Synthesis and complexation to ruthenium(II) and iron(III) *meso*-tetraphenylporphyrins of two new fluorinated alkyl isocyanides: 2-monofluoroethyl isocyanide and 2,2,2-trifluoroethyl isocyanide

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Abstract

New 2-monofluoroethyl isocyanide and 2,2,2-trifluoroethyl isocyanide ligands have been complexed to TPPRu(II) and TPPFe(III)OSO_2CF_3 in order to provide information on the fluorine effect on alkyl isocyanide binding. The comparison of IR and NMR data indicates a great similarity between the bonding properties of the fluorinated isocyanide and alkyl isocyanide ligands.

Introduction

Substrates chemically modified with fluorine or perfluoroalkyl groups are useful probes for clarifying the interaction between substrates and enzymes by use of ^{19}F NMR spectroscopy [1]. Fluorine signals are nearly as easy to detect as proton resonances and a wider range of chemical shift effects is possible than is observed in proton NMR. As part of a programme concerned with systematic examination of new probes of haemoproteins [2, 3], we report here the synthesis of two new fluorinated isocyanides: 2-monofluoroethyl isocyanide and 2,2,2-trifluoroethyl isocyanide, and their complexation to *meso*-tetraphenylporphyrin Ru(II) [4] and to *meso*-tetraphenylporphyrin Fe(III) trifluoromethanesulfonate [5]. The spectral properties of these complexes are discussed in comparison with those of free ligands and alkyl isocyanide adducts.

Experimental

IR spectra were recorded on a Nicolet 205 FT infrared spectrometer. The ^1H NMR spectra were recorded in a pulse Fourier transform mode with a Brucker AC 300 P spectrometer. Tetramethylsilane and trichlorofluoromethane were used as references. Monofluoroethylamine hydrochloride and trifluoroethylamine are commercially available (Aldrich).

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The *N*-fluoroalkyl substituted formamides, which are the starting materials for the isonitriles, are prepared from the corresponding primary amines [6]. 2,2,2-Trifluoroethylformamide is obtained from 2,2,2-trifluoroethylamine (0.05 mol) by refluxing in formic acid (8 cm^3, 4 equiv.) and toluene (20 ml) for 1 h. The crude reaction product was distilled *in vacuo*: b.p. 90 °C (10 mm); yield 93% of a colorless liquid. 2-Monofluoroethylformamide was prepared from 2-fluoroethylamine hydrochloride as described for 2,2,2-trifluoroethylamide except that 4 g of sodium formate were also added in the reaction. After filtration, the solvents were evaporated and the crude product (90% yield) was used directly for the synthesis of the isocyanide. The 2-monofluoroethyl isocyanide was classically prepared using diphosgene as dehydrating agent [7, 8]. The product distilled rapidly (35 °C/15 mm) and was collected in a receiver cooled by liquid nitrogen (yield 18%). A different way of dehydrating has been also tested using a combination of phosphorus oxychloride/tri-n-butylamine. $POCl_3$ (23 mmol) was added dropwise in a 30-min period to a stirred solution of 5 g (39 mmol) of 2,2,2-trifluoroethylformamide in 22 ml of tri-n-butylamine and 10 ml of 1,2 dichlorobenzene at 0 °C. The oily isocyanide is then collected at 40 °C/15 mm in a receiver cooled by liquid nitrogen (yield 51%). ^1H and ^{19}F NMR results are summarized in Table 1.

