Synthesis and reactions of the first fluoroalkylated Ni(II) N-confused porphyrins†

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The first fluoroalkylated Ni(II) N-confused porphyrins were synthesized with high regioselectivity and its further alkylation was studied.

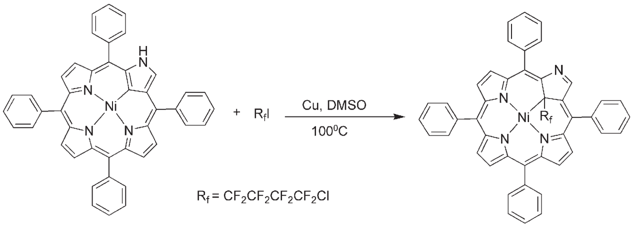
The chemistry of N-confused porphyrins (NCPs) has attracted the attention of many chemists since the first synthesis was reported independently by Furuta and by Latos-Grażyński in 1994.[1] NCPs have a number of applications in the area of supermolecular self-assembly and coordination chemistry, because of their versatile coordination modes and ability to stabilize some rare high oxidation states of metal ions.[2] The biologically relevant metal chemistry of N-confused porphyrins has been explored with the aim of generating heme-model complexes.[3] Further applications of NCPs in catalytic reactions revealed that they can outperform porphyrins and corroles in some circumstances.[4] Considerable efforts have been made to modify the structures of NCPs by, for example, halogenation,[5] nitration,[5] cyanation,[6] oxygenation,[7] internal fusion,[5,8] Diels–Alder reaction,[9] and N-alkylation.[10] These modifications have led to a much deeper understanding of the reactivities of NCPs and of their differences from other porphyrin analogues.

The introduction of fluorine or fluoroalkyl groups into the porphyrin macrocycle has profound effects on its physical and chemical properties.[11,12] In this context, we have developed several efficient methods for synthesizing fluorinated porphyrins, using, for example, a sulfinatodehalogenation reaction,[13] or copper- or palladium-catalyzed fluoroalkylation.[14,15] These direct fluoroalkylation methods have proved to be important for the preparation of certain fluoroalkylated porphyrins which are very difficult to obtain by the condensation of fluoroalkyl pyrroles and/or fluoroalkyl aldehydes.

We have synthesized a variety of fluoroalkylated porphyrins and studied their properties.[16,17] After the introduction of four trifluoromethyl groups into meso-tetraphenylporphyrin, we successfully isolated and thoroughly characterized the challenging 20 π-electron nonaromatic isophlorin which was referred to for the first time by Woodward during the synthesis of chlorophyll about half a century ago.[18] Considering their unique structure and properties, we have extended this direct fluoroalkylation method to NCPs. Herein, we report the first fluoroalkylation of Ni(II) NCPs and their subsequent reactions.

Treatment of the Ni(II) N-confused tetraphenylporphyrin (**Ni1**) with $I(CF_2)_4Cl$ in the presence of copper powder in DMSO at 100 °C for 40–60 min gave, after filtration, extraction and flash chromatography, a purple compound. The intense absorption at 435 nm (Soret band) and the weak absorptions at 567, 610 and 781 nm (Q band) observed in the UV/Vis spectrum indicated that the porphyrin-like skeleton had been preserved. Furthermore, the ^{19}F NMR and MS results showed that the fluoroalkyl group had successfully been introduced into the Ni(II) NCP. The AB pattern signals appearing at δ −93.69 and −96.07 ppm (J_{AB} = 269.8 Hz) in the ^{19}F NMR spectrum suggested that the fluoroalkyl group was attached to a chiral center. The chemical shift of C(3)H at δ 9.78 ppm and of the six β-pyrrole protons at δ 8.40–8.65 ppm was in good agreement with the 21-C substituted Ni(II) NCPs (see ESI†),[6,19] which implied that the fluoroalkyl group had been introduced at the inner carbon of compound **Ni1** (Scheme 1).

The structure of **Ni1b** was confirmed by single crystal X-ray diffraction analysis.‡ The results showed that the fluoroalkyl group was attached to the inner 21-carbon rather than to one of the peripheral carbon atoms (Fig. 1). This is in contrast to the alkylation of **Ni1**, which gave low yields of a mixture of inner 21-carbon and inverted 2-nitrogen alkylated products.[19,20] Good selectivity and yield can be achieved in the fluoroalkylation of the Ni(II) NCP **Ni1**. The C(21)-Ni distance (2.033(7) Å) in **Ni1b** is slightly longer than those (2.005(6), 2.019(4), 2.018(3) Å) observed in the inner C-substituted Ni(II) NCPs.[6,19] However, taking the deviation into account, it still doesn't exceed the upper limit of C–Ni bond length (2.02(2) Å).[21] So there is a σ-bond between C(21) and Ni atom, suggesting that the C(21) adopts an sp^3 hybridization.



Ni1 **Ni1b**

Scheme 1 Synthesis of inner 21-C fluoroalkylated NCP (**Ni1b**).

