EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Structural assignment of fluorocyclobutenes by 19F NMR spectroscopy: comparison of calculated 19F NMR shielding constants with experimental 19F NMR shifts

Authors: Kateřina Kučnirová, Ondřej Šimůnek, Markéta Rybáčková, and Jaroslav Kvicala

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800482

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800482

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201800482

WILEY-VCH

Structural assignment of fluorocyclobutenes by ^{19}F NMR spectroscopy: comparison of calculated ^{19}F NMR shielding constants with experimental ^{19}F NMR shifts

Kateřina Kučnirová,[a] Ondřej Šimůnek,[a] Markéta Rybáčková,[a] and Jaroslav Kvíčala*[a]

Abstract: While optimized reduction of perfluorocyclobutene with $LiAlH_4$ gave quantitative yield of the target 3,3,4,4-tetrafluorocyclobut-1-ene, unoptimized reductions led to complex unseparable mixtures of fluorocyclobutenes. These mixtures showed highly complex ^{19}F NMR spectra, the assignment of which proved to be quite tedious. We hence accomplished a series of single reference computations of ^{19}F NMR magnetic shielding of the corresponding fluorine atoms. Suprisingly, various DFT approaches, including both traditional and advanced functionals, gave highly diverse results with poor correlation of experimental and computed ^{19}F chemical shifts, from which individual fluorocyclobutenes could not be identified. Contrary to that, DLPNO-CCSD method, developed recently as a part of ORCA computational package, gave the shielding values which, although bearing some systematic error, enabled to assign all structures observed. Even slightly better values of the magnetic shielding were obtained by simple HF method using specially tailored IGLO-III basis set. The method developed was successfully employed for assigning the 19F NMR shifts to yet unknown fluorocyclobutenes.

Introduction

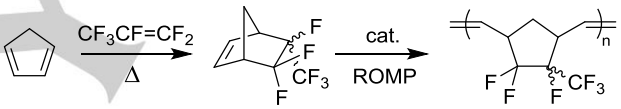
Fluorine atom due to its high electronegativity, small atomic volume and low polarizability occupies extraordinary place as a modifier of biologically active compounds. It is estimated that about 20% of recently selled pharmaceuticals contain one or more fluorine atoms. A review from 2010 claims that three of top ten blockbuster drugs in 2008 contained fluorine.[1] With increasing popularity of biological drugs, only five small organic compounds fell into twelve blockbuster drugs in 2015, but three of them bear fluorine atoms.[2] The interest in new biologically active fluorinated compounds inevitably results in the demand for new fluorine-containing building blocks and, consequently, in the development of new synthetic approaches leading to them.

Although fluoroalkenes are materials traditionally employed in organic and polymer chemistry as building blocks and monomers, they receive increasing attention in the last years as environmentally friendly substitutes for CFC's and HFC's,[3] as ligands or substrates in transition metal chemistry[4] or as peptide isosteres.[5] For analysis of the properties of fluorinated compounds, ^{19}F NMR spectroscopy can be employed with advantage. Thus, it was recently adopted for structural studies of enamines and ylides formed by reaction of fluoroalkenes and cycloalkenes with NHC ligands.[6] Fluoroalkenes were also recently studied as ligands for Ni complexes and NMR spectroscopy again chosen as the key analytical method.[7]

[a] Department of Organic Chemistry
University of Chemistry and Technology, Prague
Technická 5, 166 28 Prague 6, Czech Republic
E-mail: kvicalaj@vscht.cz

Alkene and enyne metathesis of fluoroalkenes with one or more fluorines in the side chain proceeds successfully.[8] On the other hand, 2-fluoroalkenes can[9] or need not[10] to be productive in alkene metathesis and the substitution on the other side of the double bond with an appropriate substituent, e.g. benzyl or phenyl group can be highly productive.[11] Reactions with vinyl- or vinylidenefluoride gave monofluoro- or difluoromethylene substituted ruthenium complexes, catalytic activity of which was low presumably due to their high stability.[12] Recently, successful cross metathesis of polyfluoroalkenes with vinyl ethers[13] has been published indicating critical role of the other metathesis partner. This was in excellent agreement with our computational analysis pointing at the key role of productive and non-productive cycles in fluoroalkene metathesis.[14]

Surprisingly, no ROM of fluorocycloalkenes have yet been reported with the exception of ROM polymerization of fluorinated norbornenes[8a,15] (Scheme 1) and this, in connection with our recent activity in the field of fluorinated alkene metathesis precatalysts,[16] raised our interest in fluorocycloalkenes.



Scheme 1. ROM polymerization of fluorinated norbornenes

Among potential substrates for ROM of fluorinated cycloalkenes, fluorocyclobutenes should lead to building blocks containing two-carbon fluorinated units enveloped by double bonds. While hexafluorocyclobut-1-ene (**1**) is easily available by thermal dimerization of chlorotrifluorethene followed by dehalogenation with zinc,[17] 3,3,4,4-tetrafluorocyclobut-1-ene (**3a**) can be obtained by thermal dimerization of tetrafluoroethene with chloroethene, which is potentially dangerous due to concurrent exothermic polymerization, and by subsequent reductive removal of chlorine.[18] Attempts to obtain fluorocyclobutene **3a** by reduction of fluorocyclobutene **1** with $LiAlH_4$ led to mixtures of pentafluorocyclobutenes (**2**), tetrafluorocyclobutenes (**3**) and trifluorocyclobutenes (**4**) depending on reaction conditions, from which the target fluorocyclobutene **3a** had to be isolated by preparative GC.[19] Similarly, reduction of fluorocyclobutene **1** with $Cp^*_2ZrH_2$[20] or in situ formed titanocene hydrides[21] gave mixtures of fluorocyclobutenes **2**-**4**.

