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Direct Evidence of a Radical Mechanism in the Addition Reaction of Iododifluoroesters to Olefins by Spin Trapping

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We present EPR analysis of the reaction of ethyl iododifluoroacetate with 1-tetradecene in the presence of Zn + $NiCl_2{\cdot}6H_2O$, confirming the mechanistic studies that provide evidence of a single electron transfer process. We have trapped for the first time the ethoxycarbonyldifluoromethyl radical with a variety of spin traps, such as phenyl *tert*-butyl nitrone (PBN), 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), 2-methyl-2-nitrosopropane (MNP), and 2-nitro-2-nitrosopropane (NNP), and the EPR spectra of the corresponding adducts have been recorded. In a second step the ethoxycarbonyldifluoromethyl radical adds to the olefin to furnish a second radical intermediate, which can be trapped with NNP. Evidence of this second radical was obtained by EPR only with electron-rich olefins, such as α-methylstyrene and 2,4,6-trimethylstyrene, and the new adducts were recorded and interpreted. In addition, we also report the EPR spectra of the corresponding adducts when other alkylating reagents are used, such as ethyl iodoacetate, *n*-perfluorohexyl iodide, methyl ω-iodohexadecanoate, and *n*-butyl iodide.

Introduction

Introduction of fluorine into organic molecules generally causes profound effects on the parent molecule due to its high electronegativity, the high C−F bond strength, and atomic volume similar to that of hydrogen.[1,2] For these reasons emphasis has been placed on the development and evaluation of biologically active fluorinated compounds,[3−6] particularly in the field of enzymatic inhibition.[5,7−11] A number of compounds containing the difluoromethyl group, an isosteric and isopolar replacement for oxygen,[12] have been prepared as antitumor agents[5] and enzyme inhibitors.[13,14] We have developed new fluorinated derivatives as inhibitors of insect pheromone catabolism in the search for new approaches to insect control.[8−11,15] Continuing our interest in this field we are currently involved in the synthesis of new fluorinated ketones and to this end we have considered long-chain 2,2-difluoroesters as versatile intermediates. They were prepared as reported by Burton,[16] i.e., by the addition of ethyl iododifluoroacetate to olefins in the presence of Zn + $NiCl_2{\cdot}6H_2O$. Here we report our spectroscopic studies, which confirm the postulated mechanism.

Scheme 1

$$RCH{=}CH_2 \;+\; ICF_2CO_2Et \xrightarrow{a} RCH_2CH_2CF_2CO_2Et$$

a: $NiCl_2.6H_20$, Zn, THF/H_2O, r.t.

Spin trapping can be used to uncover radical mechanisms of many organic reactions through electron paramagnetic resonance (EPR), particularly of those processes in which only low steady-state radical concentrations are present.[17−19] Free radicals, as transient intermediates in many reactions, are scavenged by spin traps, such as C-nitroso compounds and nitrones, and converted to more stable spin adducts. EPR spectra of these adducts provide valuable information about the structure of the intermediates and the mechanism of the reactions in which they are involved.

In this paper, we present for the first time spectroscopic evidence of the presence of radical intermediates in the reactions of ethyl iododifluoroacetate with alkenes (Scheme 1) by trapping the ethoxycarbonyldifluoromethyl radical and other intermediate radicals with a variety of spin traps, confirming the mechanism proposed by Burton,[16,20]

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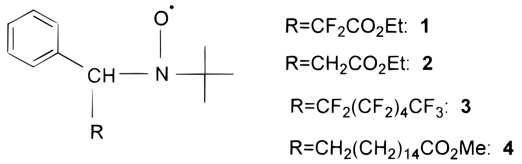
Scheme 2



in which a single electron is transferred from the metallic species (nickel) to the halogenated compound. These authors proposed the radical mechanism by using an electron scavenger and a radical inhibitor. We also supply evidence for the presence of intermediate radical species when other alkylating reagents, such as *n*-perfluorohexyl iodide, methyl *ω*-iodohexadecanoate, and *n*-butyl iodide, are used in similar addition reactions to olefins. As spin traps we used phenyl *tert*-butyl nitrone (PBN), 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO), 2-methyl-2-nitrosopropane (MNP), and 2-nitro-2-nitrosopropane (NNP). Proof of the occurrence of free radical intermediates in the reaction of fluoroalkyl iodides with alkenes and alkynes with palladium(0)[21] as catalyst or under oxidative conditions[22] has been reported. Perfluoroalkyl radicals have also been detected, e.g., by spin trapping with PBN[23] or NNP.[24] However, to our knowledge trapping of the ethoxycarbonyldifluoromethyl radical has not been described.

