The oxidation of Ni(II) N-confused porphyrins (NCPs) with azo radical initiators and an unexpected intramolecular nucleophilic substitution reaction *via* a proposed Ni(III) NCP intermediate†

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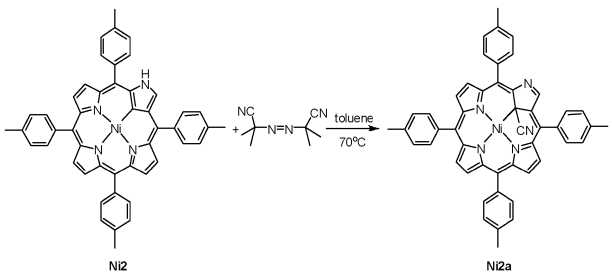
The oxidation of Ni(II) N-confused porphyrins (NCPs) with azo radical initiators resulted in an unexpected intramolecular nucleophilic substitution reaction *via* a proposed Ni(III) NCP intermediate, which could be detected by HRMS.

The organometallic chemistry of nickel, especially that of Ni(III), has attracted great interest in recent years.[1–13] Organic Ni(III) species are key intermediates in many chemical reactions[8c,9] and the formation of a Ni(III)-σ bond is also of great biological importance in some enzyme catalyzed reactions. For example, the F430 Ni(III)–methyl species plays an important role in the last chemical step of methane formation catalyzed by methylcoenzyme M reductase (MCR).[1,6] Ni(III) complexes have also been proposed as intermediates in the enzyme cycles involving both acetyl coenzyme A synthase[2] and carbon monoxide dehydrogenase.[5b,14] Our understanding of the way in which nickel functions in these enzymes is usually limited to that derived from spectroscopic methods and calculations,[3,5] and the detailed role of the nickel center is not clear at present. Synthetic modeling of nickel biosites is another promising way to investigate the precise function of the nickel ion in these biological processes. Ni(III)–C σ-bonded intermediates, synthesized by the reaction of a methyl radical with macrocyclic complexes Ni(II)L (L = cyclam derivatives), were studied by pulse radiolysis[16,17] and flash photolysis.[18] Further kinetic and thermodynamic studies demonstrated that the methyl radical formally oxidizes these Ni(II)L complexes in an equilibrium process with a relatively fast forward rate.[10] These results provide further indirect support for the proposal that Ni(III)–CH_3 species act as crucial intermediates in enzymes like carbon monoxide dehydrogenases and acetyl coenzyme A synthase.[14,15]

The porphyrin-like skeleton of F430 in MCR inspired us to search for porphyrinoid ligands that could stabilize Ni(III) species. It is known that Ni(III) porphyrins can be obtained by the oxidation of Ni(II) porphyrins (if the oxidation takes place on the nickel),[19] a fact that aroused our interest in the study of the oxidative chemistry of Ni(II) porphyrins. Organic Ni(III) species are very rare and usually show low stability,[3] and to the best of our knowledge, Ni(III) normal porphyrins have never been isolated and characterized by single crystal X-ray diffraction analysis. The stability of Ni(III) porphyrins is related to many factors, among which the nature of the porphyrin ligand itself is important. It has been shown that Ni(III) N-confused porphyrins [Ni(III) NCPs] prepared by oxidation or metathesis are stable enough for electron paramagnetic resonance (EPR) and ^{2}H NMR studies, which means that N-confused porphyrins (NCPs) do stabilize Ni(III) to some extent.[20,21]

N-Confused porphyrin (NCP), which was first reported independently by Furuta *et al.* and by Latos-Grażyński *et al.* in 1994,[22] is a porphyrin isomer in which one of the pyrrole rings is inverted. The special NNNC inner core often stabilizes atypical oxidation states or unusual coordination geometries.[9,23] The chemistry of NCP complexes with metals of biological relevance has been explored with the aim of generating heme-model complexes.[24] We have become very interested in NCP chemistry, and recently reported the synthesis and reactions of the first fluoroalkylated Ni(II) NCPs.[25] Based on our interest in the oxidative chemistry of Ni(II) porphyrins and the recognition that NCPs can stabilize Ni(III), we have studied the oxidation of Ni(II) NCPs with azo radical initiators. We found that inner 21-C-substituted Ni(II) NCPs were obtained instead of the expected Ni(III) species. However, we propose that Ni(III) NCP intermediates were involved in the formation of the observed products. Herein, we present our results.

Treatment of Ni(II) N-confused tetratolylporphyrin **Ni2** with AIBN in freshly distilled anhydrous toluene at 70 °C for 4 h gave, after flash chromatography, a purple compound **Ni2a** (Scheme 1). The intense absorption at 434 nm (Soret band) and the weak absorption at 716 nm (Q band) observed in the UV/Vis spectrum indicated that the porphyrin-like



Scheme 1 The reaction of **Ni2** and AIBN.