Ruthenium(II) carbonyl *meso*-tetraphenylporphyrin, RuTPP(CO) was prepared as previously described [4]. Addition of an excess of CF_3CH_2NC (4 equiv.) in $CHCl_3$ (25 cm^3) to 100 mg of RuTPP(CO) (0.12 mmol) at 25

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TABLE 1. Chemical shifts[a] $\delta(^1H)$, $\delta(^{19}F)$ in ppm and selected IR data[b] for fluorinated formamides and isocyanides

	FCH_2CH_2NHCHO	CF_3CH_2NHCHO	FCH_2CH_2NC	CF_3CH_2NC
^1H	4.5(FCH_2) ($^2J(HF)=45.6$ Hz) 3.6(CH_2) ($^3J(HF)=28.8$ Hz) ($^3J(HH)=4.7$ Hz) 6.57(NH) 8.2(*Z*-CHO) 8.0(*E*-CHO) ($^3J(HH)=12$ Hz)	3.9(CH_2) ($^3J(HF)=9$ Hz) 6.68(NH) 8.24(*Z*-CHO) 8.06(*E*-CHO) ($^3J(HH)=11.7$ Hz)	4.48(FCH_2) ($^2J(HF)=44.6$ Hz) 3.7(CH_2) ($^3J(HF)=23.4$ Hz) ($^3J(HH)=2.5$ Hz)	4.02(2.5)[c](CH_2) ($^3J(HF)=7.7$ Hz)
^{19}F	−224.8	−78.5	−223	−72.6
IR (cm^{-1})	1689	1704	2158	2163

[a]Solvent: $CDCl_3$. [b]Solvent: $CHCl_3$. [c]Solvent: C_6D_6.

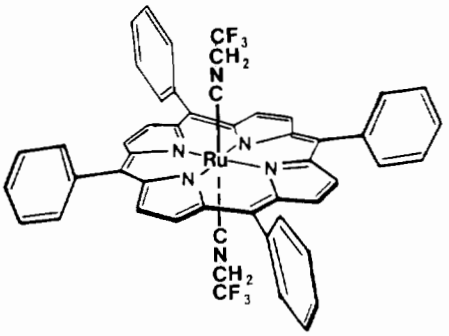

Fig. 1. The structure of 2,2,2-trifluoromethyl isocyanide adduct of Ru(II)TPP.

°C under nitrogen results in rapid formation of $RuTPP(CNCH_2CF_3)_2$, readily identified by its IR spectrum in solution ($\nu(CN)=2127\ cm^{-1}$). After purification on silica gel column (eluent: $CHCl_3$/hexane: 75/25), the yield of this bis-adduct is 72%. The absorption spectrum of $RuTPP(CNCH_2CF_3)_2$ exhibits λ_{max} at 416 nm ($\epsilon=2.9\times10^5\ M^{-1}$) and 536 nm ($\epsilon=0.17\times10^5$) in $CHCl_3$. The preparation of $RuTPP(CNCH_2CH_2F)_2$ is achieved similarly using $CNCH_2CH_2F$ instead of $CNCH_2CF_3$ (yield 70%). The absorption spectrum exhibits λ_{max} at 418 nm ($\epsilon=2.6\times10^5\ M^{-1}$) and 530 nm ($\epsilon=0.13\times10^5$) in $CHCl_3$.

$FeTPP(CNCH_2CF_3)_2(OSO_2CF_3)$ was prepared in toluene solution under nitrogen, from $FeTPP(OSO_2CF_3)$ [5] and eight equivalents of the isocyanide. This bis-adduct is precipitated by addition of hexane (yield 79%) and is readily identified by its IR spectrum ($\nu(CN)=2218\ cm^{-1}$, KBr). The electronic spectrum of $FeTPP(CNCH_2CF_3)_2(OSO_2CF_3)$ exhibits λ_{max} at 418, 509 and 573 nm in toluene.

Results and discussion

^1H and ^{19}F NMR results for the amides and for the free isocyanides are summarized in Table 1. The possibility of *E* and *Z* isomers, which have been well investigated for formamides, must be first considered. A comparison of the NMR data in Table 1 with those of *N*-ethyl formamide [9] shows that the *N*-fluoroalkyl substituted formamides exist primarily in the *Z* form. It will be noted that the *E* formamides exhibit a coupling $^3J(HH)$ of 12 Hz which was not observed for the main isomer. The percentages of the *Z* isomer in the formamides, as determined from the relative peak areas of the formyl protons, are 81% for 2-monofluoroethylformamide and 90% for 2,2,2-trifluoroethylformamide.

