A Theoretical Analysis of the ^{19}F NMR Spectrum of 5-(Perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol

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Abstract: The ^{1}H and ^{19}F spectra of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)-pyrazolidin-3-ol reported unassigned in the literature were compared with GIAO/ B3LYP/6-311++G(d,p) calculations for the different isomers and conformers, the latter structures were searched using the CREST program. The signal assignment corresponds to the *3S,4R,5R* or *3R,4S,5S* diastereoisomers.

**Keywords**: GIAO, CREST, pyrazolidine, ^{19}F NMR.

INTRODUCTION

IN the year 2000, Coe et al. reported the ^{1}H and ^{19}F NMR spectra in CDCl$_3$ of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol (**1**).[1] This compound resulted from a study of perfluoro-3,4-dimethylhex-3-en-2-one, a highly reactive α,β-unsaturated ketone, with nucleophiles including hydrazine, it is the highest fluorinated pyrazolidine.

Four of the five ^{19}F signals were not assigned, only that of the CF$_2$ at position 5 was assigned to –111 ppm. No decimal figures were given indicating that the signal was broad. In molecule **1** all the carbon atoms are stereogenic; in the case of C4 that implies that the F atoms of the CF$_2$

group are anisochronous and enantiotopic; therefore they appear as an **ab** system with a $^{2}J_{FF}$ geminal coupling constant, this added to $^{3}J_{FF}$ couplings with the adjacent CF$_3$ groups and $^{4}J_{FF}$ couplings with the CF$_3$ on C4, yield a very complex system for each fluorine atom that results on a broad signal. Is important to note that none of the remaining signals appear split indicating that **1** is not a mixture of compounds.

COMPUTATIONAL DETAILS

The CREST program was used to search all possible conformers.[2] All the minima obtained with this method has been subject to a fully optimization with the hybrid DFT computational method B3LYP and 6-311++G(d,p) basis set,[3–6] including the empirical dispersion with the D3 parameters and the Becke-Johnson damping function, D3(BJ).[7] Frequency calculations were carried out at the same computational level to verify that the structures obtained correspond to energetic minima (0 imaginary frequencies). These geometries, were used for the calculations of the absolute chemical shieldings with the GIAO method.[8,9] All the DFT calculations were carried out with the Gaussian-16 package.[10] Equations 1, 2 and 3 were used to transform σ absolute shieldings into δ chemical shifts.[11–13]
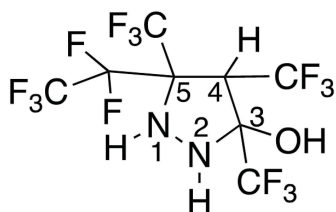
Scheme 1. Structure of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol.

δ^1H Calc. $= 31.0 - 0.97 \times \delta^1$H; (reference TMS, 0:00 ppm)

$$(1)$$

δ^{13}C Calc. $= 175.7 - 0.963 \times \delta^{13}$C; (reference TMS, 0:00 ppm)

$$(2)$$

δ^{19}F Calc. $= 162.1 - 0.959 \times \delta^{19}$F; (reference CFCl$_3$, 0:00 ppm)

$$(3)$$

The ring puckering has been calculated using the parameters (Q and φ) proposed by Cremer and Pople (CP).[14,15] The numbering for the atoms of the pyrazolidine ring start with the two nitrogen atoms as previously used in the literature.[16] Even with this limitation, the numbering could be clockwise and counter-clockwise. In the case of compound **1** the problem is simplified due to the presence of the OH group at position 3, pyrazolidin-3-ol, that defines unambiguously the ring numbering.

RESULTS AND DISCUSSION

Although Coe et al. paper has been cited only seven times between 2002–2012 and a single time after that period in 2023 according to the Web of Science[17] their results are one of the rare perfluorinated pyrazolidines with complete ^{19}F NMR results.

The correct names of the four isomers are *3R,4R,5S*-5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol, *3R,4R,5S*-5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)-pyrazolidin-3-ol, *3R,4S,5R*-5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol and *3S,4R,5R*-5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolidin-3-ol, but for the sake of simplicity we will use *RRR*, *RRS*, *RSR* and *SRS* to name them.

We initiated our investigation by investigating the number of isomers of **1**.

They are three stereogenic carbon atoms, therefore, there are $2^3 = 8$ isomers half of them being enantiomers, that will not be considered because no chiral shift reagent was used. Grimme's CREST program was used to calculate all the possible conformers for each isomer: 15 for *RRR*, 15 for *RRS*, 59 for *RSR* and 26 for *SRR*, Figure 1. In the Cremer-Pople pseudorotational wheel the four more stable isomers have the following coordinates *RRR* $Q = 0.282$, $\varphi = 359.65°$, [1]E; *RRS* $Q = 0.268$, $\varphi = 227.13°$, [2]T3; *RSR* $Q = 0.312$, $\varphi = 56.74°$, [3]T2; *SRR*, $Q = 0.255$, $\varphi = 353.07°$, [1]E. The relative energies with regard to the most stable, the RSR one, are given in Figure 1. In Figure 2 are the calculated and the experimental chemical shifts.

