the low-field signal decreases in proportion to the amount of added L-tryptophan and (2) the upfield signal sharpens, approaching the line width of free 5-fluoro-L-tryptophan (trace C).

The appearance of spectra such as trace B suggests the possibility of a simple two-site chemical exchange process in which free fluorotryptophan (5.84 ppm) undergoes exchange with protein-bound material (2.06 ppm) at an intermediate rate, leading to peaks which are somewhat broadened and shifted toward the weighted mean of the chemical shifts. Line-shape calculations show that to reproduce experimental spectra requires a rate constant for dissociation of the complex of $\sim 120\ \mathrm{s}^{-1}$. However, saturation of the resonance at 2.06 ppm does not produce any significant change in the intensity of resonance at ~5.84 ppm, a result which demands a dissociation rate constant at least two orders of magnitude smaller than that predicted on the assumptions of simple two-site exchange, when the experimental values for T_1 (~0.5 s) of the upfield peak are considered. Thus, the upfield resonance observed does not represent solely free fluorinated amino acid but must be broadened by other interactions of 5-fluorotryptophan with the protein.

Increasing the sample temperature caused the signal at low field to move upfield and to broaden to the extent that it became lost in the noise level. Concommitantly, the upfield signal shifted to lower field and became quite broad, reaching a maximum width at ~45°C and then sharpening somewhat as the temperature was raised beyond this. Experiments above 60 °C were not possible owing to denaturation of the protein and, at this temperature, fast-exchange averaging of the fluorine signals had still not taken place. Attempts to understand the change in line shape observed at the various temperatures in terms of the two-site exchange model indicated above were not successful, again suggesting that the situation is more complex than this in the system under study.

Our interpretations of these and related data are the following. 5-Fluoro-L-tryptophan appears to bind to the protein at, at least, two chemically distinguishable protein sites. One of these leads to a substantial downfield chemical shift effect (3.8 ppm), causes the amino acid to become highly immobilized, as reflected by the transverse relaxation rate, and interacts strongly enough with the small molecule that exchange of this species with bulk 5-fluoro-L-tryptophan is slow. A second class of interaction sites is recognized by an appreciable line-broadening effect on the fluorine resonance of the bound amino acid. There is very little protein-induced chemical-shift effect at these sites and exchange with bulk fluoroamino acid from them appears to be rapid. The competition experiments indicate that both sets of fluorotryptophan binding sites are also binding sites for L-tryptophan, although the exchange rates for the unfluorinated amino acid are not revealed by our data.

These initial results suggest that earlier interpretations of ^{1}H NMR studies of the tryptophan-albumin system[5-7] are likely incomplete and should be reformulated to take into account the possibility of several tryptophan binding sites with some exchange rates in the slow exchange limit.

Additional work to characterize the fluorotryptophan-human albumin system, including determination of the exchange rates, is underway in our laboratory.

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Reactions of Superoxide with Iron Porphyrins in Aprotic Solvents. A High Spin Ferric Porphyrin Peroxo Complex

Sir:

Dioxygen complexes of iron porphyrins are of interest because of their proposed involvement in a variety of biological processes. Only three types of synthetic iron porphyrin dioxygen complexes have been reported, each of which is prepared by reaction of ferrous porphyrins with O_2: $\mathrm{Fe(porph)L(O_2)}$,[1,2] an analogue of oxymyoglobin; $\mathrm{Fe(porph)O_2Fe(porph)}$,[3] a μ-peroxo bis ferric porphyrin complex; and a partially characterized adduct formed from $\mathrm{Fe^{II}(porph)}$ and O_2 in the solid state.[4] Our interest in reactions of superoxide anion, O_2^-, with metalloporphyrins led us to investigate its reactions with iron porphyrins.[5] We report here the results of our studies, which include the preparation and characterization in solution of a new type of iron porphyrin dioxygen complex which we formulate as a mononuclear peroxo complex of a high spin ferric porphyrin, i.e., $[\mathrm{Fe^{III}(porph)(O_2)}]^-$.