Results and Discussion

EPR of Spin Adducts. Nitrones as Spin Traps. (a) Phenyl *tert*-Butyl Nitrone (PBN). When benzene solutions of ethyl iododifluoroacetate (0.1 M) and PBN in the presence of Zn + $NiCl_2 \cdot 6H_2O$ were analyzed by EPR spectroscopy, a doublet of triplets was observed. The spectrum was attributed to spin adduct **1** (Scheme 2), resulting from addition of ethoxycarbonyldifluoromethyl radical to PBN (Figure 1), as confirmed independently by UV irradiation of CH_2Cl_2 solutions of ethyl bromodifluoroacetate only in the presence of PBN.

A list of the EPR spectral parameters of spin adduct **1** in benzene, CH_2Cl_2, THF, and MeOH, under the same reductive conditions as above, is depicted in Table 1. A careful analysis of the signals in benzene or in CH_2Cl_2 solutions show a small splitting with one of the fluorine atoms, as confirmed by the simulated spectrum. In THF or methanol this splitting did not appear, possibly because the line width was greater. The hyperfine splitting (hfs) values are similar in all cases except in MeOH, where they slightly increased by the higher polarity of the solvent.

Similarly, when benzene solutions of ethyl iodoacetate and PBN were analyzed by EPR in the presence of the metallic catalyst (Ni^0), a weak signal attributed to spin adduct **2** (Scheme 2) appeared as a triplet of doublets (Table 2). The low coupling values with γ-hydrogens were partially obscured as a result of the background noise of the spectrum and the wideness of the lines (see Supporting Information). When *n*-perfluorohexyl iodide or methyl *ω*-iodohexadecanoate was tested, the corresponding spin adducts **3** and **4** (Scheme 2) were detected and their EPR spectral parameters were recorded (Table 2). It should be noted that in the case of spin adduct **3**, low hfs values from the β-hydrogen and even from the two γ-fluorines are apparent in the spectrum when an accurate simulation of the spectrum is performed (Figure 2). Adduct **3** was also detected when a benzene solution of *n*-perfluorohexyl iodide and PBN was irradiated in the presence of bis(tributyltin) as initiator.

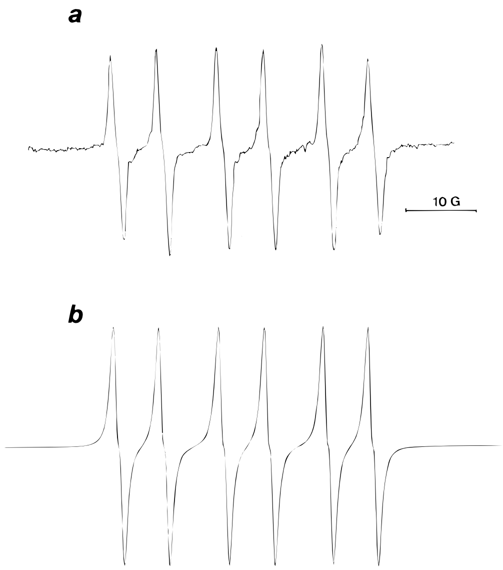


Figure 1. (a) EPR spectrum of spin adduct **1** generated from reaction of ethyl iododifluoroacetate with Zn + $NiCl_2 \cdot 6H_2O$ in benzene and PBN as spin trap at room temperature (microwave power, 5 mW; modulation frequency, 100 kHz; modulation amplitude, 0.2). (b) Computer simulation of (a) using the parameters given in Table 1.

Table 1. EPR Spectral Parameters of Spin Adduct 1, Generated from Reaction of Ethyl Iododifluoroacetate with Zn/$NiCl_2 \cdot 6H_2O$ in the Presence of PBN in Different Solvents

solvent	a^N (G)	$a^{\beta-H}$ (G)	$a^{\gamma-F}$ (G)	g	ΔH_{pp}[a] (G)
benzene	14.9	6.5	0.8(1F)	2.0058	0.7
CH_2Cl_2	15.0	6.4	0.8(1F)	2.0055	0.7
THF	14.9	6.5		2.0041	0.9
MeOH	15.5	7.25		2.0053	1.8

[a] ΔH_{pp}: peak-to-peak line width.