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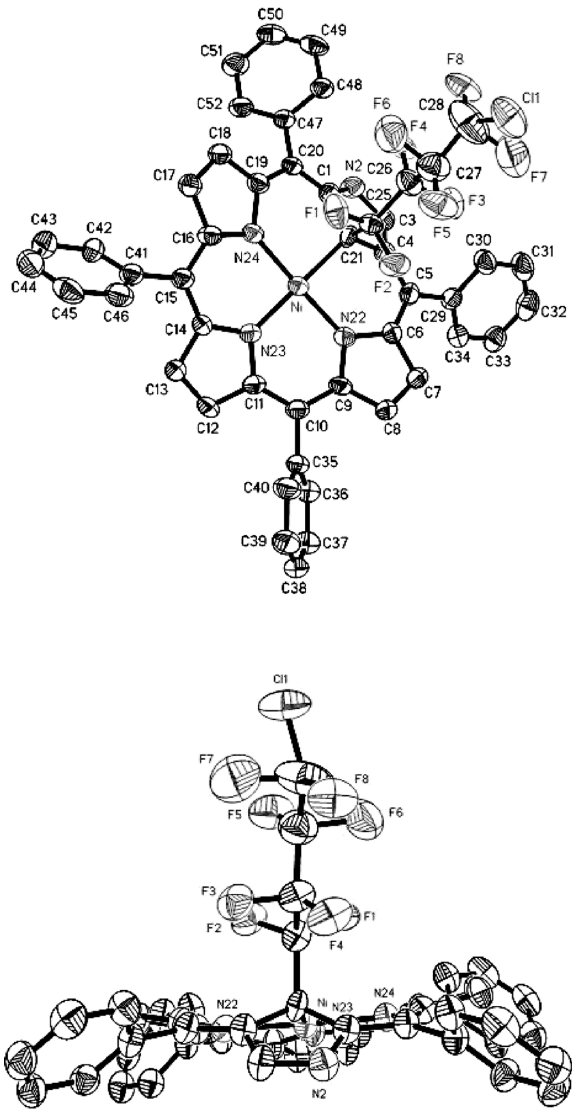


Fig. 1 Molecular structure of compound **Ni1b** with 30% thermal ellipsoids. The solvent CH_2Cl_2 was omitted for clarity: (a) top view; (b) side view.

As a result of the change in hybridization patterns, the π-delocalization of the macrocycle must take an outer path C(1)–N(2)–C(3)–C(4) in the confused pyrrole moiety. The introduction of a fluoroalkyl group to the inner core distorts the planarity of the porphyrin macrocycle. The dihedral angles (°) between the planes of the pyrrole rings and that defined by N(22)N(23)N(24) are as follows: C(21) 40.14(30), N(22) −11.81(44), N(23) 8.60(49), N(24) −14.33(43). These crystal structure features are very similar to those of the 21-C methylated Ni(II) NCP[19] and the inner C-cyanated Ni(II) NCPs.[6] The UV/Vis spectrum of **Ni1b** closely resembles that of 21-C methylated Ni(II) NCPs,[19] because of their structural similarity. The intense absorption at 435 nm (Soret band) and the weaker ones in the visible region (Q-band) (See ESI†) are the typical characteristics of metalloporphyrins.

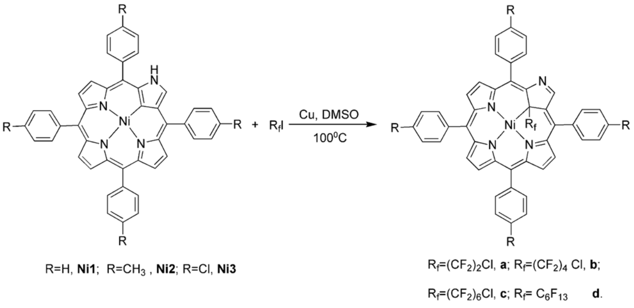
The reaction conditions were optimized using **Ni1** and $I(CF_2)_4Cl$ as model substrates. It was found that the amount of $I(CF_2)_4Cl$ and the reaction temperature have a significant effect on the yield. A large excess of $I(CF_2)_4Cl$ (30 equiv.) should be used to facilitate complete conversion of **Ni1**. It was found that 100 °C is a suitable temperature for this reaction. Higher temperatures increase the decomposition of the **Ni1**, while a much longer reaction time is required at lower temperatures.

Under the optimal reaction conditions, we investigated the fluoroalkylation of other NCPs containing electron-donating or electron-withdrawing substituents on the benzene rings (Table 1).

The desired fluoroalkylated **NiNCPs** were obtained for each substrate. The yields of **Ni3** with a chloro group at the *para*-position on the phenyl ring (entries 10–12) were much lower than those of **Ni2** with a corresponding methyl group (entries 6–8). It can therefore be inferred that the substituents on the phenyl ring influence electrophilic fluoroalkylation through their effects on the electron density of the conjugated π system of NiNCPs. The yields became rather low when $I(CF_2)_2Cl$ was used as the fluoroalkylating reagent, even with prolonged reaction times and a large excess of $I(CF_2)_2Cl$ (100 equiv.) (entries 1, 5, 9). The low boiling point of $I(CF_2)_2Cl$ and the fact that it is readily converted into tetrafluoroethylene under these reaction conditions may contribute to the decrease in yield.