For the identification of such complex mixtures, ^{19}F NMR spectroscopy represents probably the best analytical method. However, long distance fluorine-fluorine and fluorine-hydrogen coupling constants between individual atoms in fluorocyclobutenes lead often to higher order spectra[22] and hence identification of individual compouds in the mixtures can be quite difficult.[21]

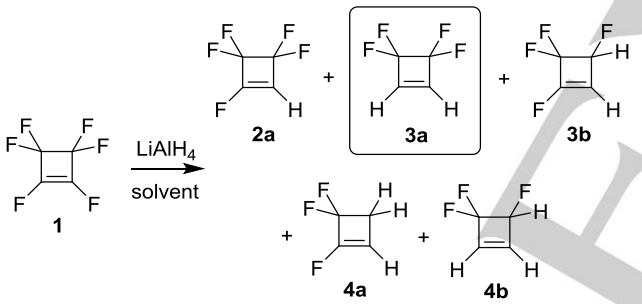
The success of computational approaches in predicting NMR shifts,[23] our previous positive experience in predicting

unexpected NMR shifts of fluorinated carbanions,[24] as well as recent rapid progress in new computational methods including electron correlation[25] initiated our computational study of ^{19}F NMR shieldings of a series of fluorocyclobutenes. This should not only show which computational approach is the most suitable for this type of calculations, but could also help in the assignment of complex NMR spectra of the mixtures of fluorocyclobutenes, obtained by various reductions of hexafluorocyclobutenes.

Results and Discussion

Reduction of hexafluorocyclobut-1-ene (**1**)

For ongoing experimental and theoretical study of the ROM of fluorocycloalkanes, 3,3,4,4-tetrafluorocyclobut-1-ene (**3a**) belongs to the most suitable substrates. Due to safety issues, we decided to prefer the synthesis starting from chlorotrifluoroethene[19] over that from tetrafluoroethene.[18] To prevent overreduction, we, contrary to the original procedure,[19] employed inverse addition of $LiAlH_4$ solution in diethyl ether to hexafluorocyclobut-1-ene (**1**) solution in diethyl ether. Using a 50% molar amount of the reduction reagent and 5 minutes addition time at -78 °C, a complex mixture of products with incomplete conversion was obtained (Fig. 2, Table 1 Entry 1).



Scheme 2. Products of $LiAlH_4$ reduction of hexafluorocyclobut-1-ene (**1**)

Analogous experiment with somewhat higher amount of reagent, the same reaction time and higher temperature (-40 °C) gave only little target product **3a** and mainly 1,4,4-trifluorocyclobut-1-ene [**4a**] (Table 1 Entry 2]. However, the use of 1.1 equiv. of $LiAlH_4$, -78 °C and slower addition (10 min) gave nearly pure target product **3a** with only small amount of the isomeric side-product **3b** (Table 1 Entry 3). Finally, using the solution of $LiAlH_4$ in diethyl ether/THF mixture and even longer addition time (15 min) gave the target product **3a** without any by-products detectable by ^{19}F NMR spectroscopy (Table 1 Entry 4).

Under the conditions of Entry 1, a complex mixture of products was formed. Although all products have been individually characterized, some of them contain stereogenic centres with high anisochronicity of CF_2 groups and other display higher order spectra. This made complete analysis of this mixture rather difficult. With the development of new DFT functionals and novel approaches to the description of electron correlation, we decided to start a short computational study of ^{19}F NMR shielding in the expected products. Its main aim was not only to find out which method or functional gives best fitting agreement with experiment, but preferably to depict the relative shifts in individual molecules. We employed two computational packages, Gaussian 09[26] and ORCA.[27]

Table 1. Optimization of $LiAlH_4$ reduction of hexafluorocyclobut-1-ene (**1**).

Entry	Reag. equiv.	Addition time (min)	Solvent	Reaction temp. (°C)	Conversion (%)	NMR yield				
						2a	**3a**	**3b**	**4a**	**4b**
1	0.5	5	Et_2O	-78	91	22	**58**	5	3	3
2	0.65	5	Et_2O	-40	100	<2	**6**	<2	82	12
3	1.1	10	Et_2O	-78	100	<2	**94**	6	<2	<2
4	1.1	15	Et_2O	-78	100	<2	**>98**	<2	<2	<2

Computations of ^{19}NMR shielding using DFT approaches in Gaussian 09

For the computations employing Gaussian 09, we chose five functionals. Three of them belong to the most advanced recent functionals, which include dispersion effects and hence are expected to give the best molecular descriptions. While hybrid ωB97X-D functional of Head-Gordon and coworkers contains empirical long range dispersion correction,[28] MN15 hybrid functional of Truhlar and coworkers includes non-empirical medium ranged dispersion correction.[25] As a representative of advanced pure functionals, we chose MN15-L of the same family.[29] Finally, we included for comparison two older hybrid functionals, traditional but still widely used B3LYP functional[30] and also popular PBE0 functional with no empirical parameters.[31]

Because ^{19}F chemical shift values are obtained from chemical shieldings by substraction of the chemical shielding of the standard, trichlorofluoromethane, we started the computations with the calculation of chemical shielding of the standard. Optimized geometry was obtained at standard DFT level using the PBE0 functional and a double zeta def2-SVP basis set.[32]

The most principle and up to date approach to computing chemical shielding of flexible molecules requires careful implementation of all significantly stable geometries or, even better, snapshots from molecular dynamics calculations.[33] Fortunately for us, both CCl_3F and fluorocyclobutenes are rigid molecules, for which static description based on minimum energy geometries was sufficient.

For the computations of chemical shielding, a triple zeta def2-TZVP basis set of the same family[32] was used. Surprisingly, the use of the above described selection of functionals led to highly diverse values of shielding (Table 2 Entry 1) with three hybrid functionals (B3LYP, PBE0 and MN15) giving closest values of shielding between 173 and 179. On the other hand, inclusion of empirical dispersion in the ωB97X-D functional gave significantly higher values of the shielding. Omitting the exchange integral in

the pure MN15-L functional resulted in even higher value of the shielding. The most probable reason causing the large differences in the shielding is the choice of the gauge origin,[23] emphasizing the neccessity of computing the shielding of the standard at the same level as the shielding of the studied substances. Only minor changes in the shielding values were observed when diffuse functions[34] were included into the basis set (Table 2 Entry 2). Similarly, only small shielding differences were found when the role of solvent was simulated using the SCRF approach (Table 2 Entry 3), or when both modifications were employed simultaneously (Table 2 Entry 4). For the solvent simulation, we employed integrated electron field-polarization continuum model approach (IEF-PCM), which is the default approach in Gaussian 09. The differences in the chemical shielding did not exceed 2 ppm. The IEF-PCM method has been reported to describe well optical rotation of chiral compounds in polar solvents as acetone or methanol, while the agreement with experiments in less polar solvents as benzene or chloroform was significantly worse. The main reason can be that the IEF-PCM method desciption of solvent-solute interaction is exclusively electrostatic.[35] Because the difference between the least and most sophisticated approach (Table 2) was negligible, def2-TZVP basis set was used further on.

