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Electrophilic Reaction of Ag(III) N-Confused Porphyrin with Alcohols

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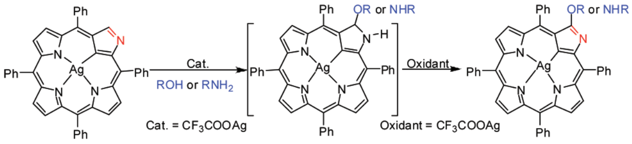
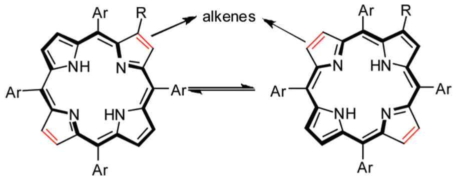
Received March 11, 2010



Experimental studies demonstrated that alcohols and amines can undergo a CF_3COOAg-catalyzed nucleophilic addition at the outer C═N position of Ag(III) NCPs, leading to C-3-alkoxylated Ag(III) NCPs, which supports the computational result that the C═N bond on the periphery of Ag(III) NCPs is partially isolated from the 18 π-electron macrocyclic conjugation system and is the active electrophilic center.

The structure and reactivity properties of N-confused porphyrins (NCPs) have been of considerable research interest since their first synthesis was reported independently by Furuta and Latos-Grażyński in 1994.[1] The special NNNC inner core of NCPs gives them quite different properties from normal porphyrins. For example, NCPs can act as trianionic, dianionic, monoanionic, or neutral ligands and are able to stabilize high oxidation states of metal ions.[2] Considerable efforts have been devoted to the investigation of the reactivity of NCPs and metal NCPs during recent years. A variety of NCP analogues have been synthesized, and studies show that the reactive center of NCPs and metal NCPs is located in the confused pyrrole ring.[2b] However, despite the substantial difference between normal porphyrins and NCPs, there remain some similarities. For example, NCP, an isomer of a normal porphyrin, possesses an 18 π-electron aromatic macrocyclic system similar to that of the normal porphyrin. Studies have shown that aromatic electron delocalization is governed by an 18 π-annulene system with two partially isolated C═C bonds (Scheme 1) on the porphyrin periphery at the antipodal position[3] and that these two partially isolated C═C bonds exhibit chemical reactivity very similar to that of alkenes (Scheme 1).[4−7]

SCHEME 1. Eighteen π-Electron Macrocyclic Conjugation Systems of Free Base Normal Porphyrins



We recently reported the synthesis of the novel 20 π-electron nonaromatic isophlorin, originally referred to by Woodward during the synthesis of chlorophyll,[8] and extended our research from normal porphyrins to NCPs with the synthesis of inner fluoroalkylated NCPs and cyano- or alkoxycarbonyl-substituted NCPs.[9] Earlier work on π-bonding systems of normal porphyrins prompted us to study the reactivity of the 18 π-electron aromatic macrocyclic system of NCPs. It is known that the π-electrons in normal porphyrins are completely delocalized over the macrocyclic system on the NMR time scale.[3c] However, in the case of divalent nickel NCPs, the 18 π-electron macrocyclic conjugation system becomes less delocalized and the C═N bond is partially isolated from the delocalization framework (Scheme 2, structure A) and could participate in the Diels−Alder reaction.[10]

Considering the fact that the NCPs could stabilize high oxidation states of metal ions, for example, Ag(III), it is expected that the C═N bond on the periphery of the trivalent siliver NCPs is also partially isolated from the delocalization framework and should show reactivities similar to those of imines.

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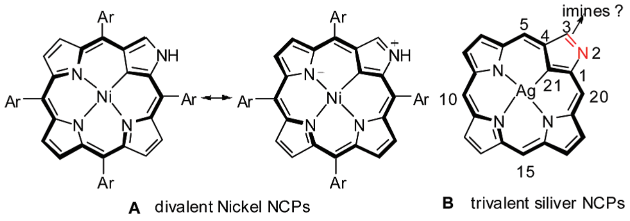
DOI: 10.1021/jo1004229

SCHEME 2. Eighteen π-Electron Macrocyclic Conjugation Systems of Ni(II) NCPs and Ag(III) NCP



(Scheme 2, structure B) As such, we chose Ag(III) NCP as the model system and examined its electrophilicity.