Table 2. EPR Spectral Parameters of Spin Adducts 2−4, Generated from Reduction of Benzene Solutions of Ethyl Iodoacetate, *n*-Perfluorohexyl Iodide, and Methyl *ω*-Iodohexadecanoate with Zn/$NiCl_2 \cdot 6H_2O$ in the Presence of PBN

	a^N (G)	$a^{\beta-H}$ (G)	$a^{\gamma-X}$ (G)	g	ΔH_{pp}[b] (G)
2	15.25	4.6		2.0055	0.9
3[a]	14.5	1.4	0.9(2F)	2.0057	1.0
4[a]	14.9	2.75		2.006	1.2

[a] Other hyperfine splittings of PBN spin adducts in gauss for $C_6H_5CH(R)N(O^\bullet)C(CH_3)_3$ are as follows: R = C_2F_5, $a^N = 14.05$, $a^{\beta-H} < 1.2$, $a^F = 1.46$;[23] R = $Cl(CF_2)_4$, $a^N = 14.0$ G;[22] R = C_2H_5, $a^N = 14.0$, $a^{\beta-H} = 3.2$;[32] R = *n*-C_4H_9, $a^N = 14.6$, $a^{\beta-H} = 3.4$;[33] R = *n*-C_4H_9, $a^N = 14.01$, $a^{\beta-H} = 3.13$.[34] [b] ΔH_{pp}: peak-to-peak line width.

From the analysis of Table 2, two comments deserve special mention. Adduct **3** showed a decrease in the hyperfine couplings in comparison to **4**, especially with regard to the β-hydrogen, which could be attributed to

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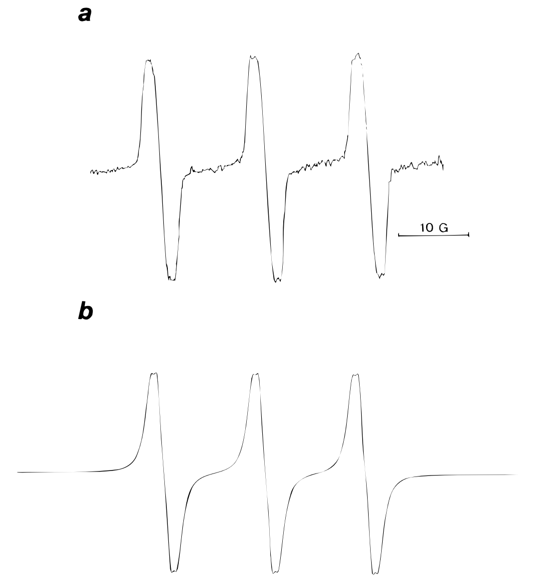
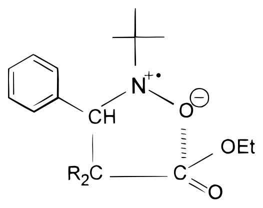


Figure 2. (a) EPR spectrum of spin adduct **3** generated from reaction of *n*-perfluorohexyl iodide with Zn + $NiCl_2{\cdot}6H_2O$ in benzene and PBN as spin trap at room temperature (microwave power, 5mW; modulation frequency, 100 kHz; modulation amplitude, 0.2). (b) Computer simulation of (a) using the parameters given in Table 2.

Scheme 3



5 (R = F, H)

the electron-withdrawing nature of the γ-CF_2 group relative to the γ-CH_2 moiety. On the other hand, the abnormal high values of the β-hydrogen couplings in spin adducts **1** (6.5 G) (Table 1) and **2** (4.6 G) relative to **3** (1.4 G) and **4** (2.75 G) might be attributed to an increase in the spin density on nitrogen, as a consequence of a supposedly stable pentacyclic conformation denoted by structure **5** (Scheme 3), which can accommodate the β-hydrogen in a pseudoaxial position. The small coupling with one of the γ-F atoms observed in the spectrum of **1** (see above) may also be assigned to that with the halogen located at the pseudoaxial position of an analogous conformation. A similar type of intramolecular cyclization resulting from H-bonding to N−O in hydroxyalkyl- and cyclopropyl-spin adducts of DMPO has been suggested.[25,26]

(b) 5,5-Dimethyl-1-pyrroline-*N*-oxide (DMPO). DMPO is an effective scavenger of different kinds of transient radicals.[25,27] When a benzene solution of ethyl iododifluoroacetate and DMPO was treated with Zn + $NiCl_2{\cdot}6H_2O$, a persistent radical with a well resolved EPR spectrum was observed (Figure 3). The spectral parameters were consistent with spin adduct **6** by trapping of the ethoxycarbonyldifluoromethyl radical (Scheme 4) (Table 3).