Table 2. Chemical shielding of CCl_3F computed by various functionals and basis sets.

Entry	Functional→ Basis set ↓	PBE0	B3LYP	MN15	MN15-L	ωB97X-D
1	def2-TZVP	178.6	173.6	177.6	216.9	188.7
2	def2-TZVPD	177.2	171.8	177.6	215.6	188.1
3	PCM-def2-TZVP	180.5	175.7	179.7	218.1	190.5
4	PCM-def2-TZVPD	179.0	173.9	179.6	216.8	189.8

The first fluorocycloalkene studied was 3,3,4,4-tetrafluorocyclobutene (**3a**). As all fluorine atoms are chemically equivalent, only one signal (although of a higher order) was observed in the ^{19}F NMR spectrum at -109.4 ppm. While the differences in computed shielding of individual fluorine atoms did not exceed 0.1 ppm for each functional, the values across the functionals varied quite significantly (Table 3). Thus, „traditional" functionals gave lowest values of shielding (299.0 for B3LYP and 302.4 for PBE0), while the use of „modern" functionals including dispersion gave reasonably higher values of shielding (306.2 for ωB97X-D and 307.8 for MN15). Strikingly high shielding (326.9) was obtained with pure MN15-L functionals. Similar trends could be observed in the chemical shift values. Quite surprisingly, the only method which gave nearly exact values of chemical shift was MN15-L functional. For all hybrid functionals, significant upfield error in the shift was observed ranging from 8.1 ppm for ωB97X-D to 20.7 for MN15 (Table 3).

Table 3. DFT computed values of magnetic shielding and chemical shift for 3,3,4,4-tetrafluorocyclobut-1-ene (**3a**).

Functional	Experiment	PBE0	B3LYP	MN15	MN15-L	ωB97X-D
Shielding		302.4	299.0	307.8	326.9	306.2
Chemical shift	-109.4	-123.8	-125.4	-130.1	-110.0	-117.5
Shift difference		-14.4	-16.0	-20.7	-0.6	-8.1

For the analysis of fluorocyclobutenes, the accuracy of absolute values of chemical shifts is not essential and some offset error can be tolerated, providing it is systematic over the range of all studied compounds. Especially desirable is then to provide good relative values of chemical shift in one molecule. With that in mind, we chose hexafluorocyclobut-1-ene (**1**) as the second studied compound. Due to symmetry of the molecule, only two signals are observed in experimental ^{19}F NMR spectra, the signal of CF_2 group resonating at -118.6 ppm and the signal of =CF group observed at -128.0 ppm. The computations of the CF_2 group gave analogous results and errors pattern as those of the CF_2 groups of 3,3,4,4-tetrafluorocyclobut-1-ene (**3a**), i.e. best fit using pure MN15-L functional, followed by ωB97X-D with largest deviation for MN15 hybrid functional (Table 4).

Table 4. DFT computed values of magnetic shielding and chemical shift for hexafluorocyclobut-1-ene (**1**).

Group	Functional	Exp.	PBE0	B3LYP	MN15	MN15-L	ωB97X-D
	Shielding		310.8	310.0	315.3	334.6	315.5
=CF	Chemical shift	-128.0	-132.2	-136.4	-137.6	-117.7	-126.8
	Shift difference		-4.2	-8.4	-9.6	10.3	1.2
	Shielding		311.3	308.1	316.7	336.3	314.1
CF_2	Chemical shift	-118.6	-132.7	-134.5	-139.0	-119.4	-125.4
	Shift difference		-14.1	-15.9	-20.4	-0.8	-6.8

However, the shielding and the chemical shift of the =CF groups displayed completely different picture. The upfield shift error typical for the CF_2 groups in **1** and **3a** was reduced quite systematically for all functionals by about 10 ppm, which led to the best fit for the ωB97X-D functional, lower errors for all other hybrid functionals and, on the other hand, to a large downfield error for pure MN15-L functional. What is worse, while in the experimental spectrum the =CF groups resonate at significantly upper field by nearly 10 ppm, computational description shows opposite or nearly equal arrangement of the shifts. The only exception is the B3LYP functional, but still the shift difference is much lower. This was the first hint that the DFT methods are

probably not optimal for the evaluation of the NMR shifts of fluorocyclobutenes.

As the second compound bearing both CF_2 and =CF group, we chose 1,4,4-trifluorocyclobut-1-ene (**4a**), which is formed as a major product by the reduction of hexafluorocyclobut-1-ene (**1**) with $LiAlH_4$ at -40 °C (Table 1). While the experimental shifts of both groups differ by only 6 ppm, all DFT method tested gave differences in shielding higher than 20 ppm (Table 5).

Table 5. DFT computed values of magnetic shielding and chemical shift for 1,4,4-trifluorocyclobut-1-ene (**4a**).

Group	Functional	Exp.	PBE0	B3LYP	MN15	MN15-L	ωB97X-D
	Shielding		280.8	280.7	286.6	305.7	287.0
=CF	Chemical shift	-105.9	-102.2	-107.1	-108.9	-88.8	-98.3
	Shift difference		3.7	-1.2	-3.0	17.1	7.6
	Shielding		306.0	302.7	312.7	330.3	309.7
CF_2	Chemical shift	-112.2	-127.4	-129.1	-135.0	-113.3	-121.0
	Shift difference		-15.2	-16.9	-22.8	-1.1	-8.8

Similarly to the computations of hexafluorocyclobut-1-ene (**1**), all hybrid functionals gave acceptable computed shifts for the =CF group, but failed to reproduce experimental shift for the CF_2 group. Interestingly, for the pure functional, the situation was exactly the opposite.

Our final studied compound was 1,3,3,4,4-pentafluorocyclobut-1-ene (**2a**, Table 6), formed as a side product in the reduction of cyclobutene **1** with lower amount of $LiAlH_4$ (Table 1 Entry 1).

Table 6. DFT computed values of magnetic shielding and chemical shift for 1,3,3,4,4-pentafluorocyclobut-1-ene (**2a**).

