A ^1H, ^{13}C, and ^{19}F Nuclear Magnetic Resonance Study of Rotational Isomerism and Long-range Coupling in Methyl (1*S*,5*R*,7*R*)-1-Ethyl-3-oxo-6-trifluoroacetyl-2,8-dioxa-6-azabicyclo[3.2.1]octane-7-carboxylate

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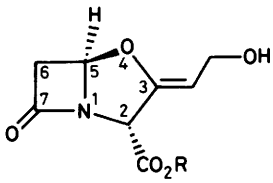
The ^1H, ^{13}C, and ^{19}F n.m.r. spectra of the title compound show that it exists in solution as a mixture of rotamers about the amide bond. Each rotamer possesses a distinct pattern of long-range ^1H,^{19}F and ^{13}C, ^{19}F couplings. Proton spin–lattice relaxation time experiments have been used to assign the n.m.r. spectra of each rotamer. These assignments show that large values of the long-range couplings are associated with a close spatial approach of the nuclei involved. The title compound was obtained *via* degradation of methyl clavulanate with acid followed by hydrogenation.

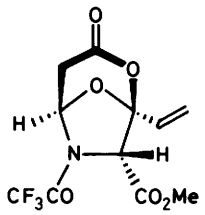
Clavulanic acid (**1**), (*Z*)-(2*R*,5*R*)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, obtained from *Streptomyces clavuligerus* is a potent inhibitor of many β-lactamases from both Gram-positive and Gram-negative organisms and also possesses weak antibacterial activity.[1] Since its discovery this microbial metabolite has been subjected to chemical modification aimed at producing new compounds with enhanced biological activity.[2] At the same time a programme designed to investigate the degradation and metabolism of clavulanic acid was started in these laboratories. It was during these studies that the reaction of methyl clavulanate[3] (**2**) with trifluoroacetic acid was examined. The acid-labile β-lactam function of (**2**) was cleaved under the reaction conditions to give an optically active rearrangement product. Elemental analysis and high resolution mass spectrometry showed the empirical formula to be $C_{11}H_{10}F_3NO_6$, and the compound was formulated as the bicyclo[3.2.1] derivative (**3**) on the basis of its spectroscopic properties. The ^1H n.m.r. spectrum (solvent [$^2H_6$]dimethyl sulphoxide) was complex, owing to restricted rotation about the amide bond, but the presence of a vinyl group was discernible. A strong i.r. absorption at 1 705 cm^{-1} was attributed to the trifluoroacetamide function.

When compound (**3**) was hydrogenated over palladised charcoal, an optically active product was obtained (85% yield), the ^1H n.m.r. spectrum of which was less complex. Both elemental analysis and high resolution mass spectrometry agreed with the formula $C_{11}H_{12}F_3NO_6$, consistent with the dihydro derivative (**4**). The i.r. spectrum showed absorptions at 1 760 and 1 705 cm^{-1}, supporting this correlation. ^1H N.m.r. spectroscopy showed that the dihydro derivative (**4**) also existed in [$^2H_6$]dimethyl sulphoxide as a mixture of rotamers.

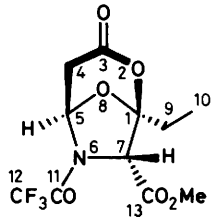
The aim of this work was to assign the ^1H,^{13}C, and ^{19}F n.m.r. spectra of each rotamer of (**4**). This aim was achieved by the use of a variety of n.m.r. techniques, but with the key assignments made on the basis of non-selective proton relaxation rate measurements. These assignments showed that large values of the stereospecific, long-range ^1H,^{19}F and ^{13}C,^{19}F couplings observed in the ^1H,^{13}C, and ^{19}F spectra of (**4**) were associated with a close spatial approach of the nuclei involved.



(**1**) R = H
(**2**) R = Me



(**3**)



(**4**)

Results and Discussion

The Table gives the ^1H, ^{13}C, and ^{19}F n.m.r. chemical shifts, $^nJ_{HH}$, $^nJ_{HF}$, and $^nJ_{FC}$ values, and proton relaxation rates for (**4**) in $(CD_3)_2SO$.