The comparison between the calculated and experimental values has been carried out using simple regression:

δ^{19}F Exp. $= -(5.3 \pm 8.0) + (0.94 \pm 0.10)RRR$, $n = 5$, $R^2 = 0.969$

$$(4)$$

δ^{19}F Exp. $= -(10.0 \pm 6.1) + (0.88 \pm 0.07)RRS$, $n = 5$, $R^2 = 0.979$

$$(5)$$

δ^{19}F Exp. $= -(12.0 \pm 5.1) + (0.85 \pm 0.06)RSR$, $n = 5$, $R^2 = 0.984$

$$(6)$$

δ^{19}F Exp. $= -(1.6 \pm 8.0) + (0.97 \pm 0.04)SRR$, $n = 5$, $R^2 = 0.996$

$$(7)$$

It is clear that the experimental data correspond to the *SRR* isomer, Eq. (7), almost isoenergetic with the *RSR*, Eq. (6). It is possible to include the ^{1}H chemical shifts leaving aside that of the OH group that is too sensitive to solvent effects, Eq. (8) (the OH proton is 5.0 ± 1.2 ppm low field).

RRR	RRS	RSR	SRR
13.5 kJ·mol⁻¹	8.4 kJ·mol⁻¹	0.0 kJ·mol⁻¹	0.1 kJ·mol⁻¹
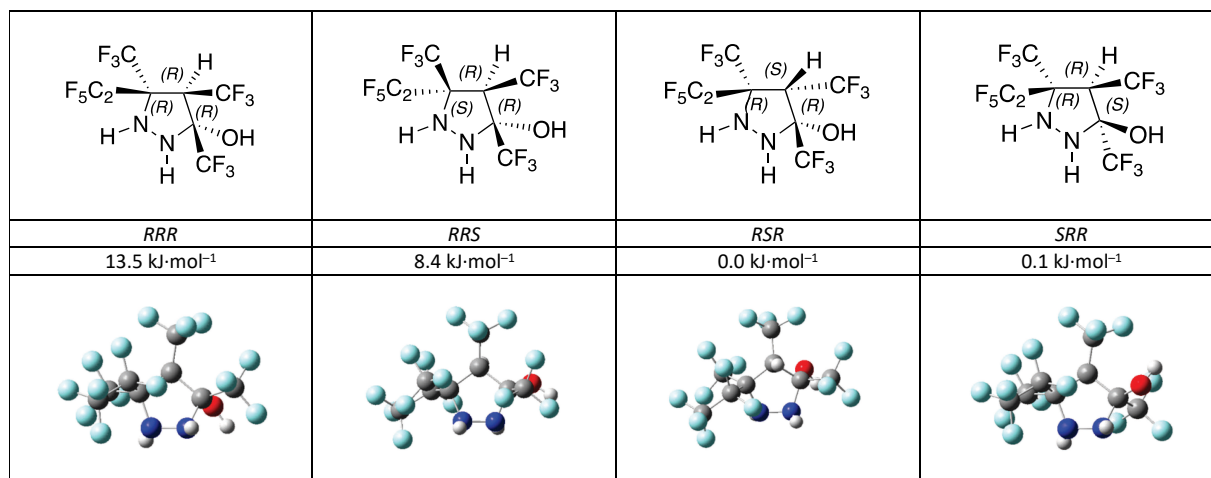
**Figure 1.** Relative energies and optimized geometries of the most stable conformer of each isomer.
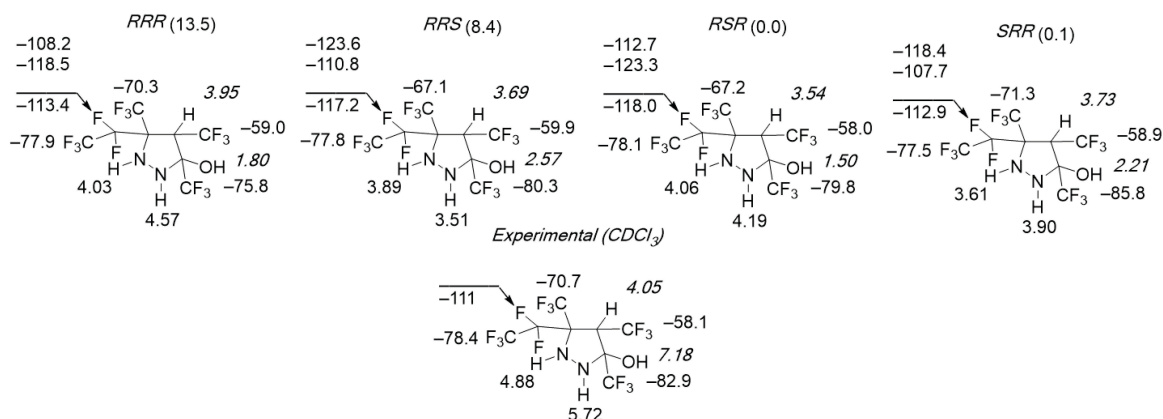
Figure 2. Calculated ¹⁹F chemical shifts of the *RRR*, *RRS*, *RSR* and *SRR* isomers with indication of the relative energy, kJ mol⁻¹, in parenthesis. The experimental data is also available.