We initially investigated the reaction of KO_2 (solubilized by crown ethers[6]) with *ferric* porphyrins, $\mathrm{Fe^{III}(porph)Cl}$. We found that three different reaction pathways occurred under different conditions. Specifically, the product obtained depended on the nature of the solvent, the presence or absence of traces of water, the concentration, and the temperature. The simplest reaction that we observed was one-electron reduction, similar to that observed for the reaction of O_2^- with $\mathrm{Mn^{III}(TPP)^+}$ [7] or $\mathrm{Cu^{II}(phen)_2^{2+}}$:[6]

$$\mathrm{Fe^{III}(porph)^+} + O_2^- \rightarrow \mathrm{Fe^{II}(porph)} + O_2 \qquad (1)$$

Such a reaction was observed in $\mathrm{Me_2SO}$ or in $\mathrm{Me_2SO/py}$, $\mathrm{CH_3CN/py}$, or toluene/py (see Table I for exact conditions). In each of these cases, the $\mathrm{Fe^{II}(porph)}$ product is stabilized against reaction with O_2 by coordination of axial ligands, i.e., $\mathrm{Fe^{II}(TPP)(Me_2SO)_2}$ or $\mathrm{Fe^{II}(TPP)(py)_2}$. By contrast, in wet solvents or in relatively nonpolar solvents such as THF, toluene, or $\mathrm{CH_2Cl_2}$, with no added base, μ-oxo dimer formation was observed (unless the solution was extremely dilute, see Table I):

$$2\mathrm{Fe^{III}(porph)^+} + O_2^- \rightarrow\rightarrow [\mathrm{Fe^{III}(porph)}]_2\mathrm{O} \qquad (2)$$

If, on the other hand, O_2^- was reacted with $\mathrm{Fe^{III}(TPP)Cl}$ in DMF at −50 °C,[8] a third type of reaction was observed. The product visible spectrum (see Table I) most closely resembled that of $\mathrm{Fe(TPP)(py)(O_2)}$ as reported by Anderson et al.[9] with a small amount of μ-oxo dimer present as well. We conclude that reaction 3 occurred as previously reported by Hill et al.[10] for the reaction of O_2^- with $\mathrm{Fe^{III}(PPIXDME)(ClO_4)}$ under similar conditions.

$$\mathrm{Fe^{III}(porph)^+} + O_2^- \rightarrow \mathrm{Fe(porph)(O_2)} \qquad (3)$$

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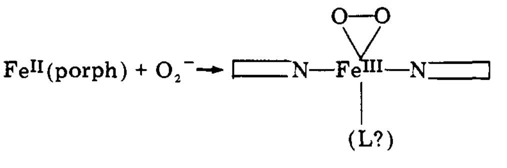
Table I. Reactions of Iron Porphyrins with Superoxide