Group	Functional	Exp.	PBE0	B3LYP	MN15	MN15-L	ωB97X-D
	Shielding		280.5	280.1	283.7	306.2	286.7
=CF	Chemical shift	-105.3	-101.9	-106.5	-106.1	-89.3	-97.9
	Shift difference		4.0	-0.6	-0.2	16.6	8.0
	Shielding		306.5	303.1	312.7	330.8	310.3
3-CF_2	Chemical shift	-112.2	-127.9	-129.5	-135.1	-113.9	-121.6
	Shift difference		-15.7	-17.3	-22.9	-1.7	-9.4
	Shielding		310.8	307.5	318.0	333.7	314.8
4-CF_2	Chemical shift	-117.2	-132.2	-133.9	-140.4	-116.7	-126.1
	Shift difference		-20.0	-21.7	-28.2	-4.5	-13.9

Again, in analogy to the previous two calculations, hybrid functionals gave acceptable shift for the =CF group, but underestimated the shielding of both CF_2 groups. Also in agreement with previous calculations, the shift of both =CF groups was described well by the pure M06L functional, which however failed to describe correctly the CF_2 group shifts.Linear regression showed for all applied DFT very poor correlation with correlation coefficient R^2 not excceding 0.7. Among them, relatively best results gave the traditional B3LYP functional (R^2 = 0.67), while worst behave quite surprisingly one of the most advanced dispersion including hybrid functionals, MN15 (R^2 = 0.51) (Fig. 1).

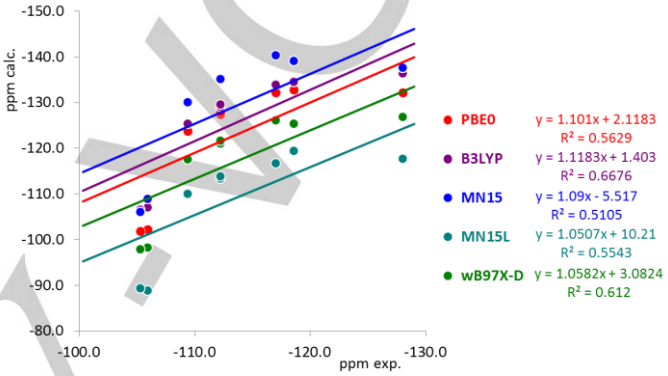


Figure 1. Correlation of experimental and DFT calculated shifts of cycloalkenes **1**, **2a**, **3a** and **4a**.

Computations of ^{19}NMR shielding using DLPNO-CCSD and HF methods in ORCA

Disappointed by the DFT method, we turned our attention to other computationally feasible methods including electron correlation. Among them, single reference multiconfiguration DLPNO-CCSD (domain-based local pair natural orbital coupled clusters) method[36], invented as a part of ORCA computational program,[27] appeared to be the most attractive due to high computational efficiency. Indeed, computations of the chemical shifts of the starting fluorocycloalkene set **1**, **2a**, **3**, **4a**, using the basis set, resulted in much better agreement between calculated and experimental shift. Although the average offset error reached nearly 20 ppm, the R^2 coefficient of the correlation between the calculated and experimental values was significantly higher (0.8861, Fig. 2). For comparison, we also compared the coupled cluster calculations with a simple Hartree-Fock (HF) approach. To our surprise, the HF approach with limited electron correlation gave even better agreement between computed and experimental values giving R^2 = 0.9456 (Fig. 4). Both approaches overestimated the magnetic shielding by 11-27 ppm for the DLPNO method and by 12-24 ppm for the HF method.

In the attempt to further improve the results of DLPNO and HF computations, we first decided to improve the geometry of starting fluorocyclobutenes by using more advanced M062X functional[37] and more flexible def2-TZVPPD[34] basis set. For the computations of the chemical shifts, we furthermore employed an IGLO-III basis set[38] with improved description of

the 1s orbital, specially tailored for NMR computations. The improved approach resulted in the improved correlation both for the DPLNO-CCSD (R^2 = 0.9416) and the HF (R^2 = 0.9685) method (Fig. 2, Table 7). Moreover, the overestimation of the chemical shifts sank to 6-14 ppm for the DLPNO method and to 7-13 ppm for the HF method.

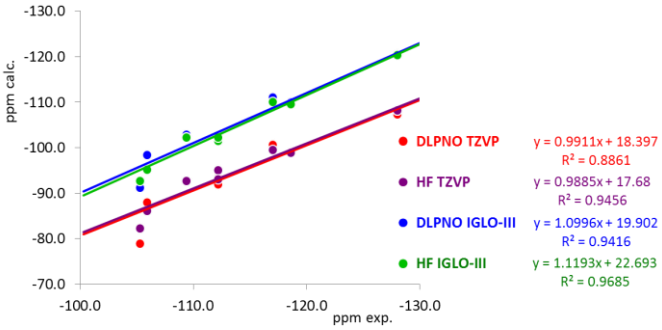


Figure 2. Correlation of experimental and DLPNO or HF calculated shifts of cycloalkenes **1**, **2a**, **3a** and **4a**.

We employed the developed approaches for the computation of the ^{19}F NMR shifts of three other fluorocyclobutenes, namely of 1,3,4,4-tetrafluorocyclobut-1-ene (**3b**) and 3,3,4-trifluorocyclobut-1-ene (**4b**), which we observed as the side-products in the reduction of hexafluorocyclobut-1-ene (**1**), as well as of 1,2,3,3,4-pentafluorocyclobut-1-ene (**2b**), reported by Lentz et al.[21] Both DLPNO and HF calculations of these cycloalkenes fitted well into the previous set of calculations, improving the correlation coefficients R^2 to 0.9907 for the DLPNO and 0.9917 for the HF approach (Fig. 2, Table 8).