We first performed computational chemistry studies to predict the most electrophilic site of the model system. This was done through the dual descriptor in conceptual density functional theory (CDFT).[11−14] In CDFT, the dual descriptor is defined as[14−18]

$$f^{(2)}(\mathbf{r}) = \left(\frac{\partial^2 \rho(\mathbf{r})}{\partial^2 N}\right)_{\nu(\mathbf{r})} \tag{1}$$

where N is the total number of electrons, $\rho(\mathbf{r})$ is the electron density, and $\nu(\mathbf{r})$ is the external potential, the framework formed by all atomic nuclei of the system. Within the frozen-orbital approximation,[14−18]

$$f^{(2)}(\mathbf{r}) \approx \rho_{\text{LUMO}}(\mathbf{r}) - \rho_{\text{HOMO}}(\mathbf{r}) \tag{2}$$

where $\rho_{\text{HOMO}}(\mathbf{r})$ and $\rho_{\text{LUMO}}(\mathbf{r})$ are highest occupied molecular orbital (HOMO) density and lowest unoccupied molecular orbital (LUMO) density, respectively. In CDFT, it is known that $f^{(2)}(\mathbf{r})$ will be positive in electrophilic regions as $\rho_{\text{LUMO}}(\mathbf{r})$ is large and negative in nucleophilic regions as $\rho_{\text{HOMO}}(\mathbf{r})$ dominates these regions. The dual descriptor contour surface of the Ag(III) NCP model system is shown at the DFT B3LYP/6-311+G(d) level of theory in Figure 1. It clearly shows that the outer C═N bond is the most electrophilic (blue in color, positive in the dual descriptor quantity) within the system.

Next, we carried out the silver(I) trifluoroacetate catalyzed nucleophilic addition of ethanol to Ag(III) NCP. Treatment of Ag(III) NCP with ethanol as the nucleophile in the presence of silver(I) trifluoroacetate in DCM at room temperature for 2 days gave, after flash chromatography, a purple compound. The intense absorption at 448 nm (Soret band) and weak absorptions at 523, 570, and 618 nm (Q-band) observed in the UV−vis spectrum indicated that the porphyrin-like skeleton had been preserved. Furthermore, the MS results showed that an ethoxyl group had been introduced into the Ag(III) NCP complex. The signals at 4.69 ppm (q, J = 7.0 Hz, 2H) and 1.19 ppm (t, J = 7.0 Hz, 3H) in the ^{1}H NMR spectrum and the absence of the C-3 H signal at 9.46 ppm suggested that the ethoxyl group was attached to C-3 (Figure 2). The chemical shifts at lower fields closely resembled those of the reported C-3-substituted Ag(III) NCPs.[19] These data confirmed that the product was the predicted C-3-ethoxylated Ag(III) NCP.

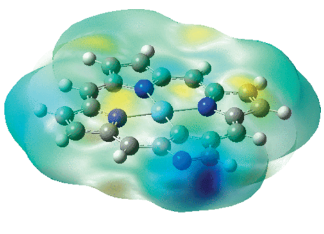


FIGURE 1. Predicted electrophilic site, the outer C═N bond (blue region in foreground), from the dual descriptor, $f^{(2)}(\mathbf{r})$, of conceptual density functional theory for Ag(III) NCP.

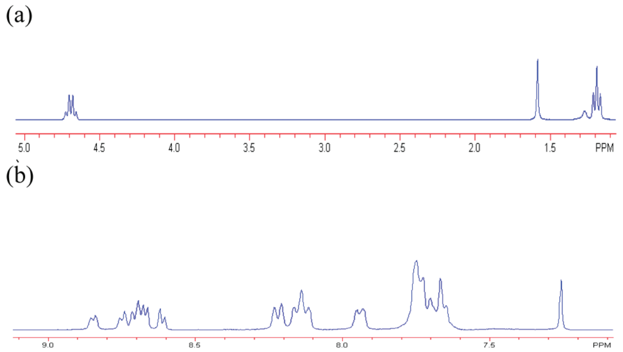


FIGURE 2. ^{1}H NMR spectrum of the ethoxylated NCP: (a) the high field region (the signals at 1.23 and 1.56 ppm are due to impurities and water, respectively) and (b) the low field region.

The reaction conditions were optimized using Ag(III) NCP and methanol as model substrates. It was found that a large amount of CF_3COOAg, which acted as both the catalyst and the oxidant, was needed and the mixture had to be heated to reflux for the reaction to proceed at a reasonable rate. The conversion of the Ag(III) NCP complex was about 50% under these conditions after 2 days. Nearly half of the Ag(III) NCP was recovered and recycled. Although a much longer reaction time would increase the conversion of the substrate, the product was found to decompose gradually. To get the best yield and make full use of the substrate, the reaction was quenched after 2 days.