starting porphyrin	conditions	product visible spectrum, λ_{max}, nm
A. Ferric Porphyrins plus Superoxide		
1. Reduction: $Fe^{III} + O_2^- \rightarrow Fe^{II} + O_2$		
Fe(TPP)Cl (0.5 mM)	O_2^- [a] (1 equiv), Me_2SO, rt	410 (sh), 427, 528, 568[b]
Fe(TPP)Cl (0.03 mM)	solid KO_2, py (3 mM), Me_2SO, rt	522, 567
Fe(TPP)Cl (0.1 mM)	O_2^- [c] (1 equiv), py (0.4 mM), CH_3CN, −40 °C	424, 527, 560
2. Addition: $Fe^{III} + O_2^- \rightarrow (FeO_2)^{2+}$		
Fe(TPP)Cl (0.1 mM)	O_2^- [c] (3 equiv), DMF, −50 °C	543, 568, 605 (sh)[d]
B. Ferrous Porphyrins plus Superoxide		
1. Oxidative Addition: $Fe^{II} + O_2^- \rightarrow Fe^{III}(O_2^{2-})$		
Fe(TPP) (0.01 mM)	O_2^-[a] (10 equiv), Me_2SO, rt	437, 547 (sh), 565, 597 (sh), 609
2. Reduction Followed by Oxidative Addition: $Fe^{III} + 2O_2^- \rightarrow Fe^{III}(O_2^{2-}) + O_2$		
Fe(TPP)Cl[e]	solid KO_2, Me_2SO, rt	437, 548 (sh), 565, 595 (sh), 609
Fe(TPP)Cl (0.5 mM)	O_2^- [a] (2 equiv), Me_2SO, rt	437, 546 (sh), 565, 595 (sh), 610
Fe(TPP)Cl (0.4 mM)	O_2^-[f] (10 equiv), CH_3CN, rt	432, 545 (sh), 563, 595 (sh), 606
Fe(TPP)Cl (0.1 mM)	O_2^- [c] (2.3 equiv), py (0.5 mM), CH_3CN, −40 °C	432, 547 (sh), 564, 591, 609
Fe(TPP)Cl (0.002 mM)	O_2^-,[f] toluene, rt	438, 547 (sh), 566, 610
Fe(OEP)Cl (2 mM suspension)	O_2^- [a] (4 equiv), Me_2SO, rt	423, 525 (sh), 545, 573, 583 (sh)
Fe(OEP)Cl	solid KO_2, Me_2SO, rt	423, 527 (sh), 545, 573, 584 (sh)

[a] KO_2/crown ether in Me_2SO. [b] Compare $Fe^{II}(TPP)(Me_2SO)_2$ prepared by dissolution of $Fe^{II}(TPP)$ in Me_2SO: λ_{max} 410 (sh), 426, 526, 565 (sh) nm. [c] KO_2/crown ether in Me_2SO, diluted 20-fold with toluene, and then added to the reaction solution by syringe. See ref 8. [d] Compare $Fe(TPP)(py)(O_2)$ in CH_2Cl_2, −78 °C, λ_{max} 547, 583 nm.[10] We believe our reaction mixture to contain a small amount of $[Fe(TPP)]_2O$ accounting for the relatively weak absorbance at 568 and 605 nm. [e] This reaction proceeds by reduction to $Fe(TPP)(Me_2SO)_2$ followed by reaction with another O_2^-. The Soret band at 427 nm due to $Fe(TPP)(Me_2SO)_2$ can be observed to appear and then disappear during the course of the reaction. [f] Solid KO_2 with 18-crown-6 added as a phase transfer catalyst.

In addition to the known species described above, we also observed the formation of a new species in some of our reactions of O_2^- with ferric porphyrins. It soon became clear that this species was the product of the reaction of O_2^- with *ferrous* porphyrins. We arrived at this conclusion after observing that addition of 1 equiv of O_2^- to $Fe^{III}(porph)^+$ in Me_2SO or CH_3CN resulted in one electron reduction to $Fe^{II}(porph)$ (reaction 1) and that addition of an additional equivalent of O_2^- caused the spectrum of the new species to appear.[5] Any attempt to isolate this new species led to formation of μ-oxo dimer as the solution was concentrated. We believe nonetheless that we have strong evidence for the identity of this species based on spectroscopic analysis of the solutions in which it is prepared. We formulate this species as a bidentate peroxo high spin ferric porphyrin complex (which may or may not have an axial ligand L) and propose that it is formed as described in reaction 4.



$$Fe^{II}(porph) + O_2^- \rightarrow \text{N}\!-\!\overset{O-O}{Fe^{III}}\!-\!\text{N}\ (L?) \qquad (4)$$