Predictive power of our approach can be documented by the computation of ^{19}F chemical shielding of 1,3,4,4-tetrafluorocyclobut-1-ene (**2b**), reported also by Lentz et al.[21] The structure of alkene **2b** was assigned mainly based on coupling constants, but these can be quite similar for isomeric 1,3,3,4-tetrafluorocyclobut-1-ene (**2c**). Using correlation equation from Fig. 3, the maximum difference between corrected computed and experimental shift in alkene **2b** did not exceed 2.5 ppm, while the maximum differences of the experimental shifts from the corrected computed shift of hypothetical fluoroalkene **2c** exceeded 10 ppm, confirming thus the assignment from Ref.[21]

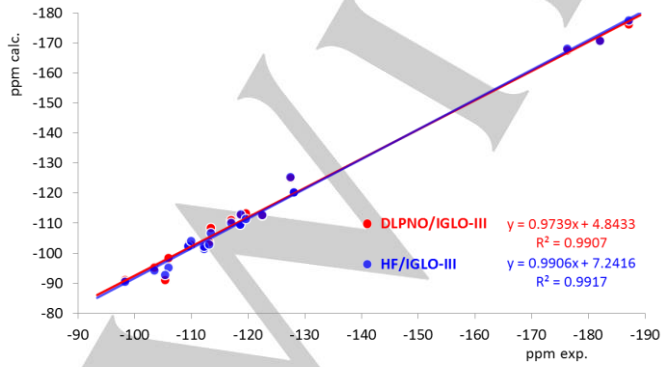


Figure 3. Correlation of experimental and DLPNO or HF calculated shifts of all considered cycloalkenes **1 - 4**.

Table 7. Computed values of magnetic shieldings and chemical shifts for fluorocyclobutenes **1**, **2a**, **3a** and **4a** using DLPNO and HF methods.

Group	Functional	Exp.	DLPNO TZVP	HF TZVP	DLPNO IGLO-III	HF IGLO-III
3,3,4,4-Tetrafluorocyclobut-1-ene (**3a**)						
	Shielding		339.4	338.4	341.0	340.6
CF_2	Chemical shift	-118.6	-92.7	-92.7	-102.9	-102.3
	Shift difference		16.7	16.7	6.5	7.1
Hexafluorocyclobut-1-ene (**1**)						
	Shielding		280.5	280.1	283.7	306.2
=CF	Chemical shift	-105.3	-101.9	-106.5	-106.1	-89.3
	Shift difference		4.0	-0.6	-0.2	16.6
	Shielding		306.5	303.1	312.7	330.8
CF_2	Chemical shift	-112.2	-127.9	-129.5	-135.1	-113.9
	Shift difference		-15.7	-17.3	-22.9	-1.7
1,4,4-Trifluorocyclobut-1-ene (**4a**)						
	Shielding		334.8	331.7	336.5	333.6
=CF	Chemical shift	-105.9	-88.0	-86.1	-98.4	-95.2
	Shift difference		17.9	19.8	7.5	10.7
	Shielding		340.2	340.8	343.1	339.8
CF_2	Chemical shift	-112.2	-93.5	-95.1	-104.9	-101.5
	Shift difference		18.7	17.1	7.3	10.7
1,3,3,4,4-Pentafluorocyclobut-1-ene (**2a**)						
	Shielding		325.7	328.0	329.3	331.0
=CF	Chemical shift	-105.3	-79.0	-82.3	-91.2	-92.7
	Shift difference		26.9	23.6	14.1	12.6
	Shielding		338.7	338.7	340.3	340.6
3-CF_2	Chemical shift	-112.2	-91.9	-93.1	-102.2	-102.2
	Shift difference		20.3	19.1	10.0	10.0
	Shielding		347.3	345.2	349.2	348.4
4-CF_2	Chemical shift	-117.2	-100.6	-99.5	-111.0	-110.0
	Shift difference		11.6	12.7	6.0	7.0

Table 8. Computed values of magnetic shieldings and chemical shifts for fluorocyclobutenes **2b**, **3b** and **4b** using DLPNO and HF methods**.**

Group	Functional	Exp.	DLPNO TZVP	HF TZVP
1,3,4,4-tetrafluorocyclobutene (**3b**)				
=CF	Shielding		333.4	332.7
	Chemical shift	-103.4	-95.2	-94.3
	Shift difference		8.2	9.1
cis-CF	Shielding		351.0	351.2
	Chemical shift	-118.7	-112.8	-112.8
	Shift difference		5.9	5.9
trans-CF	Shielding		340.8	342.4
	Chemical shift	-109.9	-102.7	-104.0
	Shift difference		7.2	5.9
CHF	Shielding		408.9	409.1
	Chemical shift	-182.0	-170.7	-170.8
	Shift difference		11.3	11.2
3,4,4-tetrafluorocyclobutene (**4b**)				
cis-CF	Shielding		346.5	345.1
	Chemical shift	-113.4	-108.3	-106.7
	Shift difference		5.1	6.7
trans-CF	Shielding		329.3	328.8
	Chemical shift	-98.3	-91.2	-90.5
	Shift difference		7.1	7.8
CHF	Shielding		405.6	406.5
	Chemical shift	-176.2	-167.5	-168.1
	Shift difference		8.7	8.1
1,2,3,3,4-pentafluorocyclobutene (**2b**)				
1-CF=	Shielding		350.7	351.0
	Chemical shift	-122.5	-112.6	-112.7
	Shift difference		9.9	9.8
2-CF=	Shielding		363.0	363.7
	Chemical shift	-127.4	-124.9	-125.3
	Shift difference		2.5	2.1
cis-CF	Shielding		351.4	349.8
	Chemical shift	-119.6	-113.3	-111.5
	Shift difference		6.3	8.1
trans-CF	Shielding		341.9	341.3
	Chemical shift	-113.1	-103.8	-102.9
	Shift difference		9.3	10.2
CHF	Shielding		414.4	415.8
	Chemical shift	-187.1	-176.3	-177.4
	Shift difference		10.8	9.7

Conclusions

We developed short and efficient synthesis of 3,3,4,4-tetrafluorocyclobut-1-ene (**3a**) as a potential substrate for ring-opening metathesis. The key reduction of intermediary hexafluorocyclobut-1-ene (**1**) is highly sensitive to reaction conditions and their inaccurate choice can result in the formation of a mixture of fluorocyclobutenes **1**-**4**. Quite suprisingly, both classical and newly introduced dispersion including DFT functionals failed to predict correctly ^{19}F chemical shieldings of fluorocyclobutenes **1**-**4**. On the other hand, both coupled cluster DLPNO method and simple HF approach gave the calculated values of ^{19}F chemical shieldings, which fitted well with the experimental values. Both methods thus can be used as a tool for the assignment of yet unknown fluorocyclobutenes.

