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The Strong β–CF_3 Shielding Effect in Hexafluoroisopropanol and 100 Other Organic Solvents Revisited with ^{17}O NMR Spectroscopy

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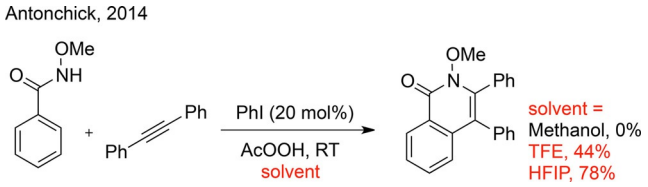
An ^{17}O NMR spectroscopy survey of more than 100 ubiquitous organic solvents and compounds, including some typical oxofluorinated solvents such as hexafluoroisopropanol, trifluoroethanol, trifluoroacetic acid, and others, is presented with D_2O as a reference. A strong alternating α,β–CF_3-substituent chemical shift effect was thus observed. This alternating deshielding–shielding effect is suspected to have a role in the exceptional properties of these oxofluorinated solvents, notably in oxidative cross-coupling reactions.

The fluorinated alcohols hexafluoroisopropanol (HFIP), trifluoroethanol (TFE), and related compounds have recently shown remarkable solvent properties, notably for cross-dehydrogenative coupling reactions (Scheme 1).[1] However, these solvent-accelerating effects, often at mild temperatures or at room temperature, are still not well understood. Thus, in this work, a comparative ^{17}O NMR spectroscopy study of these compounds is proposed. In general, ^{17}O NMR spectroscopy remains largely underappreciated for the routine characterization of organic molecules, in contrast to ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, ^{19}F NMR, and ^{15}N NMR spectroscopy. Very few exhaustive studies exist,[2] and even fewer include organic oxofluorinated compounds.[3] This is surprising, because oxygen and oxidation processes are at the heart of organic processes. This characterization technique, which is reputed to be very sensitive to electronic and steric environments,[2–4] has been notably well developed in other fields of chemistry[5] despite the relatively low abundance of ^{17}O (0.04% on earth). A selection of 100 ubiquitous organic compounds, including notorious HFIP and TFE, is thus herein revisited by ^{17}O NMR spectroscopy with the aim of revealing what makes those oxofluorinated solvents so special. Another objective of this work is to provide an updated ^{17}O NMR spectroscopy table of organic compounds with comparable measuring conditions,[6] which could arguably be useful for the development of oxidative coupling reactions.[7] All spectra are provided in the Supporting Information.



Scheme 1. A selected cross-dehydrogenative coupling reaction enabled by HFIP.[1e]

In all cases, D_2O was chosen as a $\delta = 0.0$ ppm chemical-shift reference. All measurements were performed with a standard, either D_2O ($\delta = 0.0$ ppm) or alternatively CD_3OD ($\delta = -35.3$ ppm), in a melted glass capillary, which was placed inside every NMR tube. Neat results are reported in Table 1. In general, the margin of error is considered to be $\Delta\delta \pm 0.4$ ppm or less (Bruker FT-NMR Avance I, ^{1}H: 600 MHz, ^{17}O: 81.4 MHz) on the basis of certain selected entries that were measured multiple times (see the Supporting Information). For the ^{17}O NMR lines that are described as broad (br) however, a precautionary $\Delta\delta \pm 1$ ppm precision should be considered. In a few broadest cases (very br), the values were rounded up to the nearest integer and a precautionary $\Delta\delta \pm 2$ ppm precision should be considered. The measuring temperature was 22 °C for all samples. The average ^{17}O NMR spectrum contains typically 4096 scans, representing an acquisition time of approximatively 20 min. Indicatively, in the case of methanol (Table 1, entry 3), the neat sample had a molarity of approximatively 24.7 mol L^{-1}. For convenience, only compounds that are liquid at 22 °C were considered.