1, porph = TPP
2, porph = OEP

The visible absorption spectra of **1** and **2** are shown in Figure 1. The Soret and α,β bands are observed at unusually low energies relative to those of other iron porphyrin complexes.[11] The spectra showed little variation with solvent establishing that their formation did not require participation of a particular solvent.[13,14] The ESR spectra of **1** and **2** at 77 K[5] both showed relatively narrow, sharp resonances at $g \simeq 4.2$ and weak resonances at $g \simeq 2$ and 8 typical of rhombic high spin ferric complexes such as Fe^{III}EDTA or other simple ferric chelate complexes.[15] Such a spectrum is, however, not typical of high spin ferric porphyrin complexes, which usually show resonances at $g \simeq 2$ and 6, indicative of axial symmetry. Excess O_2^- added to solutions of **1** in Me_2SO–toluene produced ad-

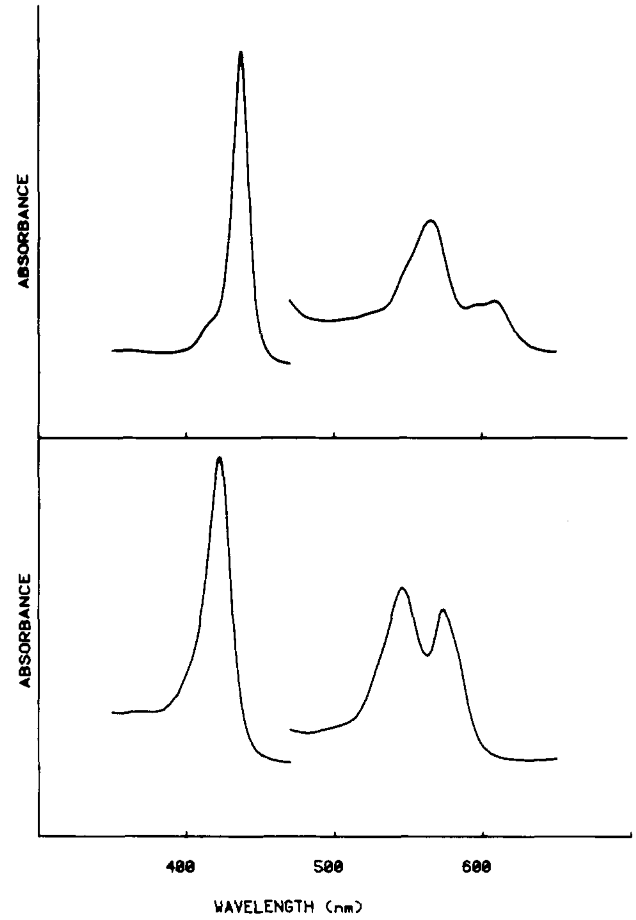


Figure 1. Visible absorption spectra of **1** (top spectrum) and **2** (bottom spectrum). Solutions were prepared by addition of 6–7 equiv of KO_2/18-crown-6 to either a 0.71 mM solution of Fe(TPP)Cl or a 1.2 mM suspension of Fe(OEP)Cl in Me_2SO. The relative absorbances are, for **1**, 23:1.0:0.42 at 437, 565, and 610 nm, respectively, and, for **2**, 12:1.0:0.89 at 423, 545, and 573 nm, respectively.

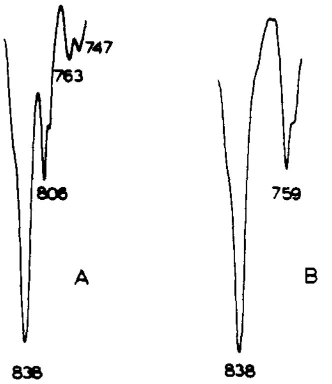


Figure 2. Infrared spectra of solutions of **2** prepared using (A) $K^{16}O_2$ and (B) $K^{18}O_2$. Peak positions are labeled in reciprocal centimeters. Solutions were prepared by addition of 7 mg of Fe(OEP)Cl in 0.8 ml Me_2SO to 0.65 mL of either a 0.11 M $K^{16}O_2$/0.25 M 18-crown-6 solution or a 0.086 M $K^{18}O_2$/0.25 M 18-crown-6 solution in Me_2SO. Spectra were obtained on a Perkin-Elmer 283 IR spectrophotometer at 1.5-cm^{-1} resolution. Spectra were averaged 16 times from 870 to 731 cm^{-1} at a scan rate of 50 cm^{-1}/min using the standard software of the Perkin-Elmer IR Data Station. Demountable cells fitted with NaCl windows and 0.5-mm Teflon spacers were used. The reference cell contained Me_2SO. The peaks at 836 and 763 are due to 18-crown-6. It was noted that some NaCl dissolved during the course of the experiment.