Experimental Section

General description of methods and materials. Temperature data were uncorrected. NMR spectra were recorded with a Varian MercuryPlus spectrometer, ^{1}H NMR spectra at 299.97 MHz and ^{19}F NMR spectra at 282.23, or with a Agilent 400-MR DDR2, ^{1}H NMR spectra at 399.94 MHz and ^{19}F NMR spectra at 376.29 MHz, using residual deuterated solvent signals as the internal standards for the ^{1}H NMR spectra or CCl_3F as the internal standard for the ^{19}F NMR spectra. Chemical shifts are given in parts per million, coupling constants in hertz. All reactions were performed in a dry inert atmosphere (Ar) in an oven-dried flasks. Chlorotrifluoroethene was kindly gifted by Spolek pro chemickou a hutní výrobu, Ústi nad Labem. Diethyl ether and THF were distilled from the solution of diphenyl ketyl radical, methanol was pre-dried with sodium and finally distilled from CaH_2.

Preparation of 1,2-dichloro-1,2,3,3,4,4-hexafluorocyclobutane. The synthesis of the title cyclobutane was performed according to Ref.[17] Thus, a 200 mL steel autoclave was cooled to -78 °C, charged with chlorotrifluoroethene (120 g, 1.03 mol), sealed and heated for 5 days while slowly raising the temperature from 125 °C to 250 °C. The heating was continued for one more day, during which the pressure rose up to 6 MPa and then slowly sank to 2 MPa. After cooling, the liquid product was

fractionally distilled yielding the target fluorocyclobutane as a mixture of *cis*- and *trans*-isomers in a 55:45 ratio (107 g, 91%, b.p. 54-59 °C. ^{19}F NMR of the product corresponded to the literature data.[39] *cis*-1,2-Dichloro-1,2,3,3,4,4-hexafluorocyclobutane, ^{19}F NMR (282.23 MHz, $CDCl_3$): δ -117.9 (dm, $^2J_{F\text{-}F}$ = 218 Hz, 2F, **F**CF-**F**CF); -129.9 (dm, $^2J_{F\text{-}F}$ = 218 Hz, 2F, FC**F**-FC**F**); -137.2 (m, 2F, C**F**Cl-C**F**Cl) ppm. *trans*-1,2-Dichloro-1,2,3,3,4,4-hexafluorocyclobutane, ^{19}F NMR (282.23 MHz, $CDCl_3$): δ -121.8 (dm, $^2J_{F\text{-}F}$ = 213 Hz, 2F, **F**CF-**F**CF); -125.7 (dm, $^2J_{F\text{-}F}$ = 213 Hz, 2F, **F**CF-**F**CF); -127.7 (m, 2F, C**F**Cl-C**F**Cl) ppm.

Preparation of hexafluorocyclobut-1-ene (1). The original procedure[40] was slightly modified. Zinc powder (56.0 g, 0.86 mol), activated by grinding with few drops of acetic acid and acetic anhydride, was placed into a 3-necked flask equipped with addition funnel and Vigreux column topped by low-temperature fraction distillation head, followed by anh. methanol (50 mL). 1,2-Dichloro-1,2,3,3,4,4-hexafluorocyclobutane was slowly added to the mixture at a rate enabling gentle reflux of the mixture. After 6 h, pure target product **1** was collected in the distillate (21.0 g, 76.5%, b.p. 0-2 °C). ^{19}F NMR (282.23 MHz, $CDCl_3$): δ -118.6 (m, 4F, C**F$_2$**); -128.0 (m, 2F, C**F**) ppm.

Preparation of 3,3,4,4-tetrafluorocyclobut-1-ene (3a). General procedure: $LiAlH_4$ was dissolved at -78 °C in diethyl ether (20 mL). The solution was slowly cannulated to a cooled flask, charged with diethyl ether or 1:1 diethyl ether/THF mixture (15 mL) and fluorocyclobutene **1** (3.1. g, 19 mmol). The reaction was stirred at low temperature for 15 min and then quenched with aq. NH_4Cl (10 mL). Aqueous layer was separated and extracted with diethyl ether (3 × 10 ml). Combined organic layers were washed with brine (10 mL) and anh. $MgSO_4$. Diethyl ether was removed by fractional distillation using a rectification column filled with steel spirals, leaving the target product **3a** as a distillation residue. Run 1 (Table 1): Reaction with 0.5 eq. of $LiAlH_4$ (360 mg, 9.5 mmol) in diethyl ether, using addition time 5 min at -78 °C, gave a 91% conversion of starting cyclobutene **1**, yielding a 22:58:5:3:3 mixture of fluorocycloalkenes **2a**, **3a**, **3b**, **4a** and **4b**. 1,3,3,4,4-Pentafluorocyclobut-1-ene (**2a**), ^{19}F NMR (282.23 MHz, $CDCl_3$):[21] δ -105.3 (m, 1F, C**F**=CH); -111.2 (m, 2F, C**F$_2$**-CF=CH); -117.0 (m, 2F, C**F$_2$**-CH=CF) ppm. 3,3,4,4-Tetrafluorocyclobut-1-ene (**3a**), ^{19}F NMR (282.23 MHz, $CDCl_3$):[21] δ -109.4 (m, 4F, C**F$_2$**) ppm. 1,3,4,4-Tetrafluorocyclobut-1-ene (**3b**), ^{19}F NMR (282.23 MHz, $CDCl_3$):[21] δ -103.4 (m, 1F, C**F=**CH)**; -**109.9 (dm, $^2J_{F\text{-}F}$ = 205 Hz, 1F, **F**CF-CFH); -118.7 (dm, $^2J_{F\text{-}F}$ = 205 Hz, 1F, FC**F-**CFH); -182.0 (dm, $^2J_{H\text{-}F}$ = 58 Hz, 1F, C**F**H) ppm. 1,4,4-Trifluorocyclobut-1-ene (**4a**), ^{19}F NMR (282.23 MHz, $CDCl_3$):[21] δ -105.9 (m, 1F, C**F=**CH); -112.2 (m, 2F, C**F$_2$**) ppm. 3,3,4-Trifluorocyclobut-1-ene (**4b**), ^{19}F NMR (282.23 MHz, $CDCl_3$): δ **-**98.3 (dm, $^2J_{F\text{-}F}$ = 205 Hz, 1F, **F**CF-CFH); -113.4 (dm, $^2J_{F\text{-}F}$ = 205 Hz, 1F, FC**F-**CFH); -176.2 (dm, $^2J_{H\text{-}F}$ = 62 Hz, 1F, C**F**H) ppm. Run 2 (Table 1): Reaction with 0.65 eq. of $LiAlH_4$ (470 mg, 12.4 mmol) in diethyl ether, using addition time 5 min at -40 °C, gave a 100% conversion of starting cyclobutene **1**, yielding a 6:82:12 mixture of fluorocycloalkenes **3a**, **4a** and **4b**. Run 3 (Table 1): Reaction with 1.1 eq. of $LiAlH_4$ (790 mg, 20.9 mmol) in diethyl ether, using addition time 10 min at -78 °C, gave a 100% conversion of starting cyclobutene **1**, yielding a 94:6 mixture of fluorocycloalkenes **3a** and **3b**. Run 4 (Table 1): Reaction with 1.1 eq. of $LiAlH_4$ (790 mg, 20.9 mmol) in a mixture of diethyl ether and THF, using addition time 15 min at -78 °C, gave a 100% conversion of starting cyclobutene **1**, yielding pure fluorocycloalkene **3a**.