^1H and ^{19}F N.m.r. Spectra.—The ^1H n.m.r. spectrum of (**4**) was complex, with doubling of many of the resonances. Above room temperature, pairs of resonances coalesced, and at *ca.* 440 K a reasonably well resolved spectrum of a single averaged species was obtained. The original doubled spectrum returned on cooling. This behaviour showed that (**4**) existed as a mixture (1.0:1.0) of *cis*- and *trans*-rotamers about the N(6)–C(11) bond.

Closer examination of the spectra showed that within the pairs of coalescing resonances, multiplicities often did not match. Two-dimensional ^1H *J*-spectroscopy[4] was used to unravel the complex patterns and obtain higher resolution. The *J*-spectra immediately showed that the extra splittings on certain resonances were due to heteronuclear coupling, *i.e.* to ^{19}F, since these splittings were not modulated across the second dimension (F_1) of the spectra.[5,6] Connectivities between pairs of coupled resonances were established by homonuclear decoupling experiments.

The ^{19}F spectrum of (**4**) in $(CD_3)_2SO$ was composed of a sharp doublet and a broad doublet, each due to the CF_3 resonance of a specific rotamer. Single-frequency ^{19}F decoupling in the ^1H n.m.r. spectrum was used to determine the connectivities between coupled protons and ^{19}F nuclei. In one rotamer (**4a**) the CF_3 group had a well resolved five-bond coupling (^5J) to H-5 and a ^6J coupling to H′-4, which served to broaden the ^{19}F resonance, although both couplings were resolved in the ^1H n.m.r. spectrum. Decoupling the CF_3 group also caused a slight decrease (*ca.* 0.5 Hz) in the half-band width ($\nu_{\frac{1}{2}}$) of the H-7 singlet and a marked increase in its relative intensity. Thus the CF_3 group also had a small unresolved ^5J coupling to H-7.

Table. ^1H, ^{13}C and ^{19}F N.m.r. chemical shifts (δ) coupling constants (J/Hz) and proton relaxation rates (R_1/s^{-1}) for (**4**) in $(CD_3)_2SO$

Atom	δ_H	$^2J_{H,H}$	$^3J_{H,H}$	$^5J_{H,F}$	$^6J_{H,F}$	R_1[b]	δ_C[h]	M[c]	δ_F
1(**a**)							110.8	–	
1(**b**)							108.3	–	
3(**a**)							163.8	–	
3(**b**)							163.7	–	
4(**a**)	3.23	18.4	3.9			2.77 ± 0.04	37.9	–	
4(H′)(**a**)	3.01	18.4	0.8		0.8	2.77 ± 0.04			
4(**b**)	3.15	18.4	3.9			2.67 ± 0.04	35.4	–	
4(H′)(**b**)	2.90	18.3	0.8			2.57 ± 0.04			
5(**a**)	6.50		4.0, 0.8	1.7		0.89 ± 0.02	84.8br	+	
5(**b**)	6.30		4.0, 1.0	*ca.* 0.1[d]		0.66 ± 0.03	86.1	+	
7(**a**)	4.87			*ca.* 0.5[d]		0.33 ± 0.02	67.8	+	
7(**b**)	5.18			1.8		0.43 ± 0.0	67.2br	+	
9(**a**)	1.95[a1]	14.7	7.4			*i*	26.4[k]	–	
9(H′)(**a**)	1.77[a2]	14.7	7.3			*i*			
9(**b**)	1.94[a1]	14.8	7.4			*i*	25.9[k]	–	
9(H′)(**b**)	1.76[a2]	14.8	7.4			*i*			
10(**a**)	1.02		7.3			1.72[j]	6.32	+	
10(**b**)	1.02		7.3			1.72[j]	6.25	+	
11(**a**)							152.8[e]	–	
11(**b**)							154.4[e]	–	
12(**a**)				1.6, *ca.* 0.5[d]	br		115.3[f]	–	−71.05
12(**b**)				1.8, *ca.* 0.1[d]			115.1[g]	–	−70.58
13(**a**)							166.8[l]	–	
13(**b**)							165.6[l]	–	
14(**a**)	3.79[a3]						53.4	+	
14(**b**)	3.75[a3]						53.1	+	