ditional ESR signals due to free superoxide ($g \simeq 2.11, 2.00$), but no other changes were observed. The rhombic character of the ESR spectra suggested to us that **1** and **2** might be peroxide complexes of high spin ferric porphyrins with the peroxide bound in a bidentate fashion,[16] lowering the effective symmetry of the Fe^{III}. A rhombic ESR spectrum has also been observed for $Mn^{IV}TPP(O_2)$ which is likewise believed to contain bidentate peroxide.[17]

The hypothesis that **1** and **2** were peroxide complexes of Fe^{III} was attractive because a similar oxidative addition of O_2^- to Fe^{II} to give an Fe^{III} peroxide product had previously been observed for Fe^{II}EDTA in aqueous solution,[18] but definitive identification of **1** and **2** as complexes containing dioxygen ligands required evidence that the O_2 moiety was contained in the final product. This was provided by infrared spectroscopy. As shown in Figure 2, an infrared band at 806 cm^{-1} shifts to 759 cm^{-1} when $K^{18}O_2$[19] rather than $K^{16}O_2$ was used to prepare solutions of **2**. This band falls near the low end, but within the range of known O-O vibrations due to metal-bound peroxide ligands,[20,21] and the $^{18}O/^{16}O$ frequency ratio, 0.942, is exactly that expected ($\sqrt{16/18}$) for an isolated O-O stretch. A shoulder at 796 cm^{-1} shifts by the same amount, suggesting two slightly different populations of O-O bonds. This might reflect a degree of ion pairing of the bound O_2^{2-} to the crown-ether-complexed K^+. We also searched for the O-O stretch by resonance Raman spectroscopy, since laser excitation into the $O_2^{2-} \rightarrow Fe^{3+}$ charge-transfer band (~525 nm) of the peroxo adduct of Fe^{III}EDTA enhances O-O bands at 825 and 878 cm^{-1}.[22] Problems with laser-induced decomposition were encountered, but overcome by cooling the samples to 170 K. With 528.7-nm excitation, a weak band at 780 cm^{-1} was observed to shift to 731 cm^{-1} upon $K^{18}O_2$ substitution. The 25-cm^{-1} lowering relative to the infrared frequencies may be an environmental effect associated with the frozen solutions.

The intense high frequency porphyrin Raman bands could be obtained at 20 °C in $(CD_3)_2SO$ in sealed glass tubes. The oxidation state marker, band I,[23] was observed at 1370 cm^{-1}, as expected for Fe^{III}. The spin-state markers,[23] bands II (1487 cm^{-1}), IV (1560 cm^{-1}), and V (1617 cm^{-1}) are in the range observed[23,24] for high spin Fe^{III}. They are between the values observed for five-coordinate (1495, 1572, 1632 cm^{-1}) and symmetrically six-coordinate (1475, 1560, 1610 cm^{-1}) high spin Fe^{III} hemes.[24] This suggests that the porphyrin core is somewhat expanded,[24] via interaction of crown ether or of solvent Me_2SO with Fe^{III}, on the side opposite the bound peroxide.