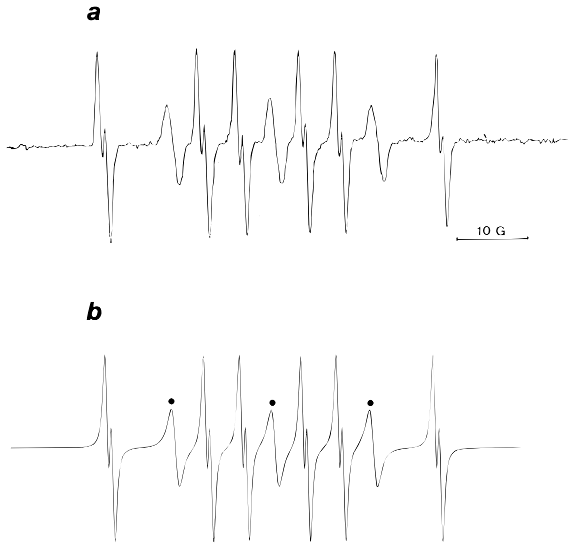


Figure 3. (a) EPR spectrum of spin adduct **6** formed by reaction of ethyl iododifluoroacetate in the presence of Zn + $NiCl_2{\cdot}6H_2O$ in benzene and DMPO as spin trap at room temperature (microwave power, 5mW; modulation frequency, 100 kHz; modulation amplitude, 0.5). (b) Computer simulation of (a) using the parameters given in Table 3. The signals marked with filled dots are due to DMPO decomposition.

Scheme 4

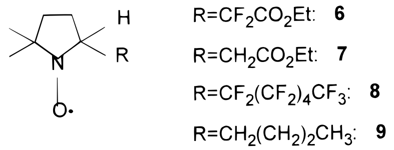


Table 3. EPR Spectral Parameters of Spin Adducts 6−9, Generated from Reduction of Benzene Solutions of Ethyl Iododifluoroacetate, Ethyl Iodoacetate, *n*-Perfluorohexyl Iodide, and *n*-Butyl Iodide in the Presence of DMPO

	a^{N} (G)	$a^{\beta-H}$ (G)	$a^{\gamma-H}$	g	$\Delta H_{pp}{}^{b}$ (G)
6	14.0	19.1	0.8	2.0058	0.4
7	14.0	16.75		2.0058	0.6
	14.6	22.0		2.0058	0.9
8[a]	13.5	14.5		2.0062	1.1
9[a]	14.6	21.1		2.0058	0.8

[a] Other hyperfine splittings of DMPO spin adducts in gauss for $(CH_3)_2C(CH_2)_2CHR{-}N(O^{\bullet})$ are as follows: R = CF_3, $a^{N} = 13.22$, $a^{\beta-H} = 15.54$, $a^{F} = 1.01$;[25] R = C_2H_5, $a^{N} = 14.0$, $a^{\beta-H} = 20.5$;[35] R = *n*-C_7H_{15}, $a^{N} = 14.2$, $a^{\beta-H} = 21.8$.[36] [b] ΔH_{pp}: peak-to-peak line width.

As before, ethyl iodoacetate, *n*-perfluorohexyl iodide, and in this case *n*-butyl iodide were allowed to react with Zn + $NiCl_2{\cdot}6H_2O$ in the presence of DMPO under similar conditions. In all cases, the signals and the spectral parameters were consistent with those expected for spin adducts **7**−**9**, in which radicals produced by scission of the iodo-carbon bond are attached to the β-carbon of DMPO (Table 3). A well-resolved γ-hydrogen coupling was observed only for spin adduct **6**, being obscured by the line width in all other cases.

Whereas adducts **8** and **9** appeared as a doublet of triplets, adduct **7** initially displayed an EPR spectrum of a mixture of two radicals (each as a doublet of triplets) in ca. 1:1 ratio, which increased with time in favor of that with larger splitting values (Supporting Information).