[a] Assignment uncertain between pairs labelled *a*1, *a*2, *a*3. [b] Average of two determinations on different samples, plus and minus half the range. [c] Sign of signal in spin-echo spectrum. [d] Very approximate value derived from change in proton half-band width upon irradiation of ^{19}F. [e] $^2J_{FC} = 39$ Hz. [f] $^1J_{FC} = 287$ Hz. [g] $^1J_{FC} = 286$ Hz. [h] Except for the C-5 and C-7 pairs, no other ^{13}C resonance pairs are explicitly assigned to a given rotamer. [i] The outside lines of the multiplets due to H-9 exhibited significantly faster (*ca.* 45%) relaxation than the inside lines. Owing to the complex overlap of lines within the multiplets no R_1 values are given. This differential relaxation behaviour was not apparent *within* any other multiplets. [j] Single determination. [k] Assigned upfield of C-4 on basis of lower expected $\Delta\delta$ value ($\delta_A - \delta_B$) and higher ^{13}C NT_1 values 0.67 s (25.9 p.p.m.) and 0.70 s (26.4 p.p.m.). [l] Assigned downfield of C-3 on the basis of the higher expected $\Delta\delta$ value.

In the other rotamer, (**4b**) the CF_3 group had a well resolved ^5J coupling to H-7. A very slight decrease (*ca.* 0.1 Hz) in $\nu_{\frac{1}{2}}$ of H-5 on decoupling the CF_3 group indicated the possible presence of a very small unresolved ^5J coupling to the latter proton. Thus, in rotamer (**4a**) the CF_3 group suffered well-resolved long-range coupling to H-5 and H′-4 and an unresolved coupling to H-7, whereas in the other rotamer (**4b**) the CF_3 group suffered well-resolved long-range coupling to H-7 with a barely perceptible coupling to H-5.

^{13}C *N.m.r. Spectra.*—The ^{13}C spectrum of (**4**) in $(CD_3)_2SO$ was also doubled at ambient temperature. When the temperature of the solution was raised, the pairs of doubled resonances gradually coalesced until at *ca.* 400 K only the resonance assigned to C-4 remained broad. As in the proton spectrum there was asymmetry within pairs of coalescing resonances. In particular, the ^{13}C resonances of C-5 of (**4a**) and C-7 of (**4b**) were noticably broadened relative to the resonance of C-5 of (**4b**) and C-7 of (**4a**). These resonances were all assigned by single-frequency proton decoupling in the ^{13}C spectrum. Thus, the ^{13}C nuclei with broadened resonances [C-5 of (**4a**) and C-7 of (**4b**)] were those with attached protons having large values of $^5J_{HF}$. The broadening in the ^{13}C resonances was therefore ascribed to unresolved, stereospecific, four-bond $^{13}C,^{19}F$ coupling. In $CDCl_3$ solution values of $^4J_{F,5} \simeq 4.1$ Hz [for (**4a**)] and $^4J_{F,7} \simeq 2.6$ Hz [for (**4b**)] were measured.

Thus, both ^{13}C and ^1H spectra showed the effects of long-range coupling to ^{19}F. However, the coupling patterns of the two rotamers were totally different. This situation can be compared with that in *N*,*N*-dimethyltrifluoroacetamide[7–9] [a crude model for (**4**)], in which both methyl groups suffer long-range coupling to the CF_3 group but with one $^5J_{HF}$ coupling twice as large as the other. Various groups have interpreted the larger coupling on the basis of a 'through-space'[7,8,10] or a 'through-bond'[9] mechanism. In this work, non-selective proton spin-lattice relaxation time experiments were used to assign the room temperature ^1H and hence the ^{13}C and ^{19}F resonances of (**4**) to a particular rotameric form.