The reaction of Ag(III) NCP with several alcohols was investigated under the optimal conditions. As shown in Table 1, alcohols such as methanol, ethanol, isopropanol, allyl alcohol, benzyl alcohol, cyclopropylmethanol, and cyclohexanol all react with Ag(III) NCP, and in each case a moderate yield of the corresponding C-3-alkoxy-substituted Ag(III) NCP was obtained. As the size of the alcohols increased, yields tended to be lower (Table 1, entries 1−3, 7), and *tert*-butyl alcohol, the bulkiest of the alcohols tested, did not react at all. These results indicate that the reaction is sensitive to the steric hindrance of the alcohol.

Primary and secondary amines were also employed as nucleophiles in this study. According to TLC analysis,

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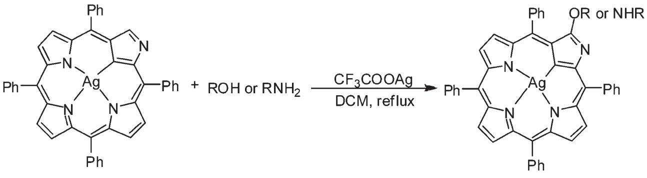
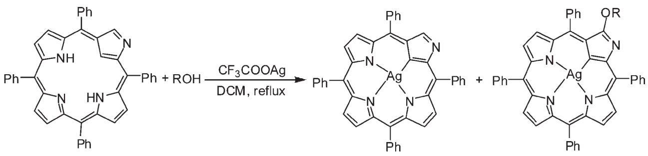
TABLE 1. Reaction of Ag(III) NCP with Alcohols or Primary Amines



entry	ROH or RNH_2	conversion[a] (%)	product	yield[b] (%)
1	methanol	61	**Ag1**	80
2	ethanol	58	**Ag2**	78
3	isopropanol	51	**Ag3**	72
4	allyl alcohol	60	**Ag4**	81
5	benzyl alcohol	58	**Ag5**	74
6	cyclopropylmethanol	58	**Ag6**	81
7	cyclohexanol	52	**Ag7**	70
8	benzyl amine	60	**Ag8**	tr[c]

[a] Conversion of the Ag(III) NCP. [b] Isolated yield, based on the consumed Ag(III) NCP. [c] Most of the product was decomposed on the silica gel chromatography.

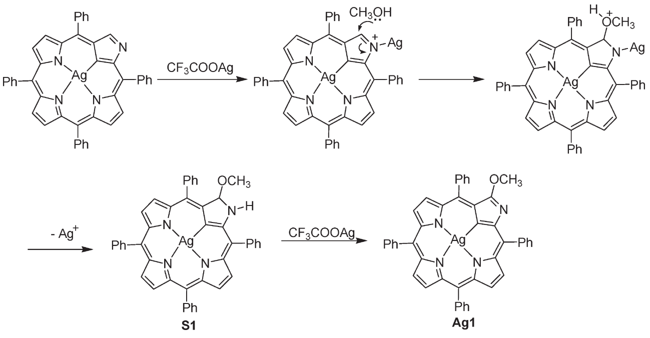
TABLE 2. One-Pot Synthesis of C-3-Alkoxylated Ag(III) NCPs



entry	ROH	yield C[a] (%)	product	yield D[a] (%)
1	methanol	5	**Ag1**	36
2	ethanol	7	**Ag2**	37
3	isopropanol	10	**Ag3**	20
4	allyl alcohol	8	**Ag4**	34
5	benzyl alcohol	11	**Ag5**	21
6	cyclopropylmethanol	12	**Ag6**	34
7	cyclohexanol	18	**Ag7**	26

[a] Isolated yields. Yield C: Ag(III) NCP. Yield D: C-3-alkoxylated Ag(III) NCP.

SCHEME 3. Proposed Mechanism



primary amines such as butylamine, isopropylamine, and benzylamine all reacted with Ag(III) NCP. However, the products were not stable on silica gel chromatography and decomposed quickly. So, only a trace amount of **Ag8** was obtained (Table 1, entry 8). Secondary amines, such as diethylamine, piperidine and morpholine, did not react at all, perhaps because of their steric hindrance.

The mechanism of the reaction of alcohols with Ag(III) NCP is proposed to be Ag(I)-catalyzed nucleophilic addition followed by oxidation (Scheme 3). Taking methanol as an example, Ag(I) first coordinates with the outer N atom of the Ag(III) NCP, and nucleophilic addition of methanol at the C-3-position then takes place. Release of the silver cation then produces the intermediate **S1**, which on oxidation by the excess CF_3COOAg yields **Ag1**.