The IR and ESR evidence support our formulation of **1** and **2** as peroxide complexes of high spin ferric porphyrins.[25] It should be emphasized here that these complexes are not at the same oxidation level as oxy heme species such as oxymyoglobin or $Fe(porph)(L)(O_2)$.[2] These new iron porphyrin dioxygen complexes are in fact one electron reduced from that level. They are therefore of interest as potential analogues of intermediates in the catalytic cycles of hemoproteins such as cytochrome P-450 and cytochrome oxidase where dioxygen bound to heme is reduced. We are therefore particularly interested in the reaction chemistry of **1** and **2**. In our initial experiments, we found that **1** reacted in Me_2SO with py to give $Fe^{II}(TPP)(py)_2$, with SO_2 to give $Fe^{II}(TPP)(Me_2SO)_2$, and with CO to give $Fe^{II}(TPP)(CO)(Me_2SO)$. The stoichiometries and mechanisms of these reactions are as yet unknown but will be the subject of our future studies.

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References and Notes

(1) Abbreviations used in this paper follow: PPIXDME, protoporphinato-IX-dimethyl ester; TPP, *meso*-tetraphenylporphinato; OEP, octaethylporphinato; DMF, dimethylformamide; THF, tetrahydrofuran; phen, 1,10-phenanthroline; ESR, electron spin resonance; py, pyridine; rt, room temperature; sh, shoulder.

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(25) Visible and ESR spectra identical with those that we observe for **1** and **2** have been seen for the reaction product of $Fe^{I}(TPP)^-$ or $Fe^{I}(OEP)^-$ and O_2 lending support to our formulation of **1** and **2** as dioxygen complexes: C. A. Reed, private communication; D. Dolphin, private communication.

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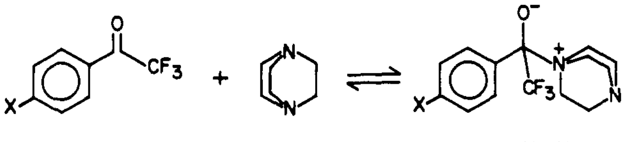
Zwitterionic Adducts between a Strongly Electrophilic Ketone and Tertiary Amines

Sir:

We report evidence for the existence of zwitterionic adducts, e.g. **3**, between electrophilic ketones, such as α,α,α-trifluoroacetophenone (**1**), and tertiary amines, such as 1,4-diazabicyclo[2.2.2]octane (Dabco, **2**). This report complements the observation of adducts between ketones and strong electrophiles such as boron trifluoride,[1] which have weak boron-oxygen bonds.



1 a,X = H
b,X = F

2

3 a,X = H
b,X = F

The interactions between carbonyl compounds and nucleophilic reagents such as amines are well documented both in the ground state[2] and in the excited state.[3] The excited-state reactions are dominated by electron transfer and hydrogen abstraction, whereas the ground-state interactions, with few exceptions,[4] involve addition. Primary and secondary amines add to the carbonyl double bond giving rise to hemiaminals which may lose water to form imines or enamines or react with a second molecule of amine to form the more stable aminals. Zwitterions may be short-lived intermediates in these reactions.[5] Ground-state interactions between carbonyl groups and tertiary amine moieties have been inferred from weakened carbonyl stretching frequencies[6] and from transannular N···C=O distances in medium-sized ring compounds.[7] Interactions between ketones and amines, whether of the charge-transfer type or due to nucleophilic approach of the amine, are expected to be particularly strong for ketones whose electron affinity (and electrophilic nature) is enhanced by electron-withdrawing substituents. This prediction is confirmed by the spectroscopic data observed in solutions containing trifluoroacetophenone and tertiary amines.

The addition of tertiary amines to acetonitrile solutions containing trifluoroacetophenone or its derivatives results in characteristic changes in the IR, UV, and NMR spectra. For example, addition of a fivefold excess of Dabco causes the complete disappearance of the carbonyl stretching band at 1791 cm^{-1}. Similarly, the UV absorption bands at 255 and 290 nm decrease with increasing Dabco concentration. Even more significant changes are observed in the NMR spectra: the reaction of Dabco with *p*-fluorotrifluoroacetophenone results in the observation of a new ^{19}F signal, nearly 9 ppm upfield of the CF_3 signal of the ketone, and in a new set of ^{13}C resonances as well. The most dramatic ^{13}C shift is observed for the quartet representing the carbon bonded to oxygen: this resonance is shifted upfield by ~105 ppm. Substantial downfield shifts are observed for the trifluoromethyl and for the ipso carbons, ~8 and ~7 ppm, respectively, whereas the remaining aromatic carbons show minor upfield shifts (Figure 1, Table I).