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skeleton had been preserved. The ^{1}H NMR and mass spectra indicated that the product might be the 21-CN substituted Ni(II) NCP, and further comparisons of these data with those of an authentic 21-CN substituted Ni(II) NCP prepared according to the reported procedure[26] confirmed our speculation.

The reaction conditions were optimized using **Ni1** as a model substrate. It was found that the amount of AIBN and the reaction temperature have a significant effect on the yield; 4 equiv. of AIBN should be used to facilitate complete conversion of **Ni1** and 60 °C is a suitable temperature for this reaction. A much longer reaction time is required at lower temperatures (Table 1, entries 1 and 2), while higher temperatures didn't increase the yield of **Ni1a** (Table 1, entry 4).

Under the optimal reaction conditions, we investigated the reaction of the Ni(II) NCPs **Ni1**, **Ni2** with azo radical initiators, namely, AIBN, dimethyl 2,2′-azobis(2-methylpropionate) and diethyl 2,2′-azobis(2-methylpropionate) (Table 2). The desired inner-substituted Ni(II) NCPs (**Ni1a–Ni1c**, **Ni2a–Ni2c**) were obtained for each substrate in yields of ~40% in each case. Most of the starting Ni(II) NCPs (~60%) decomposed under this reaction condition. To the best of our knowledge, these are the first examples of azo radical initiators being used for the introduction of cyano or alkoxycarbonyl substituents to organic compounds.

To understand the reaction mechanism, some inhibition experiments were carried out. The addition of an electron scavenger, 1,4-dinitrobenzene (20 mol%), or a free radical inhibitor, hydroquinone (20 mol%), to the mixture of **Ni2** and AIBN suppressed the reaction, and no products were formed over a period of 4 h. These results imply that the generation of the radical $CN(CH_3)_2C^{\bullet}$ is essential for the reaction and excludes a simple nucleophilic substitution mechanism. We propose a mechanism involving the Ni(III)–alkyl species shown in Scheme 2 (which is shown for dimethyl 2,2′-azobis(2-methylpropionate) as an example). Firstly, the $(COOCH_3)(CH_3)_2C^{\bullet}$ radical oxidizes Ni(II) NCP to form an NCP Ni(III)–alkyl species, the intermediate **A**. Subsequent intramolecular nucleophilic attack results in the formation of a four-membered ring, intermediate **B**. The opening of the four-membered ring and cleavage of the Ni(III)–alkyl σ-bond gives the final product.

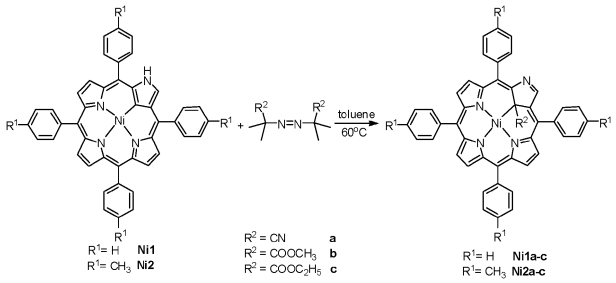
According to the reported EPR and ^{2}H NMR studies, the oxidation of Ni(II) NCP takes place on the nickel atom rather than the NCP ring.[20] This means that only Ni(III) NCP was formed in the oxidation process and no π-cation radicals were produced. So, we speculate that the Ni(III) intermediate **A** was generated in the first step of the reaction. However, as a result of the instability of the Ni(III) NCP species, the intermediates could not be isolated. The high concentration of alkyl radical makes it difficult to detect the small amount of Ni(III) intermediates by EPR spectroscopy. For that reason, we tried to identify the Ni(III) intermediates by mass spectrometry, which is a useful tool for the characterization of some active intermediates. *In situ* low resolution mass spectroscopic analysis of the reaction mixture of **Ni2** and **b** gave a *m*/*z* signal at 827.3 (Scheme 3), and further analysis by high resolution mass spectroscopy (HRMS) gave a *m*/*z* signal at 827.2880, which is in agreement with the calculated *m*/*z* of 827.28905 for the proposed Ni(III) intermediate (see the ESI†). Although this result strongly supports the intermediacy of the proposed Ni(III) species, we cannot completely exclude the π-radical cation mechanism at present.[27]

Table 1 The reaction of **Ni1** and AIBN at different temperatures

Entry	Temperature/°C	Time/h	Conversion (%)	Yield[a] (%)
1	20	108	<5	<5
2	40	36	100	41
3	60	4	100	45
4	70	4	100	42