EPR of Spin Adducts. C-Nitroso Compounds as Spin Traps. The main advantage of using C-nitroso

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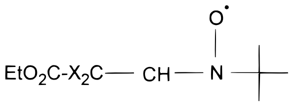
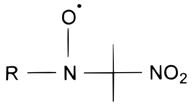
Scheme 5



X=F: **10**

X=H: **11**

Scheme 6

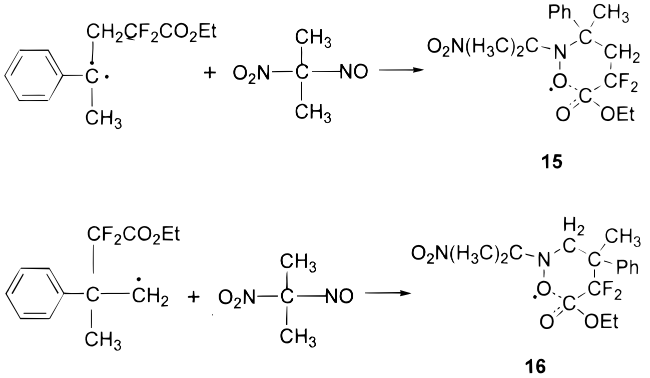


R=CF_2CO_2Et: **12**

R=CH_2CO_2Et: **13**

R=$CF_2(CF_2)_4CF_3$: **14**

Scheme 7



compounds as spin traps is that the information on the structure of the transient radical can be directly extracted from the EPR spectrum.[18]

(a) 2-Methyl-2-nitrosopropane (MNP). When a solution of ethyl iododifluoroacetate (0.1 M) and MNP in benzene was introduced into the cavity of the EPR spectrometer, a strong and very persistent signal of a radical ($a^N = 12.6$ G, $a^{2F} = 25.7$ G, $g = 2.0062$, $\Delta H_{pp} = 0.4$ G) was immediately observed. The spectrum was assigned to spin adduct **10** (Scheme 5) by trapping of the ethoxycarbonyldifluoromethyl radical (see Supporting Information). UV irradiation of the same solution devoid of spin trap and in the presence of bis(tributyltin) enhanced the intensity of the signal.

To detect spin adducts of other transient radicals when 1-tetradecene was present, new EPR experiments with solutions of ethyl iododifluoroacetate (0.1 M) in benzene and MNP were tested in the presence of an excess of olefin. However, in all cases the strong signal of spin adduct **10** masked any contribution from other expected radicals, indicating that spin trapping of the ethoxycarbonyldifluoromethyl radical is faster than addition of the radical to the olefin.

To assess the influence of the fluorine atoms in the splitting of adduct **10**, a benzene solution of ethyl iodoacetate (0.1 M) and MNP in the presence of bis(tributyltin) was exposed to daylight and examined by EPR. The spectrum ($a^N = 14.6$ G, $a^{2H} = 7.75$ G, $g = 2.0058$, $\Delta H_{pp} = 0.3$ G) was attributed to spin adduct **11** (see Supporting Information) and showed a slightly higher a^N value than **10**. Similarly, the splitting corresponding to the two β-hydrogens was smaller than that of the fluorinated derivative.