Non-selective Proton Spin–Lattice Relaxation Rate Experiments.—Before discussing the relaxation rate experiments themselves, the factors that could cause relaxation rate differences between corresponding protons in the two rotamers will be considered. In this special case, the effects of temperature, solvent, and solute concentration[11] were neglected since all measurements were carried out on a single equilibrium mixture (1.0:1.0) of the rotamers at ambient temperature.

A Dreiding model of (**4**) showed that the fused bicyclic ring

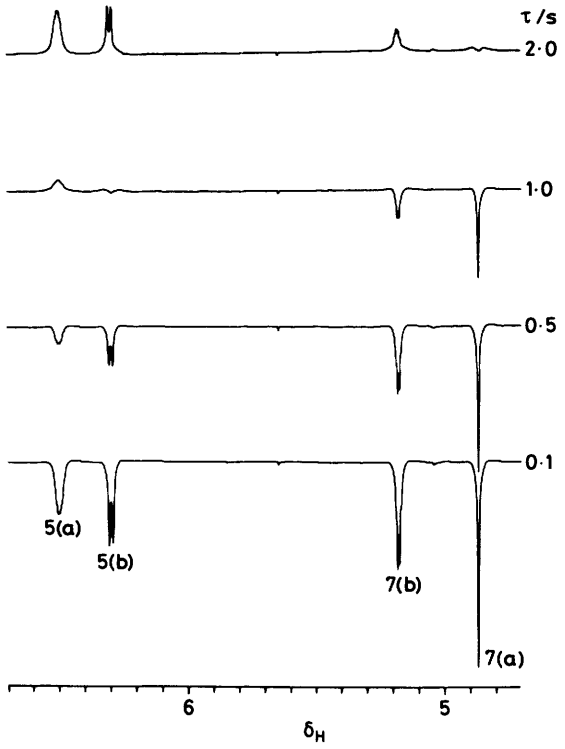


Figure 1. A series of expansions of four partially relaxed 250 MHz ^{1}H n.m.r. spectra of (4) in $(CD_3)_2SO$ from a non-selective inversion-recovery experiment

system was fairly rigid, although the C(1)O(2)C(3)C(4)C(5)O(8) ring could flip between boat and chair forms. The $^3J_{5,4}$ values for the rotamers were identical and it was therefore concluded that both had the same skeletal conformation to a first approximation. The ^{13}C NT_1 values (N = number of attached protons) of C-5, C-7 and C-4 of (**4a**) and (**4b**) were 0.49 and 0.53, 0.49 and 0.53, and 0.60 and 0.53 s, respectively. The errors in the methine and methylene NT_1 values were estimated to be written $\pm$0.03 and $\pm$0.06 s respectively. These NT_1 values showed that within experimental error there was no difference between the solution mobilities of the rotamers. A third factor considered was chemical exchange-induced spin–lattice relaxation or scalar relaxation of the first kind.[12,13] This effect would arise because interactions (such as scalar couplings) between the CF_3 groups and the skeletal protons become random functions of time in the presence of rotation around the amide bond. However, calculations showed that this effect was negligible, owing to the involvement of a large inverse term comprising of the difference in Larmor frequency between ^{19}F and ^{1}H nuclei. On the basis of the foregoing arguments it was concluded that any differences in relaxation behaviour between corresponding protons in the rotamers could not be due to scalar relaxation of the first kind, differences in skeletal conformation, or differences in solution mobilities, but would be due to differing spatially-mediated dipolar interactions with the CF_3 groups.