With the aim of producing a useful set of data and to illustrate the high chemical-shift sensitivity of ^{17}O NMR spectroscopy, proximal isotopic effects were also studied (Table 2). Clearly, in comparison to other nuclei such as ^{13}C, ^{17}O NMR spectroscopy is very susceptible to isotope chemical-shifting effects. D_2O and H_2O are, for example, separated by a full $\Delta\delta = 3.3$ ppm. For comparison, the ^{13}C NMR signal of CD_2Cl_2 ($\delta = +53.84$ ppm) and that of CH_2Cl_2 ($\delta = +54.24$ ppm) are separated by only $\Delta\delta = 0.4$ ppm.[6] $CDCl_3$ and $CHCl_3$ are moreover separated by only $\Delta\delta = 0.3$ ppm.[6] In contrast, even remote isotopic differences can be detected with ^{17}O NMR spectroscopy (notably in [D_6]DMSO, $^{13}CD_3OD$, and $Ph^{15}NO_2$; see Table 2).

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Table 1. ^{17}O NMR (^{17}O: 81.4 MHz, $T = 22\,^{\circ}C$, relaxation delay of 50 ms, at least 2048 scans) neat chemical shifts from D_2O ($\delta = 0.0$ ppm).[a]

Entry	Compound	δ [ppm]	Description
1	H_2O	+3.1	–
2[b]	H_2O	+3.5	–
3	MeOH	−32.9	m
4	EtOH	+9.4	–
5[b]	PrOH	+3.0	–
6[b]	$CF_3(CH_2)_2OH$	−2.3	–
7[b]	BuOH	+2.8	–
8[b]	$Me(CH_2)_4OH$	+4.7	–
9[b]	$Me(CH_2)_5OH$	+3.5	br
10	*i*PrOH	+42.5	br
11	$(CF_3)_2CHOH$ (HFIP)	−8.5	br
12	CF_3CH_2OH (TFE)	−20.2	–
13[b]	HCF_2CH_2OH	−20.5	–
14[b]	CCl_3CH_2OH (TCE)	+18	very br
15	$(CF_3)_3COH$	+4.5	–
16	*t*BuOH	+67.6	br
17	BnOH	+7.9	br
18[b]	glycol	−5.5	br
19[b]	1,3-propanediol	−1	very br
20[b]	cyclobutanol	+45.3	br
21[b]	cyclopentanol	+37	very br
22[b]	diethylene glycol	−2	very br
23	2-methoxyethanol	−22.4, −5.4	–
24	allyl alcohol	+1.9	–
25	propargyl alcohol	+3.3	–
26	Et_2O	+17.1	–
27[b]	$CF_3CH_2OCH_2CF_3$	−26.0	–
28	$(iPr)_2O$	+63.6	–
29	*t*BuOMe	+19.9	–
30	cyclopentyl methyl ether	+5.1	–
31	THF	+19.5	–
32	tetrahydropyran	+12.1	–
33	1,4-dioxane	+2.4	–
34	morpholine	+7.0	–
35	1,2-dimethoxyethane	−21.2	–
36	diglyme	−21.1	–
37	$MeOCHCl_2$	+68.9	–
38	anisole	+50.6	–
39	$PhOCF_3$	+113.6	–
40	$PhOCF_2H$	+118.4	-
41	1,2-dimethoxybenzene	+37.2	br
42	enflurane[c]	+127.7	m
43	$HC(Cl)(F)CF_2OMe$	+41.1	–
44	$HCF_2OCH(Cl)CF_3$	+97.3	–
45	$MeOCH_2CF_3$	−35.6	lowest δ of table
46	HCF_2CF_2OMe	+38.4	–
47	2-bromotetrafluoroethyl trifluoro-vinyl ether	+98.8	–
48	perfluoro(propyl vinyl ether)	+98.5	–