Computational details. DFT calculations were performed using Gaussian 09W program suite[26] or the ORCA computational program.[27] Vibrational frequencies were calculated for all species to characterize them as minima.

ACKNOWLEDGMENTS

This work was supported by specific university research (MSMT No. 21-SVV/2018). Computational resources were supplied by the Ministry of Education, Youth and Sports of the Czech Republic under the Projects CESNET (Project No. LM2015042) and CERIT-Scientific Cloud (Project No. LM2015085) provided within the program Projects of Large Research, Development and Innovations Infrastructures.

Keywords: fluorocyclobutene • ^{19}F NMR spectroscopy • computational chemistry • DFT • DLPNO-CCSD

[1] D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071-1081.
[2] http://www.pharmacompass.com/radio-compass-blog/top-drugs-by-sales-revenue-in-2015-who-sold-the-biggest-blockbuster-drugs. Retrieved 1 April 2017.
[3] C. Hogue, *Chem. Eng. News* **2011**, 31-32.
[4] a) M. Ohashi, S. Ogoshi, *Catalytic Transformations of Fluorinated Olefins in Organometallic Fluorine Chemistry* (Eds.: T. Braun, R. P. Hughes), *Topics in Organometallic Chemistry 52*, Springer, Dordrecht, **2015**, pp. 197-216; b) D.L. Orsi, R. A. Altman, *Chem. Commun.* **2017**, *53*, 7168-7181.
[5] H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855−12862.
[6] a) M. C. Leclerc, Serge I. Gorelsky, B. M. Gabidullin, I. Korobkov, R. T. Baker, *Chem. Eur. J.* **2016**, *22*, 8063 – 8067; b) A. J. Arduengo III, J. C. Calabrese, H. V. Rasika Dias, F. Davidson, J. R. Goerlich, A. Jockisch, M. Kline, W. J. Marshall, J. W. Runyon, *Phosphorus Sulfur* **2016**, *191*, 527-534.
[7] W. Xu, H. Sun, Z. Xiong, X. Li, *Organometallics* **2013**, *32*, 7122−7132.
[8] a) S. Fustero, A. Simón-Fuentes, P. Barrio, G. Haufe, *Chem. Rev.* **2015**, *115*, 871−930; b) S. Imhof, S. Randl, S. Blechert, *Chem. Commun.* **2001**, 1692–1693; c) A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784.
[9] a) S. S. Salim, R. K. Bellingham, V. Satcharoen, R. C. D. Brown, *Org. Lett.* **2003**, *5*, 3403-3406; b) V. De Matteis, F. L. van Delft, J. Tiebes, F. P. J. T. Rutjes, *Eur. J. Org. Chem.* **2006**, 1166–1176.
[10] M. Marhold, A. Buer, H. Hiemstra, J. H. van Maarseveenb, G. Haufe, *Tetrahedron Lett.* **2004**, *45*, 57-60.
[11] D. Guérin, A.-C. Gaumont, I.Dez, M. Mauduit, S. Couve-Bonnaire, X. Pannecoucke, *ACS Catalysis* **2014**, *4*, 2374-2378.
[12] a) M. L. Macnaughtan, M. J. A. Johnson, J. W. Kampf, *Organometallics* 26, **2007**, 780-782; b) T. M. Trnka, M. W. Day, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2001**, *40*, 3441-3444.
[13] Y. Takahira, Y. Morizawa, *J. Am. Chem. Soc.* **2015**, *137*, 7031−7034.
[14] M. Rybáčková, J. Hošek, O. Šimůnek, V. Kolaříková, J. Kvíčala, *Beilstein J. Org. Chem.* **2015**, *11*, 2150-2157.
[15] W. J. Feast, M. Gimeno, E. Khosravi, *Polymer* **2003**, *44*, 6111-6121..
[16] a) J. Kvíčala, M. Schindler, V. Kelbichová, M. Babuněk, M. Rybáčková, M. Kvíčalová, J. Cvačka, A. Březinová, *J. Fluorine Chem.* **2013**, *153*, 12-25; b) M. Babuněk, O. Šimůnek, J. Hošek, M. Rybáčková, J. Cvačka, A. Březinová, J. Kvíčala, *J. Fluorine Chem.* **2014**, *161*, 66-75; c) J.Hošek, M. Rybáčková, J. Čejka, J. Cvačka, J. Kvíčala, *Organometallics* **2015**, *34*, 3327-3334; d) P. Lipovská, L. Rathouská, O. Šimůnek, J. Hošek, V. Kolaříková, M. Rybáčková, J. Cvačka, M. Svoboda, J. Kvíčala, *J. Fluorine Chem.* **2016**, *191*, 14-22; e) J. Hošek, O. Šimůnek, V. Kolaříková, P. Lipovská, K. Kučnirová, A. Edr, N. Štěpánková, M. Rybáčková, J. Cvačka, J. Kvíčala, *ACS Sustainable Chem. Eng.* **2018**, *6*, 7026−7034.
[17] A. T. Blomquist, E. A. LaLancette, *J. Am. Chem. Soc.* **1961**, *83*, 1387-1391.

