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Atropisomerism about a heptafluoroisopropyl to aryl bond in 5-amino-4-heptafluoroisopropyl indazole

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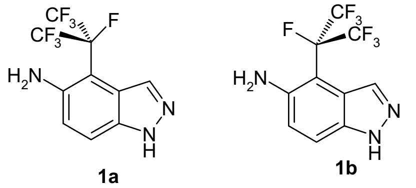
ABSTRACT

The atropisomerism about a heptafluoroisopropyl to aryl bond in 5-amino-4-heptafluoroisopropyl indazole is reported. The through-space hydrogen fluorine coupling of the indazole H-3 proton with the tertiary F atom is shown to be useful to distinguish the two rotamers. The same atropisomerism is also observed in the analogous indole, benzofuran, and naphthaline derivatives.

In the context of a program directed toward the synthesis of new aniline analogues, we prepared 5-amino-4-heptafluoroisopropyl indazole **1** by adapting a described method.[1] The reaction of 5-amino-indazole with heptafluoroisopropyl iodide and sodium dithionite in a mixture of water and *t*-butylmethylether at room temperature gave **1** in 70% yield.[2] The ^{1}H NMR spectrum of **1** shows two species in a 60:40 ratio. The two species are demonstrated to be interconverting rotamers (see Scheme 1) by the temperature dependence of the ^{1}H NMR spectrum as well as by saturation transfer in a 1D NOE difference experiment.

The major difference between the ^{1}H NMR spectra of the two rotamers is the observation of a through-space hydrogen fluorine coupling[3] between the indazole H-3 proton and the tertiary F atom (J_{HF} = 7.9 Hz, also observable in the proton coupled ^{19}F NMR spectrum) in the major rotamer **1a**. The signal of the indazole H-3 proton of the other rotamer is a broad singlet. This broadening is partly caused by a coupling with the six CF_3 F atoms (J_{HF} = 1.3 Hz, as measured in the proton coupled ^{19}F NMR spectrum). Independent proof of the assignment of the configuration of the two rotamers is found in the ^{13}C NMR spectrum: C(5) of the major isomer **1a** exhibits a $^3J_{CF}$ of 8 Hz, while no such splitting is resolved in the signal of C(5) of the minor rotamer **1b** due to the Karplus dependence of this vicinal coupling constant.[4] Furthermore, the signal of C(3) in **1a** shows a through-space coupling with the tertiary F atom (J_{CF} = 24.8 Hz), while such a coupling is absent in the signal of C(3) in **1b**. The NMR data of **1a** and **1b** are collected in Table 1. The ^{1}H and ^{13}C signal assignments listed are supported by gHSQC and gHMBC experiments.



Scheme 1. Structure of the two rotameric 4-heptafluoroisopropyl indazoles.

The cause for the observed atropisomerism is the bulkiness of the two trifluoro methyl groups, which are rotated out of the plane of the aryl system, while the tertiary F atom is located in the plane of the aryl system. Such a conformation has been shown for heptafluoroisopropyl substituted phthalonitriles by X-ray crystallography.[5]

The barrier of rotation around the heptafluoroisopropyl to aryl single bond in **1** was determined[6] from the coalescence temperature of H-6 in $CDCl_2CDCl_2$ (108 °C) to be 19.4 kcal/mol.

The indole, benzofuran, and naphthaline derivatives analogous to **1** were also measured (see Scheme 2). They show likewise two rotamers in their ^{1}H NMR spectra. Based on the analysis of **1**, the rotamer analogous to **1a** can easily be assigned using the large through-space coupling of the proton in peri position to the heptafluoroisopropyl substituent. These rotamers analogous to **1a** are shown in Scheme 2 together with the through-space proton fluorine coupling constant. The relative amount of the rotamer drawn in Scheme 2 is 57% for **2**,[2] 63% for **3**,[2] and 48% for **4**.[2]

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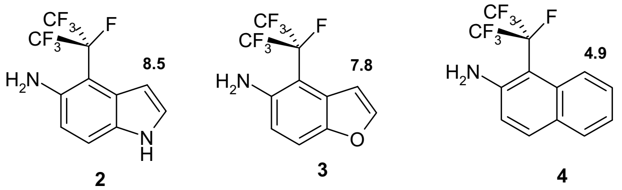
Table 1
^{1}H, ^{19}F, and ^{13}C NMR data[a] of **1a** and **1b**

Position	**1a**, δ_H or δ_F	**1b**, δ_H or δ_F	**1a**, δ_C/J_{CF} (Hz)	**1b**, δ_C/J_{CF} (Hz)
3	8.11 (br d, 7.9)	7.96 (br s)	131.9/24.8	130.6/0
3a			121.1/0	118.8/0[c]
4			96.3/25.1	91.0/12.8
5			141.0/8.0	144.3/0
6	6.85 (dd, 8.8, 1.4)	6.80 (dd, 9.0, 0.9)	121.6/0	122.1/0
7	7.45 (dd, 8.8, 0.8)	7.43 (dd, 9.0, 0.8)	115.0/0	115.1/0
7a			135.3/0	134.6/0
CF_3[b]	−76.2 (d, 5.9)	−76.8 (dd, 5.2, 1.3)	121.3/ 287.3, 28.6	121.2/287.9, 28.4
CF[b]	−171.6 (m, $\sum J = 43$)	−180.8 (sept b, $\sum J = 31$)	95.0/m	95.7/m

[a] δ_H or δ_F, resp., in $CDCl_3$ (mult., J in Hz), recorded at 500 or 470 MHz; δ_C in DMSO-d_6, recorded at 125 MHz.
[b] cf. ^{19}F chemical shifts in heptafluoroisopropyl benzene.[7]
[c] Broad signal.



Scheme 2. Through-space coupling (Hz) between the tertiary F atom and the proton in peri position to the perfluoroisopropyl substituent in **2**–**4**.

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Supplementary data

Full ^{13}C NMR spectra (125 MHz) and ^{1}H NMR (500 MHz) spectra for compounds **1** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.006.

References and notes

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2. *General procedure, for example: Synthesis of 5-amino-4-heptafluoroisopropyl indazole* (**1**): To a mixture of water (15 mL) and *t*-butylmethylether were added successively 5-aminoindazole (37 mmol, 5.0 g, 1.0 equiv), heptafluoroisopropyl iodide (44.4 mmol, 13.14 g, 1.20 equiv), sodium dithionite (44.4 mmol, 7.73 g, 1.2 equiv), sodium bicarbonate (44.4 mmol, 3.73 g, 1.2 equiv) and tetrabutylammonium hydrogen sulfate (4.07 mmol, 1.38 g, 0.11 equiv). The resulting mixture was stirred at room temperature overnight. The phases were separated. Hundred milliliters of *t*-butylmethylether were added to the aqueous phase. The mixture was filtered and the phases were separated. This operation was repeated one more time. The organic phases were mixed and dried with sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica gel with cyclohexane/ethyl acetate (3:1), yielding 5-amino-4-heptafluoroisopropyl indazole (7.9 g, 70% yield).
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