49	furan	+240.1	t, $^2J_{O,H} \approx 15$ Hz
50	2-ethylphenol	+76	very br
51	3-(trifluoromethyl)phenol	+82	very br
52	2-bromophenol	+82.4	br
53	2-fluorophenol	+55.3	br
54	3-fluorophenol	+80	very br
55	3-chlorophenol	+74.5	br
56	3,5-bis(trifluoromethyl)phenol	+80	very br
57	formic acid	+260.8	–
58	acetic acid	+258.1	–
59	trifluoroacetic acid	+243.9	–
60	Ac_2O	+273.8	–
61	propionic acid	+251.9	–
62	$CF_3CH_2CO_2H$	+259.5	–
63	butyric acid	+254.0	–
64	isobutyric acid	+248.9	–
65	acetyl chloride	+509.7	–
66	propanoyl chloride	+501.4	–
67	pentanoyl chloride	+504.8	–
68	benzoyl chloride	+487.3	–
69	oxalyl dichloride	+524.3	–
70	ethyl chlorformate	+172.9, +351.2	–
71	isobutyric acid	+248.9	–
72	triflic acid	+147.0	–
73	MeOAc	+141.0, +363.3	–
74	EtOAc	+171.8, +364.7	–
75	BuOAc	+167.2, +365.8	–
76	*t*BuOAc	+205.1, +377.8	–
77	*i*PrOAc	+196.8, +365.1	–
78	PhOAc	+202.0, +372.8	br
79	*t*BuOAc	+205.1, +377.8	–
80	methyl isobutyrate	+134.2, +353.2	–
81	$MeOCOCH(CF_3)_2$	+149.1, +375.4	–
82	dimethyl carbonate	+92.7, +240.6	–
83	diethyl carbonate	+122.5, +241.4	–
84	DMF	+326.4	–
85	dimethyl acetamide	+345.4	–
86	*N*-methylpyrrolidin-2-one	+301.3	–
87	DMPU[d]	+234.7	–
88	DMI[e]	+207.9	–
89	γ-butyrolactone	+179.5, +338.6	–
90	$BrCF_2COOEt$	+157.6, +345.4	–
91	propanal	+587.6	–
92	isobutyraldehyde	+580.7	–
93	benzaldehyde	+562.5	–
94	*p*-anisaldehyde	+68, +542	very br
95	salicylaldehyde	+84.7, +506.0	–
96	furfural (2-furaldehyde)	+238.1, +530.7	–
97	*trans*-cinnamaldehyde	+569.2	br
98	acetone	+575.5	–
99	hexachloroacetone	+539.3	br
100	2-butanone	+564.4	–
101	4,4,4-trifluorobutan-2-one	+582.0	–
102	3-pentanone	+551.9	–
103	acetophenone	+553.3	–
104	α,α,α-trifluoroacetophenone	+548.5	–
105	pivalophenone	+568.0	br
106	cyclohexanone	+563.7	–
107	acetylacetone	+579.7, +278.6	(two tautomers)
108	dipivaloylmethane[f]	+270.8	–
109	DMSO	+18.4	–
110	nitromethane	+610.0	–
111	nitrobenzene	+573.8	–
112	$(tBuO)_2$	+270.3	–
113	$tBuO_2H$	+209, +249	very br
114	$(MeO)_3P$	+46.4	d, $^1J_{O,P} = 156$ Hz
115	$(MeO)_3PO$	+23.0, +75.5	d, $^1J_{O,P} = 160$ Hz
116	PhNCO	+115.9	–
117	EtNCO	+91.1	–

[a] D_2O as standard. [b] D_2O standard replaced by CD_3OD. [c] 2-Chloro-1,1,2,-trifluoroethyl-difluoromethyl ether. [d] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [e] 1,3-Dimethyl-2-imidazolidinone. [f] 2,2,6,6-Tetramethyl-3,5-heptanedione.