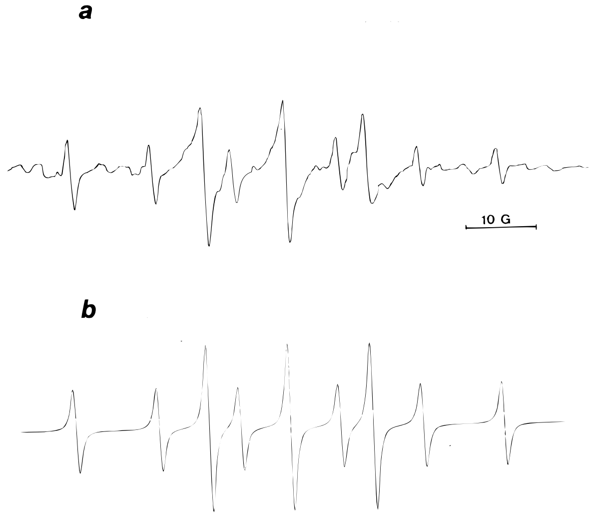


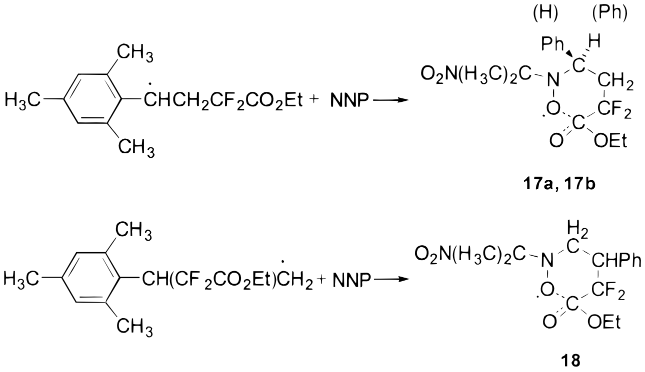
Figure 4. (a) EPR spectrum of spin adduct **12** formed by photolysis of a benzene solution of ethyl iododifluoroacetate in the presence of bis(tributyltin) and NNP at room temperature (microwave power, 5mW; modulation frequency, 100 kHz; modulation amplitude, 0.5). (b) Computer simulation of (a) using the parameters given in Table 4.

Table 4. EPR Spectral Parameters of Spin Adducts 12–14 from Benzene Solutions of Ethyl Iododifluoroacetate, Ethyl Iodoacetate, and *n*-Perfluorohexyl Iodide, Respectively, in the Presence of NNP

	a^N (G)	a^{2F} (G)	a^{2H} (G)	a^{6H} (G)	g	ΔH_{pp}[b] (G)
12	11.8	19.0			2.0062	0.6
13	14.12		7.7	0.4	2.0059	0.37
14[a]	10.75	14.5			2.0063	1.0

[a] The spectral parameters of **14** are in good agreement with those reported for similar spin adducts.[36] [b] ΔH_{pp}: peak-to-peak line width.

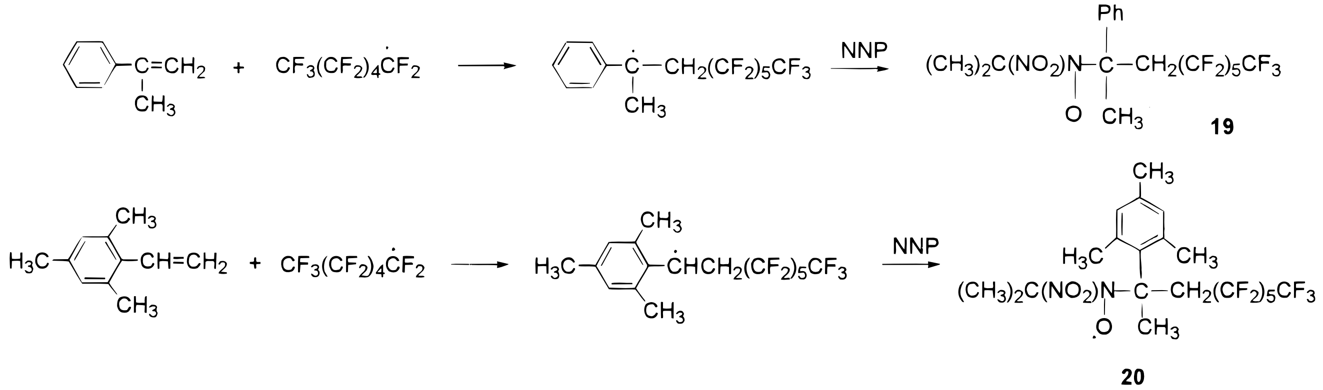
Scheme 8



(b) 2-Nitro-2-nitrosopropane (NNP). Following the strategy reported by Chen et al,[21] we tried NNP as a spin trap. Thus, a benzene solution of ethyl iododifluoroacetate (0.3 M) and NNP, in the presence or absence of 1-tetradecene and with bis(tributyltin) as initiator, gave after exposure to daylight an EPR spectrum (Figure 4), whose spectral parameters were as expected for spin adduct **12** (Scheme 6, Table 4).