Dehydration of *N*-alkylformamides represents the method of choice for the preparation of isocyanides [6]. Among the dehydrating agents, application of phosphorus oxychloride in the presence of tri-n-butylamine was found particularly effective in order to prepare 2,2,2-trifluoroethyl isocyanide (yield 51%). Application of diphosgene in the synthesis of the isocyanides was also investigated during the course of this study [8]. For instance, the 2-fluoroethyl isocyanide was obtained only with 18% yield. Attempts to improve the yield of this isocyanide by performing the $POCl_3$ reaction were unsuccessful. Indeed heating must be avoided during the reaction; furthermore the product becomes unstable at the beginning of the distillation as if traces of impurities catalyze the polymerization of the isonitrile.

Determination of the isocyanide stretching frequencies in haeme isocyanides provides an opportunity to demonstrate clearly the sensitivity of ligand binding to the electronic properties of the second axial ligand and the porphyrin. For example, the data in Tables 1, 2 and 3 suggest that the observed isocyanide stretching frequencies upon complexation are influenced by the electronic nature of the fluorine atom on the isocyanide ligand. As expected, the $\nu(CN)$ stretching frequency of CF_3CH_2NC is lowered upon coordination of the isocyanide to RuTPP, decreasing from 2163 cm^{-1} for the free ligand to 2127 cm^{-1} in $RuTPP(CNCH_2CF_3)_2$ ($\Delta\nu=36\ cm^{-1}$) while the $CNCH_2CH_3$ frequency shows

TABLE 2. Chemical shifts[a] $\delta(^1H)$, $\delta(^{19}F)$ in ppm and selected IR data[b] for ferrous isocyanide complexes

	RuTPP($CNCH_2CH_2F$)$_2$	RuTPP($CNCH_2CF_3$)$_2$	Ru(*p*-CF_3TPP)[$CNC(CH_3)_3$]$_2$[c]
^1H	8.39(pyr), 8.08(*ortho*) 7.65(*meta* + *para*) 2.66(CH_2F) (^2J(HF) = 46.6 Hz, (^3J(HH) = 4.9 Hz) 1.52(CH_2) (^3J(HF) = 23.2 Hz)	8.45(pyr), 8.05 (*ortho*) 7.73(*meta*), 7.62(*para*) 1.75(CH_2) (^3J(HF) = 7.5 Hz)	8.34(pyr), 8.25 (*ortho*) 7.94(*meta*) −0.48(CH_3)
^{19}F	−224.2	−74.8	
IR (cm^{-1})	2133	2127	2140

[a]Solvent $CDCl_3$. [b]Solvent $CHCl_3$. [c]From ref. 10.

TABLE 3. Chemical shifts $\delta(^1H)$, $\delta(^{19}F)$ in ppm and selected IR data for ferric isocyanide complexes

	FeTPP($CNCH_2CF_3$)$_2$$OSO_2CF_3$[a]	FeTPP[$CNC(CH_3)_3$]$_2ClO_4$[b]
^1H	15.8(*meta*), 10.7(pyr), 1.2(*para*) −1.57(*ortho*), −6.3(CH_2) (^3J(HF) = 7.8 Hz)	13.75(*meta*), 9.73(pyr) 3.21(*para*), 0.96(*ortho*) −1.87(t-Bu)
^{19}F	−72.9(−79.5, OSO_2CF_3)	
IR (Cm^{-1})	2218 (KBr)	2220

[a]Solvent C_6D_6. [b]Solvent CD_2Cl_2, from ref. 11.

only a small shift upon complexation to form RuTPP($CNCH_2CH_3$)$_2$ ($\Delta\nu$ = 16 cm^{-1}) [10]. This is consistent with a greater π-acceptor ability of the fluorinated isocyanide ligand compared with that of the ethyl isocyanide ligand and with a concomitant increase in back-π-bonding from ruthenium to the CN bond. On the contrary, the ν(CN) stretching frequency of CNR is increased upon coordination of the fluorinated isocyanide to iron(III) porphyrin (see below), increasing from 2163 cm^{-1} for the free ligand to 2218 cm^{-1} in FeTPP($CNCH_2CF_3$)$_2$(OSO_2CF_3). This increase of the frequency which indicates a higher bond order in the complex than in the free ligand, is consistent with a positive formal charge on the iron [11].