Figure 1 shows four partially relaxed ^{1}H n.m.r. spectra of (**4**) (from an inversion-recovery experiment) in the region of H-5 and H-7. It is clear that the relaxation of H-5(**a**) and H-7(**b**) is faster than that of H-5(**b**) and H-7(**a**), respectively. With a delay (τ) of 1.0 s the resonance of H-5(**b**) is approximately nulled[11] whereas that of H-5(**a**) is upright. An equivalent condition holds for H-7(**a**) (nulled) and H-7(**b**) (upright) with τ 2.0 s. All other resonances showed identical relaxation behaviour within rotameric pairs. The enhanced relaxation rates of H-5(**a**) and H(7(**b**)

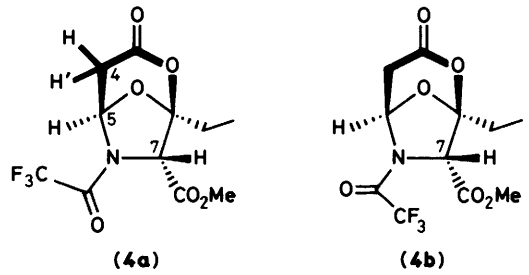


Figure 2. Structures of rotamers (**4a**) and (**4b**)

implied[14] close spatial approach of the CF_3 groups to H-5 in (**4a**) and to H-7 in (**4b**). This result immediately showed that (**4a**) and (**4b**) possessed the structures shown in Figure 2. Furthermore the result proved that in this system large values of the long-range heteronuclear couplings $^5J_{HF}$ and $^4J_{CF}$ are associated with a close spatial approach of the nuclei involved.

The relaxation enhancement at H-7(**b**) was less than that at H-5(**a**). This was ascribed to a closer approach of CF_3(**a**) to H-5(**a**) than of CF_3(**b**) to H-7(**b**). Dreiding models supported this conclusion and gave a value of *ca.* 1.2 for the ratio r_{av}[CF_3(**b**), H-7(**b**)]/r_{av}[CF_3(**a**),H-5(**a**)].

In rotamer (**4a**) but not (**4b**) H′-4 exhibited a six-bond coupling to the CF_3 group. At the τ time resolution (0.1 s) of the first T_1 experiments no difference was observed between the relaxation rates of H′-4 in (**4a**) and (**4b**). In order to determine whether or not H′-4 in (**4a**) suffered any relaxation enhancement, a second pair of inversion-recovery experiments was conducted with the τ values concentrated around the null-points of the H-4 and H′-4 resonances (Figure 3). The broadness of H′-4(**a**) ($^6J_{HF}$ *ca.* 0.8 Hz, unresolved) relative to H′-4(**b**) ($^6J_{HF}$ *ca.* 0 Hz) is marked. In analogy with the previous results H′-4 in (**4a**) relaxed faster (null *ca.* 0.25 s) than in (**4b**) (null *ca.* 0.27 s). This result assigned H′-4 as the proton on C-4 oriented towards the trifluoroacetyl moiety (Figure 2), since models showed that whatever the conformation of the six-membered lactone ring in (**4a**) H′-4 had a closest approach of $\leqslant$ 2 Å to a ^{19}F nucleus whereas H-4 had a closest approach of *ca.* 2.5 Å and *ca.* 2.9 Å in the lactone boat and chair conformations, respectively. The relaxation rate enhancement for H′-4 also showed that for $^6J_{HF}$ as well as $^5J_{HF}$ and $^4J_{FC}$ the large values of the couplings were associated with a close approach of the coupled nuclei. Surprisingly, H-4 appeared to relax faster in (**4a**) (null of high-field lines *ca.* 0.25 s) than in (**4b**) (null of high-field lines *ca.* 0.26 s), although no difference in $v_{\frac{1}{2}}$ was perceptible. However, although this relaxation enhancement was reproducible it was very small and close to or inside experimental error. Whilst the proton R_1 values were sensitive to the spatial proximity of the CF_3 groups, the ^{13}C NT_1 values (see earlier) showed no variation between rotamers. This was expected since the major contribution to the relaxation of C-4, -5, and -7 is dipolar relaxation from their directly attached protons. Little variation in ^{13}C relaxation behaviour would therefore be expected between the rotamers.

Finally, no attempt was made to determine whether the conformation of the six-membered lactone ring was boat-like or chair-like since a conclusive analysis of the $^3J_{54}$ proton couplings in this strained heterocyclic ring system was not possible.