$$\text{Exp.} = (0.99 \pm 0.06)SRR,\ n = 7,\ R^2 = 1.000 \qquad (8)$$

Note that Eq. (7) and Eq. (8) have not only better correlation coefficients but non-significant intercepts and slopes closer to 1 than in equations 4–6. Coe et al.[1] reported that H4 shows a quadruplet due to its $^4J_{HF}$ coupling constant of 9 Hz with a CF₃ at –82.9 ppm, that we have assigned to 3-CF₃ (the 5-CF₃ is also separated by four bonds

from H4). The sequence of reactions to prepare pyrazolidine 1 is summarized in Figure 3.[18]

The authors do not explain how they assigned the *E / Z* isomerism of hexenones **3** but in the paper that describes pyrazolidine **1** they represented the hexanone as the **3***E* isomer.[1] Fortunately, they reported the ¹⁹F chemical shifts of both isomers.[18] We decided to carry out GIAO calculations of **3***E* and **3***Z* (Figure 4).
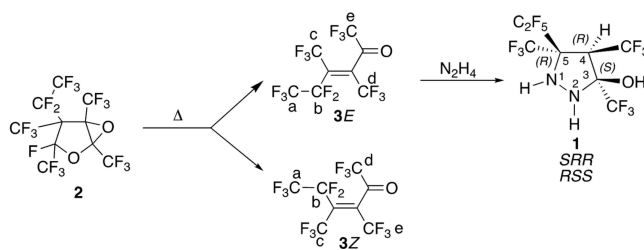
Figure 3. Pyrolysis of the 2,6-dioxabicyclo[3.1.0]hexane **2** afforded a mixture of *Z* and *E* forms of 1,1,1,5,5,6,6,6-octafluoro-3,4-bis(trifluoromethyl)hex-3-en-2-one, with the *E* in slight excess, that were separated by Gas-Liquid Chromatography (GLC).

Figure 4. Optimized geometries and relative energies of the two conformers of each isomer.

Table 1. ¹⁹F experimental and calculated chemical shifts (ppm).

Group[a]	Exp. **3***E*	Exp. **3***E*	**3***E*1	**3***E*2	**3***Z*1	**3***Z*2
a	−80.7	−84.4	−77.57	−77.84	−81.94	−71.44
b	−109.1	−107.5	−106.86	−107.49	−103.60	−97.20
c	−56.3	−59.5	−54.95	−55.17	−55.10	−56.58
d[b]	−76.0	−78.4	−73.17	−76.54	−53.34	−54.00
e[b]	−57.5	−59.0	−53.62	−55.17	−74.87	−77.35

[a] The fluorine atoms in each group are defined in Figure 3

[b] These signals were erroneously assigned experimentally.

The correlation matrix proves that the assignment of isomers was correct but that of signals of groups d and e was erroneous. After this was corrected, the regression equations are:

$$\delta\,^{19}\text{F Exp. } 3E = -(3.2 \pm 1.9) + (0.99 \pm 0.02)\, 3E1,$$
$$n = 5,\ R^2 = 0.998 \tag{9}$$

$$\delta\,^{19}\text{F Exp. } 3Z = -(6.4 \pm 2.0) + (0.97 \pm 0.03)\, 3Z1,$$
$$n = 5,\ R^2 = 0.998 \tag{10}$$

The most stable calculated isomers are the best correlated.

CONCLUSION

Although the *SRR* or *RSS* configuration of compound **1**, in particular the *RR* or *SS* stereochemistry of position 4 and 5 of the pyrazolidine, and the *E* isomerism of the starting olefin have been established, this cannot be used to prove that they are related because we have proved otherwise that the *E* and *Z* isomers of non-fluorinated compounds, that loss water to form 2-pyrazolines, yield the same compound, same configuration.[19]

Note that our empirical equations 1–3 to transform absolute shielding in the gas phase into chemical shifts in solution have again proven to be reliable and useful for determining the structure of isomers and diastereoisomers.

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