Table 2. ^{17}O NMR (Bruker 600, ^{17}O: 81.4 MHz, RT: 22 °C) chemical shifts of some isotopically enriched compounds compared to natural abundance analogues.[a]

Entry	Compound	δ [ppm]	$\Delta\delta$ [ppm]
1[b]	D_2O/H_2O	+0.0/+3.3	−3.3
2[b]	CD_3OD/MeOH	−35.3/−32.9	−2.4
3	$^{13}CD_3OD/CD_3OD$	−35.8/−35.3	−0.5
4[b]	[D_8]THF/THF	+17.7/+19.5	−1.8
5[b]	AcOD/AcOH	+257.4/+258.1	−0.7
6[b]	[D_6]acetone/acetone	+576.2/+575.5	−0.7
7[b]	[D_6]DMSO/DMSO	+16.1/+18.4	−2.3
8[b]	$CD_3NO_2/MeNO_2$	+609.9/+610.0	−0.1
9	$Ph^{15}NO_2/PhNO_2$	+573.3/+573.8	−0.5

[a] D_2O as standard. [b] The chemical shift of this compound is the average of five different measuring experiments, see the Supporting Information.

Before discussing the chemical-shift trends in more detail, notably, as a result of the general broadness of the signals, spin–spin NMR couplings are seldom observed. In one exceptionally sharp case, for example, that of furan, a rare $^2J_{^{17}O,^1H}$ could be simulated, which is depicted in Figure 1. Given the

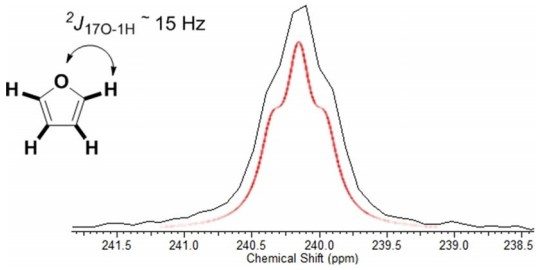

Figure 1. The limits of spin–spin NMR couplings: experimental (——) and simulated (——) ^{17}O NMR profile (81.4 MHz) of furan, $\delta = +240.1$ ppm, and the detectable $^2J_{^{17}O,^1H} \approx 15$ Hz (triplet).

general broadness of the signals, however, such an NMR coupling should be taken with caution. Moreover, the steric environment of the oxygen atom is well known to impose a very large effect on the ^{17}O NMR chemical shift.[4] This is conspicuous in Table 1 upon comparing methyl, ethyl, isopropyl, and *tert*-butyl substituents, in stark contrast to linear alkyl chains (see Figure 2). Some explanative theories have been developed in the past that suggest intramolecular β C–H···O interactions.[4] Fluorine substituent effects, however, have been less documented.[3] Those differ considerably from non-fluorinated alkyl chains (Figure 2, red plot). Moreover, their position with respect to the oxygen atom is decisive. In Figure 3, some α and β CF_3 substituents are compared frontally to their Me analogues. Clearly, whereas an α-positioned trifluoromethyl group (such as in CF_3–O) will have, as expected, a strong deshielding effect on the oxygen atom owing to a strong withdrawing inductive effect, exactly the reverse occurs on the β position (CF_3–C–O). This causes solvents such as HFIP and TFE to possess extremely shielded oxygen atoms ($\delta = -8.5$ and −20.2 ppm, respectively) in comparison to their non-fluorinated analogues. A few other similar cases are illustrated in Figure 3.

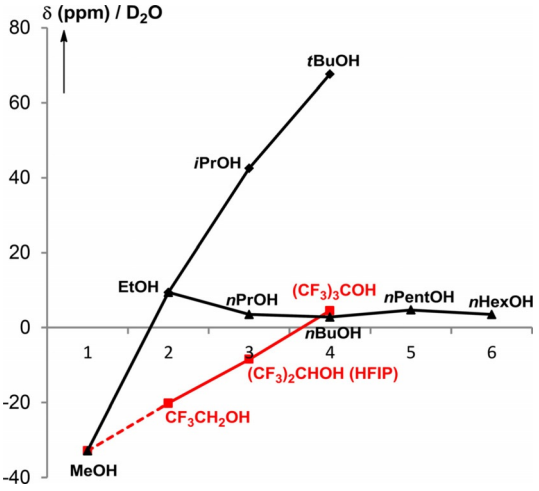

Figure 2. Substituent chemical shift (SCS) effects: ^{17}O NMR chemical shift from D_2O (vertical axis) versus number of carbon atoms (horizontal axis).

