** protons of *E*-alkyl groups exhibit long-range through-space spin–spin coupling with fluorines in the *ortho*-position.

In *N,N*-diethyl compounds **2** and **4**, the magnitude of the long-range spin–spin coupling constant between methylene protons is not negligible.

Considering four possible conformations with twisted planes of the amide moiety and the aromatic ring, resulting from competition between steric repulsion and the tendency for maximization of conjugation, in the case of **1** the conformation with the methyl group closer to fluorine is preferred, whereas in the case of **2** there is no preference.

Free energies of activation of carbonyl-ring rotation for **2** and amide rotation for **1–4** have been determined.

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