The ^1H NMR spectrum of RuTPP($CNCH_2CH_2F$)$_2$ displays two groups of signals corresponding to the porphyrin ring protons [(8.39 (pyr), 8.08 (*o*-Ph) and 7.65 ppm (Ph, *meta* and *para* hydrogens)] and the ligand (2.66 (CH_2F) and 1.52 ppm (CH_2)), respectively. The chemical shifts of the former are very similar to those of FeTPP(py)$_2$ [12] and are expected for diamagnetic complexes. The proton resonances of CH_2 groups are markedly upfield by the shielding effect of the porphyrin ring.

As a ligand of the heme iron of bacterial cytochrome P-450, ethyl isocyanide binds more tightly to the ferrous state than the ferric state [13]. However we recently reported the preparation of new low-spin ferric isocyanide complexes of tetraphenylporphyrin [11]. In order to examine the chemical shift dependence of ^{19}F through the paramagnetic effect, FeTPP($CNCH_2CF_3$)$_2$(OSO_2CF_3) was also prepared. The ^1H NMR spectrum displays two groups of signals corresponding to the porphyrin ring protons (15.8 (Ph *m*-H), 10.7 (pyr. H), 1.2 (Ph *p*-H) and −1.6 (Ph *o*-H) ppm) and to the ligand (−6.3 ppm). The chemical shifts of the porphyrin ring protons are very similar to those previously reported with non-fluorinated alkyl isocyanides [11]. These complexes have been described as complexes of low spin Fe(III) on the basis of proton measurements. The hyperfine shifts were separated into their dipolar and contact contributions. A negligible dipolar shift and a small contact shift for pyrrole protons account for the unusual downfield shifts [11]. The alternative formulation of Fe(II) porphyrin cation radical may also be suggested. The existence of such a compound has been previously reported with tetrabenzoporphyrin which has a very low oxidation potential [14]. However, in this latter case the absorption spectrum is typical of porphyrin oxidation [15]. The absorption spectrum of FeTPP($CNCH_2CF_3$)$_2$(OSO_2CF_3) closely resembles that of the low-spin state Fe(III) (S = 1/2) and is completely different from the absorption spectra of porphyrin cation radicals. Furthermore the 55 cm^{-1} IR shift occurring upon ligand complexation is probably due to a positive charge on the metal. Hence, all available evidence indicates a low-spin Fe(III) state.

In contrast with the CH_2 proton resonance of the ligand which showed a large upfield shift ($\Delta\delta$ = 8.8 ppm), the fluorine chemical shift of the paramagnetic

complex ($\delta = -72.9$ ppm) showed a small isotropic shift relative to that of the diamagnetic ruthenium complex ($\Delta\delta = 1.9$ ppm). In the case of the paramagnetic complex, the dipolar and the contact contributions must be taken into account; these may have opposite signs or/and a small magnitude which would explain the small change in isotropic shift. It is important to note that the dipolar contribution of the phenyl proton shifts of $FeTPP[CNC(CH)_3]_2ClO_4$ was found to be negligible [11]. ^{19}F NMR studies of paramagnetic Fe(III) porphyrins substituted with CF_3 groups also showed small isotropic shifts relative to that of Zn(II) diamagnetic porphyrins [16]. Interactions between the amino acid residues and haeme in haemoproteins, which may have an effect on the ^{19}F chemical shift, are currently being explored.

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