It should be noted here that β–CF_3 shielding effects are not restricted to ^{17}O NMR spectroscopy. ^{13}C NMR spectroscopy is also susceptible, although to a lesser extent. A CF_3 substituent will typically deshield an α-carbon atom but shield a β-carbon atom. The case of isopropanol versus trifluoroisopropanol illustrates this point.[8]

Comparing CF_3 with CCl_3 and CF_2H

Interestingly, hexachloroacetone and HFIP display similarly strong ^{17}O NMR β-shielding effects ($\Delta\delta = -36.2$ and −51.0 ppm, respectively). Surprisingly, however, β-trichloroethanol behaves very differently form β-trifluoroethanol ($\Delta\delta = +8.4$ and −29.6 ppm, respectively). A reasonable interpretation could arise from the involvement of chlorine atoms in significant intra- and intermolecular H-bonding networks (O–H···Cl). Indeed, chlorine is a better H-bond acceptor than fluorine, and this difference may account for a greater deshielding of the oxygen atoms in chloroalcohols. The two latter solvents may thus possess very different solvation and catalytic properties.

In contrast, trifluoroethanol (TFE) and difluoroethanol have very close chemical shifts, $\delta = -20.2$ and −20.5 ppm, respectively. The difference is therefore beneath the margin of error (estimated at $\Delta\delta \pm 0.4$ ppm). Likewise, trifluoroanisole and difluoroanisole are separated by only $\Delta\delta = 4.8$ ppm, in spite of the proximity of the fluorine atoms with respect to the oxygen atom (Figure 3). Thus, the CF_3 and CF_2H groups have a surprisingly similar impact on the shielding of proximal oxygen atoms.

In conclusion, the ^{17}O NMR spectrum of TFE and especially that of HFIP shows a strong shielding effect of the β–CF_3 functional groups, in comparison to the non-fluorinated analogues ($\Delta\delta = -29.6$ and −51.0 ppm, respectively). In the case of HFIP, the severely increased shielding on the oxygen atom may in