Similarly, solutions of ethyl iodoacetate (0.6 M) or *n*-perfluorohexyl iodide (0.5 M) with the spin trap and bis(tributyltin) showed the corresponding spin adducts **13** and **14**, by trapping of the ethoxycarbonylmethyl radical and perfluoro-*n*-pentylmethyl radical, respectively (Table 4, Scheme 6). It is worth noting that small

Scheme 9



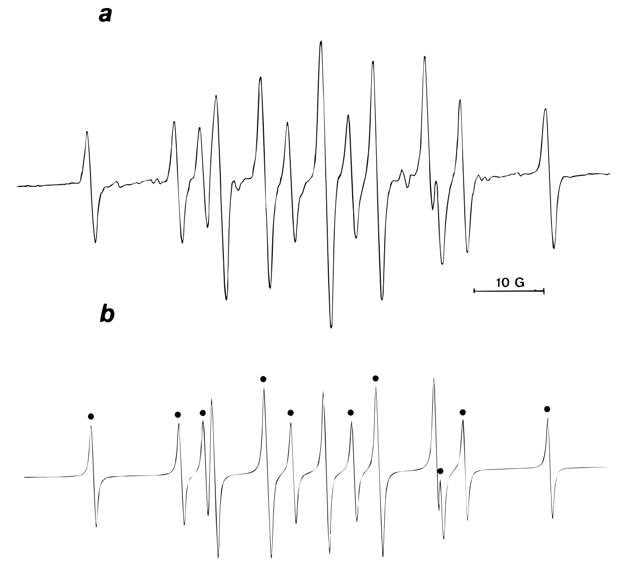


Figure 5. (a) EPR spectrum of spin adducts **15** and **16** (with filled dots) formed by photolysis of a benzene solution of ethyl iododifluoroacetate and α-methylstyrene in the presence of bis(tributyltin) and NNP at room temperature (microwave power, 5mW; modulation frequency, 100 kHz; modulation amplitude, 0.5). (b) Computer simulation of (a) using the parameters given in the text.

hyperfine splittings with the γ-hydrogens of the methyl groups were only observed in spin adduct **13**.

To detect other transient radicals in the reaction of iododifluoroacetate with the olefin, we needed to increase the addition rate of the ethoxycarbonyldifluoromethyl radical to the double bond, and to this goal we attempted the reaction with two electron-rich olefins: α-methylstyrene and 2,4,6-trimethylstyrene. When solutions of ethyl iododifluoroacetate (0.5 M) and α-methylstyrene (0.8 M) in benzene, in the presence of NNP and bis(tributyltin), were exposed to daylight, a strong and persistent complex signal, simulated as a mixture of two spin adducts, immediately appeared. Neither of them corresponded to spin adduct **12**, and they were assigned to adducts **15** and **16** (spectral parameters of **15**: $a^{N} = 15.5$ G, $g = 2.0061$; **16**: $a^{N} = 12.5$ G, $a^{H} = 16.0$ G, $a^{H} = 24.75$ G, $g = 2.0063$) (Figure 5, Scheme 7). While the intensity of the peaks corresponding to adduct **15** initially increased to a maximum and then decreased in a short time, those of adduct **16**, corresponding to the most stable transient benzyl radical, continuously increased to become the only signal in the spectrum in ca. 1 h.[28] Thus, in this case, the initially generated ethoxycarbonyldifluoromethyl radical added to the double bond of the olefin, either in the α- or β-position, to give two second transient radicals, which were then trapped by NNP to provide spin adducts **15** and **16**.

When 2,4,6-trimethylstyrene (0.6 M) was used, similar results were obtained. Thus, the EPR spectrum showed a strong and persistent signal, which after simulation appeared to be a mixture of three spin adducts with similar g-values. The spectral parameters ($a^{N} = 12.88$ G, $a^{H} = 22.5$ G; $a^{N} = 12.75$ G, $a^{H} = 22.5$ G; $a^{N} = 12.75$ G, $a^{H} = 15.25$ G, $a^{H} = 32.75$ G) were in agreement with the assigned structures **17a**, **17b**, and **18** (Scheme 8)[29] (Supporting Information). Species **17a** and **17b** are two conformers of spin adduct **17** that are distinguishable by EPR. As before, no traces of the spin adduct **12** were detected, and therefore, generation of these adducts implied a reaction sequence similar to that for α-methylstyrene.