^{1}H and ^{19}F N.m.r. Spectra of (**4**) *in Deuteriochloroform.*—The ^{1}H and ^{19}F spectra in $CDCl_3$ were different from those in $(CD_3)_2SO$, with a (**4a**):(**4b**) ratio of *ca.* 3:4. The ^{19}F chemical shifts of the CF_3 group in (**4a**) and (**4b**) were inverted, the ^{1}H shifts of H-5 in the rotamers were coincident, with the order of the shifts of H-4 from low field to high field being H′-4(**a**), H′-

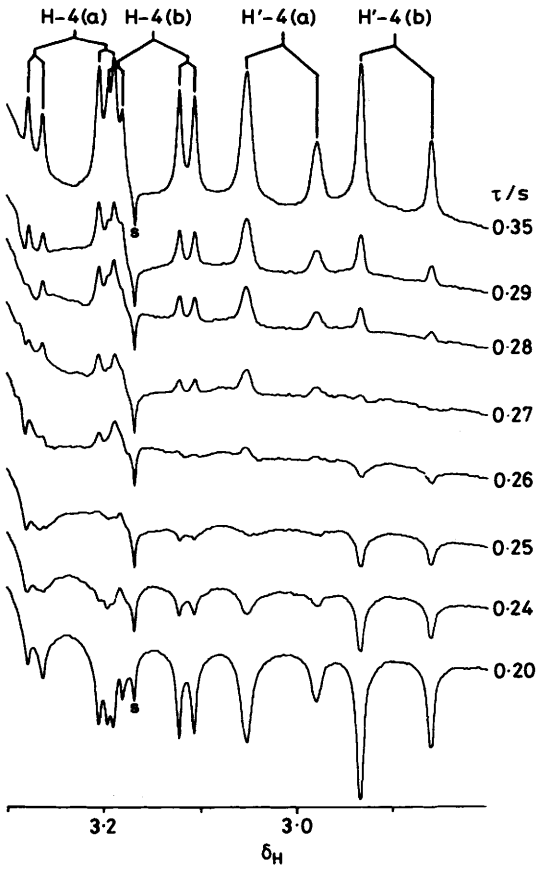


Figure 3. A series of expansions of eight partially relaxed 250 MHz ^{1}H n.m.r. spectra of (**4**) in $(CD_3)_2SO$ from a non-selective inversion-recovery experiment. The peak marked *S* is due to an impurity

4(**b**), H-4(**b**), and H-4(**a**). These changes illustrate the dangers of making resonance assignments in rotameric systems solely on the basis of chemical shifts,[7,9,15] and underline the power of the relaxation methods used here.

Conclusion

The ^{1}H, ^{19}F, and ^{13}C n.m.r. spectra of (**4**) in $(CD_3)_2SO$ are complicated by rotational isomerism around the amide bond. Each rotamer possesses a distinct pattern of long-range ^{1}H,^{19}F and ^{13}C,^{19}F coupling. Proton spin–lattice relaxation time experiments were used to assign the spectral resonances to the individual rotamers. It was clearly shown from the relaxation behaviour of the proton resonances that large values of the long-range couplings to ^{19}F were associated with a close approach of the ^{19}F nuclei. However these results did not give any insight into the actual mechanism of these four-, five-, and six-bond couplings. It is concluded that relaxation methods are a powerful tool in delineating the geometry of slowly interconverting molecules such as (**4a**) and (**4b**).

Experimental

Mass spectra were determined with a V.G. Micromass 70-70F instrument. Merck silica gel 60 was used for column chromatography, with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures as eluant. Solvents were removed by rotary evaporation under reduced pressure with the bath temperature below 30 °C.