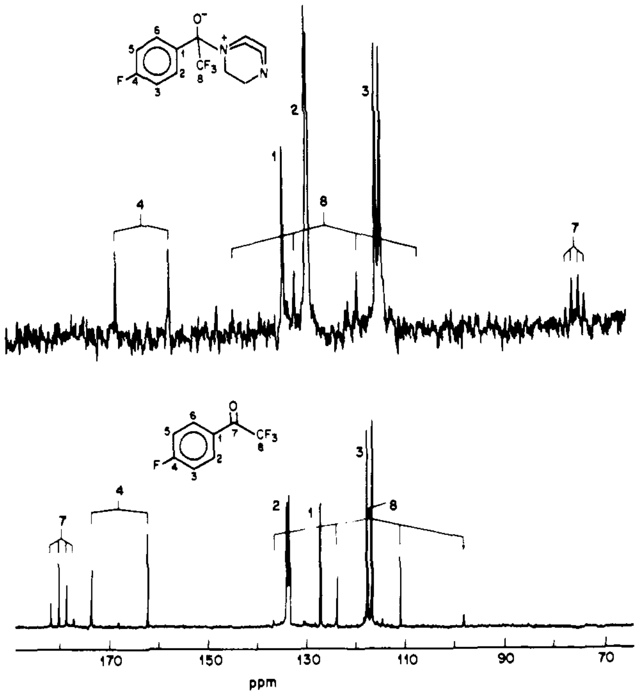


Figure 1. Proton decoupled ^{13}C NMR spectrum of 1.0 M *p*-fluoro-α,α,α-trifluoroacetophenone in acetone-d_6 (bottom) and of its Dabco adduct recorded in an acetone-d_6 solution containing 0.2 M *p*-fluorotrifluoroacetophenone and 1.0 M Dabco (top).

These results document significant changes in the vicinity of the carbonyl carbon, whereas only minor changes are indicated for the para and meta positions of the benzene ring. Accordingly, we propose that the new species is formed by nucleophilic attack of the amine on the carbonyl group and that it is zwitterionic in nature. The ^{13}C NMR chemical shift is a particularly sensitive tool to monitor such a change. For example, the transannular interaction of a tertiary amino group with a carbonyl function in a ten-membered ring, where the N···C distance lies between 2.56 and 2.58 Å,[8] results in an upfield shift of the carbonyl resonance (by 11 ppm)[9] and in a

Table I. ^{19}F and ^{13}C Chemical Shifts[a] and Coupling Constants[b] of *p*-Fluorotrifluoroacetophenone and Selected Adducts

	p-F-TFA	DABCO Adduct	Hydrote	Methonolote
$C^{19}F_3$ (s)[c]	+5,9	-2.7	-6,4	-5.8
$^{13}CF_3$ (o)[c]	117.8 (291)	126.3 (285)	126.1 ( )	124.2 (287)
C-O (o)	180.3 (35)	75.8 (28)	93.9 (31)	97.5 (32)
ipso-C (d)[c]	127.6 (3)	135.0 (3)	135.4 (3)	132.1 (3)
ortho-C (d)	134.2 (9)	130.0 (9)	130.7 (9)	131.4 (9)
meto-C (d)	117.6 (22)	115.6 (22)	115.4 (22)	115.9 (22)
poro-C (d)	168.2 (257)	163.7 (246)	164.2 (243)	164.7 (247)

[a] In parts per million relative to trifluoroacetic acid and to Me_4Si, respectively; downfield shifts are denoted as positive. [b] In hertz in parentheses. [c] s = singlet; q = quartet; d = doublet.

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