To determine whether other fluorinated radicals, such as perfluoro-n-pentylmethyl radical, behaved similarly to the ethoxycarbonyldifluoromethyl radical, we also considered the reaction of n-perfluorohexyl iodide with the electron-rich olefins and with nonactivated olefins. Benzene solutions of the fluorinated alkyl halide (0.4 M) and α-methylstyrene (0.9 M) with NNP in the presence of bis(tributyltin) as initiator displayed a strong and persistent 1:1:1 triplet, which increased with time. The parameters of the signal ($a^{N} = 15.12$ G, $a^{2H} = 0.5$ G, $g = 2.0056$) suggested the presence of spin adduct **19** (Scheme 9). When the olefin was 2,4,6-trimethylstyrene (0.5 M), the spectrum displayed a triplet of doublets ($a^{N} = 14.6$ G, $a^{H} = 10.6$ G, $g = 2.0058$), which was assigned to spin adduct **20** (Scheme 9). Both **19** and **20** were probably formed by initial addition of the perfluoro-n-pentylmethyl radical to the β-carbon of the double bond to give the corresponding benzyl radicals, which were trapped by NNP.[30] The absence of the radical resulting from addition to the α carbon of the olefin could be due to the slow formation of the perfluoro-n-pentylmethyl radical, which immediately reacts with the olefin to furnish the thermodynamically more stable benzyl radical. As before, signals corresponding to adduct **14** were not detected,

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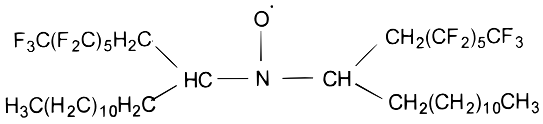
[28] Blank experiments in the absence of electrophile gave a very weak triplet (1:1:1, $a^{N} = 15.05$ G, $g = 2.0057$), which increased slowly with time. Although the nitrogen splitting of this signal was similar to that of **16**, the intensity of the latter was ca. 10 times higher.

[29] Blank experiments in the absence of electrophile gave a very weak triplet of doublets (1:1:1, $a^{N} = 14.5$ G, $a^{H} = 10.4$ G, $g = 2.0060$).

[30] Blank experiments showed similar spectra to **19** and **20**, due to the slight difference (only in δ substitution) of the adducts structures in the presence or absence of the perfluorinated compound.

again indicating that the initial radical reacts faster with the electron-rich olefins than with the spin trap.

The EPR spectrum of the reaction of *n*-perfluorohexyl iodide with a nonactivated olefin (1-tetradecene) was identical to that of adduct **14**, again showing that the perfluoro-*n*-pentylmethyl radical was also trapped by NNP before it could react with the olefin. This result is in contrast to that described by Chen et al.,[21] who reported the selective addition of perfluoroalkyl radicals to 1-heptene in the presence of NNP and catalyzed by Pd(0) before they were captured. However, when our solution was left overnight and then UV-irradiated, the signals corresponding to **14** were replaced by others in which a weak triplet of triplets ($a^{N} \approx 12.9$ G, $a^{2H} \approx 5.0$ G, $g = 2.0059$) was noticed. This group of signals was assigned to spin adduct **21**, a radical of nitroxide structure similar to that reported by Chen.[21]



21

In conclusion, we report for the first time the spin trapping of ethoxycarbonyldifluoromethyl radical by nitrones or C-nitroso compounds. This transient electrophilic radical was generated from ethyl iododifluoroacetate by chemical reduction with Zn + $NiCl_2{\cdot}6H_2O$ and by photochemical irradiation in the presence of bis(tributyltin). In the presence of nonactivated olefins, the radical is preferentially captured by the spin trap (NNP) instead of being attached to the olefin. With electron-rich olefins, such as α-methylstyrene or 2,4,6-trimethylstyrene, however, the rate of the addition to the olefin is faster and a second intermediate radical is captured by the spin trap. This was the only radical species detected by EPR. Similar behavior has also been found when other fluorinated electrophilic reagents, such as perfluorohexyl iodide, are used in their Ni^{0}-catalyzed addition reactions to olefins.

Experimental Section

EPR spectra were recorded on a Varian E-109 spectrometer at room temperature. *g*-Values of the radicals were determined with dpph ($g = 2.0037$) as standard. Solutions of the appropriate organic compounds and the spin traps in benzene, CH_2Cl_2, THF, or MeOH in a quartz tube were degassed by passing a stream of dry argon through the solutions before introduction into the cavity of the spectrometer. Samples were irradiated with an Oriel high-pressure mercury lamp (500 W), model 68810. UV light was filtered through a continuous flux of cold water to avoid sample heating. When necessary, blank experiments were also run under the same conditions. EPR simulations were carried out with the WINSIM program.[31]

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Supporting Information Available: Copies of experimental and simulated EPR spectra of spin adducts **1** in CH_2Cl_2, THF, and MeOH, and **2**, **4**, **7**−**11**, **13**, **14**, **17a**, **17b**, and **18**−**21** (as referred in the text) are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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