Methyl (1S,5R,7R)-3-*Oxo*-6-*trifluoroacetyl*-1-*vinyl*-2,8-*dioxa*-6-*azabicyclo*[3.2.1]*octane*-7-*carboxylate* (**3**).—Methyl clavulanate[3] (4.0 g) was dissolved in dichloromethane (20 ml) and the solution stirred at −20 °C while trifluoroacetic acid (8 ml) was added dropwise over 10 min. The solution was allowed to warm to room temperature and the stirring continued for a further 2 h. The solution was evaporated and the residue triturated repeatedly with toluene. Chromatography of the residue gave the bicyclic *lactone* (**3**) as a colourless oil (2.0 g), $[\alpha]_D^{20}$ −5.5° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 780, 1 765, and 1 705 cm^{-1} (Found: C, 42.55; H, 3.3; N, 4.7%; M^+ 309.0464. $C_{11}H_{10}F_3NO_6$ requires C, 42.7; H, 3.3; N, 4.5%; M^+ 309.0467).

Methyl (1S,5R,7R)-1-*Ethyl*-3-*oxo*-6-*trifluoroacetyl*-2,8-*dioxa*-6-*azabicyclo*[3.2.1]*octane*-7-*carboxylate* (**4**).—The bicyclic lactone (**3**) (1.5 g) in dry tetrahydrofuran (30 ml) was shaken with 10% palladium–charcoal (300 mg) under hydrogen (1 atm) for 0.5 h. The catalyst was removed by filtration and was washed with tetrahydrofuran. The solvent was removed and the resulting oil chromatographed to give the *dihydro derivative* (**4**) as a colourless oil (1.4 g), $[\alpha]_D^{20}$ + 26.2° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 765 and 1 705 cm^{-1} (Found: C, 42.4; H, 4.0; N, 4.5%; M^+ 311.0622. $C_{11}H_{12}F_3NO_6$ requires C, 42.4; H, 3.9; N, 4.55%; M^+ 311.0616).

N.m.r. Studies.—All n.m.r. experiments were conducted in 5 mm probes.

250 MHz ^{1}H N.m.r. spectra were run with a Bruker WM 250 instrument [*ca.* 0.09M-solution in $(CD_3)_2SO$, with tetramethylsilane as reference]. Normally ^{1}H free induction decays (f.i.d.s) were acquired with a sweep width of 3 205 Hz into 16 K data points, but some spectra were run at higher digital resolution, as required. The ^{1}H spin–lattice relaxation time experiments were performed with a 180°–τ–90°–acquire (inversion recovery) pulse sequence,[13] with a delay between sequences of five times the longest T_1 involved. The values of τ were chosen in preliminary experiments and the 180° pulse (*ca.* 15 μs) was calibrated carefully before each experiment. The R_1 values were calculated by the 'null point' method.[11] A 2D *J*-resolved spectrum was run using a standard Bruker program. The sweep width in F_2 was 1 650 Hz and in F_1 25.8 Hz. F.i.d.s of 4 K points were acquired with 32 scans for each of 128 values of the evolution time. The raw data were zero-filled once and subjected to Gaussion multiplication (LB −0.3, GB 0.3) in each dimension, prior to double Fourier transformation. The experiment was repeated with F_1 doubled in order to avoid folding.

63 MHz ^{13}C N.m.r. spectra were acquired for a *ca.* 0.6M-solution in $(CD_3)_2SO$ and were referenced to the solvent at δ 39.6. F.i.d.s were acquired over 16 129 Hz into 16 K data points. 500—1 000 Scans were acquired prior to exponential multiplication (2 Hz) and Fourier transformation. The spin-echo ^{13}C spectrum was acquired with a standard Bruker microprogram and a refocusing time of 8 ms. The ^{13}C spin–lattice relaxation time experiment was performed with an inversion-recovery pulse sequence and a relaxation delay of 8.0 s. T_1 Values were calculated by use of a two- or three-parameter fitting to the exponential function within the Bruker DISNMR software.

188 MHz ^{19}F N.m.r. spectra and 200 MHz ^{1}H{^{19}F} spectra were acquired with a ^{1}H/^{19}F dual probe on a Bruker WP 200 instrument for a *ca.* 0.1M-solution in $(CD_3)_2SO$. The ^{19}F f.i.d.s were acquired with a sweep width of 636 Hz into 16 K data points. The spectra were referenced to $CFCl_3$ (δ_F 0).

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