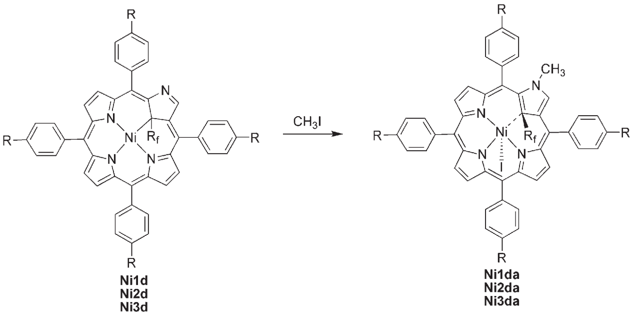
To understand the reaction mechanism, some inhibition experiments were carried out. The addition of an electron scavenger, *p*-dinitrobenzene (20 mol%), or a free radical inhibitor, hydroquinone (20 mol%), to the reaction mixture of **Ni1** and $I(CF_2)_2Cl$ had no effect on the reaction. These negative results implied the existence of fluoroalkylcoppers as reaction intermediates instead of fluoroalkyl radicals. This led us to propose that the reaction mechanism may involve the addition of a fluoroalkylcopper species across the C=C double bond to form a new unstable copper species on the

Table 1



Entry	R	R_fI	Product	Yield[b] (%)
1	H	$I(CF_2)_2Cl$[a]	**Ni1a**	37
2	H	$I(CF_2)_4Cl$	**Ni1b**	88
3	H	$I(CF_2)_6Cl$	**Ni1c**	78
4	H	IC_6F_{13}	**Ni1d**	78
5	CH_3	$I(CF_2)_2Cl$[a]	**Ni2a**	32
6	CH_3	$I(CF_2)_4Cl$	**Ni2b**	92
7	CH_3	$I(CF_2)_6Cl$	**Ni2c**	91
8	CH_3	IC_6F_{13}	**Ni2d**	90
9	Cl	$I(CF_2)_2Cl$[a]	**Ni3a**	33
10	Cl	$I(CF_2)_4Cl$	**Ni3b**	62
11	Cl	$I(CF_2)_6Cl$	**Ni3c**	56
12	Cl	IC_6F_{13}	**Ni3d**	58

[a] 100 equiv. was used. [b] Isolated yield.



Scheme 2 Reactions of 21-C fluoroalkylated Ni(II) NCPs with methyl iodide.

confused pyrrole ring. This is similar to our previous report on the fluoroalkylation of porphyrins.[17] The new unstable copper species breaks down to a radical and subsequently loses a hydrogen atom to yield the fluoroalkylated NCPs. This mechanism is quite different from that proposed for methylation, in which Ni(IV) or Ni(III) species might be involved in the transition state.[19] The mechanism based on the property of C=C double bond may open up new route for the modification of Ni(II) NCPs.

To explore the possibility for further functionalization of the fluoroalkylated NiNCPs, methyl iodide was chosen as an alkylating reagent. It was found that reactions between 21-C fluoroalkylated Ni(II) NCPs and methyl iodide proceeded smoothly, giving the N-methylated NiNCPs in good yields (Scheme 2). The structures of these N-methylated products were assigned by MS and UV/Vis spectroscopy, as well as elemental analysis (see ESI†). The UV/Vis absorption spectra of these paramagnetic organometallic Ni(II) complexes, 2-aza-2-methyl-21-fluoroalkyl-5,10,15,20-tetraphenyl-21-carbaporphyrinatonickel(II) iodides, are quite similar to that of 2-aza-2, 21-dimethyl-5,10,15,20-tetraphenyl-21-carbaporphyrinatonickel(II) iodide.[19]

In conclusion, we have developed for the first time an effective route for the synthesis of fluoroalkylated N-confused porphyrins. The fluoroalkyl group was introduced specifically onto the inner carbon of the porphyrin ring system. No regioisomeric products were found. The structure was determined by single-crystal X-ray diffraction. Subsequent methylation reactions proceeded smoothly under mild conditions. Further studies on the properties and applications of fluoroalkylated N-confused porphyrins are now under way.

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Notes and references

‡ *Crystal data* for **Ni1b**: $C_{49}H_{29}Cl_3F_8N_4Ni$, M = 990.82, triclinic, space group $P\bar{1}$, a = 11.3724(16), b = 14.584(2), c = 14.714(2) Å, α = 63.602(3), β = 77.491(3), γ = 85.060(3)°, V = 2133.8(5) Å^3, T = 293(2) K, Z = 2, μ(Mo-Kα) = 0.719 mm^{-1}, $R1$ = 0.0906, $wR2$ = 0.2163 ($I > 2\sigma(I)$); $R1$ = 0.1792, $wR2$ = 0.2551 (all data). Reflections collected/unique: 11252/7808 (R_{int} = 0.0952). Disorders at the fluoroalkyl chain and the solvent CH_2Cl_2 were found.

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