Bearing in mind the fact that the Ag(III) NCP was made by reaction of NCP with CF_3COOAg,[20] we conducted sequential metalation and alkoxylation in one pot (Table 2). The expected C-3-alkoxylated Ag(III) NCPs were obtained, together with the intermediate Ag(III) NCP. However, the yields of the C-3-alkoxylated Ag(III) NCPs were much lower than those obtained by the two-pot procedure.

In summary, we have shown that the outer C=N bond of Ag(III) NCP is an active electrophilic center. This was predicted by computational methods and then verified experimentally. The computational chemistry was carried out by employing the dual descriptor from the conceptual density functional theory. Experimental studies demonstrated that alcohols can undergo a CF_3COOAg-catalyzed nucleophilic addition at the outer C=N position of Ag(III) NCPs, leading to C-3-alkoxylated Ag(III) NCPs. Primary amines undergo similar additions. As expected, the C=N bond is partially isolated from the 18 π-electron macrocyclic conjugation system and shows reactivity similar to that of imines. In addition, this work provides a useful one-pot synthesis of C-3-alkoxylated Ag(III) NCPs from NCP. Further studies of the 18 π-electron aromatic macrocyclic system of metal NCPs are in progress.

Experiment Section

Typical Procedure for Synthesis of C-3-Substituted *N*-Confused Porphyrins (Ag2). A mixture of Ag(III) NCP (72 mg, 0.1 mmol), EtOH (2 mL), and CF_3COOAg (200 mg, 0.9 mmol) was stirred in CH_2Cl_2 (10 mL) at reflux for 2 days. Then the reaction mixture was cooled to room temperature, and CH_2Cl_2 (10 mL) was added. After being washed with water (3 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4 and evaporated by rotary evaporator to dryness. After chromatography on silica gel column using CH_2Cl_2 as an eluent (the first band was collected) and crystallization from CH_2Cl_2/MeOH, the C-3-substituted N-confused porphyrin **Ag2** was obtained. Further chromatography using CH_2Cl_2/EtOH (100:1 V/V) as an eluent and crystallization from CH_2Cl_2/MeOH gave Ag(III) NCP.

Ag2: yield (based on the consumed Ag(III) NCP): 78%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.84 (m, 1H), 8.77−8.59 (m, 5H), 8.25−8.10 (m, 6H), 7.94 (m, 2H), 7.81−7.61 (m, 12H), 4.69 (q, J = 6.9 Hz, 2H), 1.19 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 141.8, 140.7, 140.2, 139.4, 139.2, 138.4, 137.1, 135.1, 134.9, 133.9, 132.3, 130.6, 129.0, 128.8, 128.1, 127.9, 127.9, 127.3, 126.99, 126.95, 126.8, 126.7, 126.2, 124.6, 123.0, 121.4, 120.0, 63.9, 14.1. UV−vis (CH_2Cl_2): λ_{max} (relative intensity) 448 (28.7), 523 (2.6), 570 (2.0), 618 (1.0) nm. HRMS (MALDI): calcd for $[C_{46}H_{31}AgN_4O + H]^+$ 763.1622, found 763.1630.

Typical Procedure for One-Pot Synthesis of C-3-Alkoxylated *N*-Confused Porphyrins. A mixture of NCP (61 mg, 0.1 mmol), alcohol (2 mL), and CF_3COOAg (200 mg, 0.9 mmol) was stirred in CH_2Cl_2 (10 mL) at reflux for 2 days in air atmosphere. Then the reaction mixture was cooled to room temperature, and CH_2Cl_2 (10 mL) was added. After being washed with water (3 × 20 mL), the organic layer was dried over anhydrous Na_2SO_4 and evaporated by rotary evaporator to dryness. After chromatography

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on silica gel column using CH_2Cl_2 as an eluent and crystallization from CH_2Cl_2/MeOH, the C-3-alkoxylated N-confused porphyrin was obtained. Further chromatography using CH_2Cl_2/EtOH (100:1 v/v) as an eluent and crystallization from CH_2Cl_2/MeOH gave Ag(III) NCP.

Acknowledgment. We thank the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Science Foundation (20772147, 20972179) for financial support. We thank Dr. John Clough of Syngenta Jealott's Hill International Research Centre for his suggestions and proofreading.

Supporting Information Available: Computational method, total energy, atomic coordinates, and detailed experimental procedures for the synthesis and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.