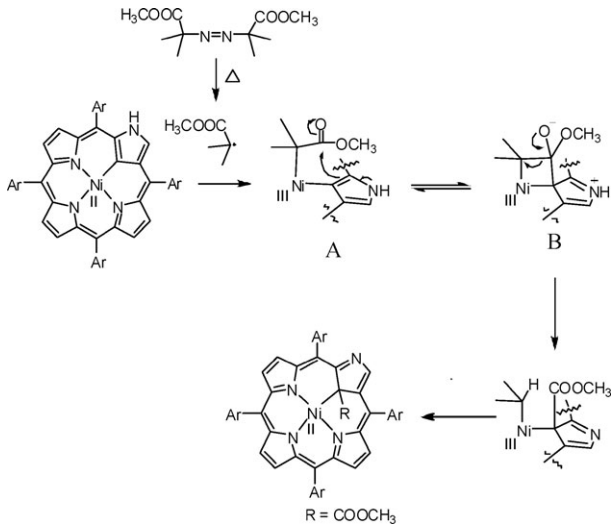
[a] Isolated yield of compound **Ni1a**.

Table 2 The reactions of the **Ni1**, **Ni2** with azo radical initiators



Entry	R^1	R^2	Product	Yield[a] (%)
1	H	CN	**Ni1a**	45
2	H	$COOCH_3$	**Ni1b**	38
3	H	$COOC_2H_5$	**Ni1c**	37
4	CH_3	CN	**Ni2a**	42
5	CH_3	$COOCH_3$	**Ni2b**	40
6	CH_3	$COOC_2H_5$	**Ni2c**	39

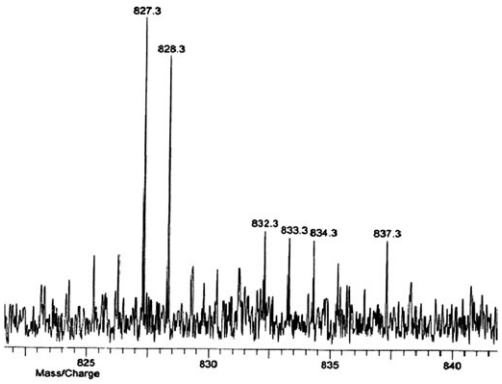
[a] Isolated yield.



Scheme 2 Proposed mechanism.

Demetallation of **Ni1a–Ni1c** proceeded smoothly in the presence of concentrated hydrochloric acid, leading to the corresponding free base inner-substituted NCPs **1a–1c** in good yields. The structure of **1b** was confirmed by single crystal X-ray diffraction analysis (Fig. 1).‡

In conclusion, we have shown that Ni(II) NCPs, upon treatment with certain azo radical initiators, undergo an unexpected cyanation or alkoxycarbonylation at the inner



Scheme 3 The *in situ* partially enlarged low resolution mass spectrum of the reaction mixture of **Ni2** and **b**.

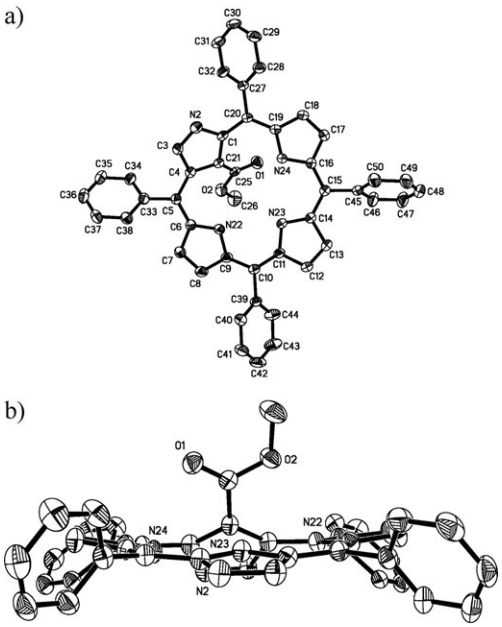


Fig. 1 The molecular structure of compound **1b**. The solvent CH_2Cl_2 was omitted for clarity. (a) Top view. (b) Side view.

21-C-position. We propose that Ni(III)–alkyl NCPs, which could be detected by HRMS, are the key intermediates in this transformation. Further intensive efforts relating to synthetic modeling of Ni(II)–F430 are being made in our laboratory, and investigations on the synthesis and properties of stable Ni(III) NCPs, as well as the applications of Ni(III) NCPs in biomimetic nickel chemistry, will be carried out in the near future.

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Notes and references

‡ Crystal data for **1b**·CH_2Cl_2 (CCDC 715233): $C_{47}H_{34}Cl_2N_4O_2$, M = 757.68, monoclinic, a = 11.6814(10), b = 17.6688(15), c = 19.2955(17) Å, β = 104.487(2)°, V = 3855.9(6) Å^3, T = 293(2) K, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 0.214 mm^{-1}, $R1$ = 0.0740, w$R2$ = 0.2085 ($I > 2\sigma(I)$); $R1$ = 0.1225, w$R2$ = 0.2336 (all data). Reflections collected/unique: 20843/7564 (R_{int} = 0.0692).

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