[18] a) D.D. Coffman, P.L. Barrick, R.D. Cramer, M.S. Raasch, *J. Am. Chem. Soc.* **1949**, 71, 490–496; b) J. Mizukado, Y. Matsukawa, H.-D. Quan, M. Tamura, A. Sekiya, J. Fluorine Chem. **2006**, *127*, 79–84.

[19] G. Fuller, J. C. Tatlow, *J. Chem. Soc.* **1961**, 3198-3203.

[20] B. M. Kraft, E. Clot, O. Eisenstein, W. W. Brennessel, W. D. Jones, *J. Fluorine Chem.* **2010**, *131*, 1122–1132.

[21] M. F. Kuehnel, P. Holstein, M. Kliche, J. Krüger, S. Matthies, D. Nitsch, J. Schutt, M. Sparenberg, D. Lentz, Chem. Eur. J. **2012**, *18*, 10701-10714.

[22] R. K. Harris, V. J. Robinson, *J. Magn. Res.* **1969**, *1*, 362-377.

[23] a) A. C. de Dios, *J. Progr. Nucl. Magn. Spectr.* **1996**, *29*, 229-278; b) A. Navarro-Vázquez, *Magn. Reson. Chem.* **2017**, *55*, 29-32; c) J. C. Facelli, M. B. Ferraro, *Concepts Magn. Reson.* **2013**, *42*, 261–289; D. Casarini, L. Lunazzi, A. Mazzanti, *Eur. J. Org. Chem.* **2010**, 2035–2056.

[24] a) J. Kvíčala, R. Hrabal, I. Bartošová, O. Paleta, A. Pelter, J. Fluorine Chem. **2002**, *113*, 211-218; b) J. Kvíčala, J. Czernek, S. Böhm, O. Paleta, *J. Fluorine Chem.* **2002,** *116*, 121-127.

[25] R. Peverati, D. G. Truhlar, *Phil. Trans. R. Soc. A* **2012**, *372*, 20120476.

[26] Gaussian 09, Revision D.01, M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian, Inc., Wallingford CT, **2013**.

[27] F. Neese, Wiley interdiscipl. *Rev. – Comp. Mol. Sci.* **2012**, *2*, 73-78.

[28] J.-D. Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, 10, 6615–6620.

[29] H. S. Yu, X. He, D. G. Truhlar, *J. Chem. Theory Comput.* **2016**, *12*, 1280-1293.

[30] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652; b) P. J. Stephens, F. J. Devlin, C. F. Chablowski, M. J. Frisch, J. Phys. Chem **1994**, *98*, 11623-11627.

[31] C. Adamo, V. Barone, *J. Chem. Phys.* **199**9, *110*, 6158-6170.

[32] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys*. **2005**, *7*, 3297-3305.

[33] a) S. C. Silva, S. M. M. Rodrigues, V. Nardini, A. L. L. Vaz, V. Palaretti, G. V. José da Silva, R. Vessecchi, G. C. Clososki, *J. Mol. Struct.* **2018**, *1163*, 280-286; b) D. P. Demarque, D. R. Pinho, N. P. Lopes, C. Merten, *Chirality* **2018**, *30*, 432–438; c) A. Bröhl, B. Albrecht, Y. Zhang, E. Maginn, R. Giernoth, *J. Phys. Chem. B* **2017**, *121*, 2062−2072; d) P. A. G. Soares, I. N. L. Queiroz, V. H. Pomin, *J. Biomol. Struct. Dyn.* **2017**, *35*, 1069-1084; e) M. Dračínský, H. M. Möller, T. E. Exner, J. Chem. Theory Comput. **2013**, *9*, 3806−3815.

[34] D. Rappoport, F. Furche, J. Chem. Phys. **2010**, *133*, 134105.

[35] B. Mennucci, J. Tomasi, R. Cammi, J. R. Cheeseman, M. J. Frisch, F. J. Devlin, S. Gabriel, P. J. Stephens, *J. Phys. Chem. A* **2002**, *106*, 6102-6113.

[36] W. B. Schneider, G. Bistoni, M. Sparta, M. Saitow, C. Riplinger, A. A. Auer, F. Neese, *J. Chem. Theory Comput.* **2016**, *12*, 4778-4792; b) C. Riplinger, P. Pinski, U. Becker, E. F. Valeev, F. Neese, *J. Chem. Phys.* **2016**, *144*, 024109.

[37] Y. Zhao, D. G. Truhlar, *Theor. Chem. Accounts* **2008**, *120*, 215–241.

[38] W. Kutzelnigg, U. Fleischer, M. Schindler in *NMR Basic Principles and Progress, Vol. 23* (Ed.: J. Seelig), Springer-Verlag, Heidelberg, **1990**, pp. 165-262.

[39] V. J. Gazzard, R. K. Harris, *Org. Magn. Reson*. **1974**, *6*, 404-406.

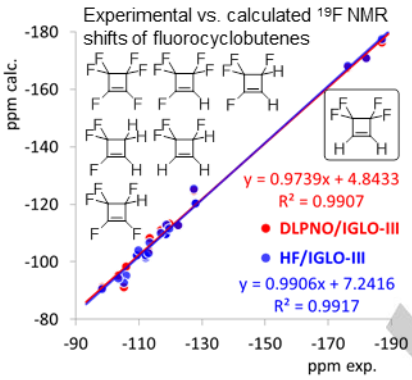
[40] A. L. Henne, W. J. Zimmerschmied, *J. Am. Chem. Soc.* **1947**, *49*, 281-283.

10.1002/ejoc.201800482

WILEY-VCH

FULL PAPER

3,3,4,4-Tetrafluorocyclobut-1-ene, a promising substrate for ring-opening metathesis, was synthesized. Surprisingly, while DFT calculations using both traditional and modern functionals failed to describe correctly ^{19}F NMR shielding constants of fluorocyclobutenes, correct relative values were obtained by DLPNO-CCSD or HF calculations, enabling thus reliable assignment of ^{19}F NMR signals of both unknown and known fluorocyclobutenes.



Fluorocyclobutenes

*Kateřina Kučnirová,Ondřej Šimůnek, Markéta Rybáčková, Jaroslav Kvíčala**

Page No. – Page No.

Structural assignment of fluorocyclobutenes by ^{19}F NMR spectroscopy: comparison of calculated ^{19}F NMR shielding constants with experimental ^{19}F NMR shifts