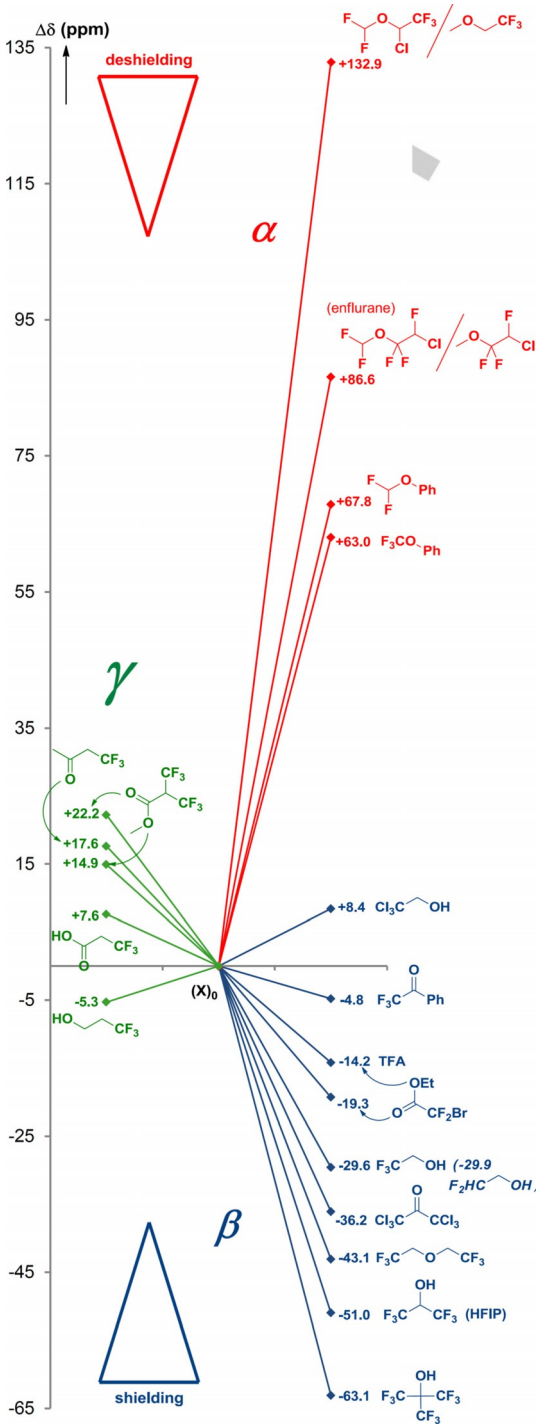

Figure 3. α, β, and γ CX_n substituent chemical shift (SCS) effects compared to a non-halogenated analogue, Δδ chemical shift (^{17}O NMR, vertical axis, ppm).

part be linked to its efficiency as a solvent in terms of high polarity and ability to stabilize charged transition states. Perfluoro-*tert*-butyl alcohol [$(CF_3)_3COH$] displays the largest β–CF_3 shielding effect of the study ($\Delta\delta = -63.1$ ppm).[9] A propos perfluoro-*tert*-butyl alcohol, Larossa very recently demonstrated the use of the corresponding potassium salt, $(CF_3)_3COK$, as a privileged base in a frontier C–H arylation reaction of benzoic acids catalyzed by a Ru catalyst.[10,11] The β–CCl_3 effects were also found to be pronounced, which indicates that oxochlorinated solvents may also have interesting properties for cross-dehydrogenative coupling reactions. In general, this study shows the importance of the relative position of the CF_3 group and related functional groups on the shielded or deshielded character of neighboring oxygen atoms. These effects might impact solvent design in the development of future chemical reactions. Furthermore, ^{17}O NMR spectroscopy of organic compounds can be utilized on a routine basis, with relatively short acquisition times. The large span of ^{17}O NMR shifts allows for the rapid and unambiguous recognition of all the typical functional groups of organic chemistry. Moreover, the strong sensitivity of ^{17}O to remote steric, electronic, H-bonding, and even isotopic alterations make this characterization technique indispensable for organic chemistry.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorine · NMR spectroscopy · oxidative couplings · shielding effects · substituent effects

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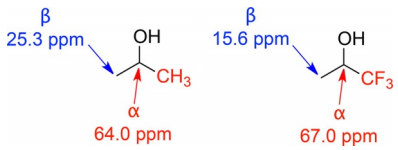
[7] This study was inspired by difficulties that occurred during the identification of an unknown compound. In this case, a current dataset of ^{17}O NMR chemical shifts would have been helpful to classify the reaction product.

[8] See for example: K. B. Wiberg, W. E. Pratt, W. F. Bailey, *J. Org. Chem.* **1980**, *45*, 4936. See also as example the cases of isopropanol and trifluoro-isopropanol, values in $CDCl_3$ from the SDBS database:.



[9] In a recent polymerization reaction: H. Miyaji, K. Satoh, M. Kamigaito, *Angew. Chem. Int. Ed.* **2016**, *55*, 1372; *Angew. Chem.* **2016**, *128*, 1394, HFIP and $(CF_3)_3COH$ solvents were found to display similar reaction rates. However, polymer lengths were greater and polydispersity was narrower under HFIP. Thus, there are no indications at this time that $(CF_3)_3COH$ might be a generally better solvent than HFIP. The trends in Figure 3 must thus be taken with caution with regards to solvent performance, the latter presumably resulting from multiple effects.

[10] M. Simonetti, D. M. Cannas, A. Panigrahi, S. Kujawa, M. Kryjewski, P. Xie, I. Larrosa, *Chem. Eur. J.* **2017**, *23*, 549.

[11] It should be noted that, just as with other nuclei, ^{17}O NMR chemical shifts and pKa values cannot be directly correlated. Comparing acetic acid (+258.1 ppm) and triflic acid (+147.0 ppm) clearly illustrate this point.

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