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Probing Nitrobenzhydrol Uncaging Mechanisms Using FerriCast

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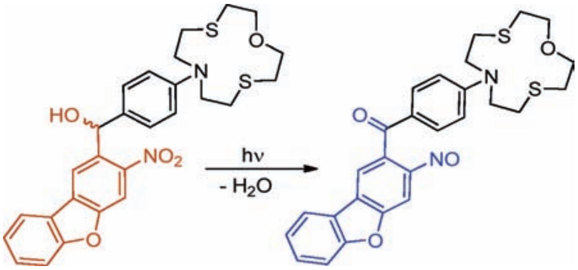
ABSTRACT



The FerriCast derivative FC-NDBF was synthesized from 3-methyl-2-nitrodibenzofuran (NDBF). The photochemistry of the target Fe^{3+} photocage and several related congeners provides mechanistic insight into the uncaging quantum yields of nitrobenzhydrol-derived ligands.

For over 30 years, photolabile protecting groups have been incorporated into photocages to study biological processes.[1] Photocages render analytes inert until investigators initiate activity with light. While most photocages are for organic molecules, metal ions including Ca^{2+} and Cu^{2+} can be caged with photoactive chelators.[2,3] Tsien designed Nitr-photocages for Ca^{2+} based on converting a nitrobenzhydrol-based ligand into a benzophenone.[4] Upon uncaging, electrons on a coordinated aniline delocalize onto a conjugated carbonyl group, which decreases the affinity for the metal ion. *Cast* chelators, a name evocative of *casting off* a metal ion, exploit this strategy to cage Mg^{2+},[5] Zn^{2+},[6] Hg^{2+}, and Pb^{2+}.[7]

FerriCast (FC-DMNB) incorporates 7-phenyl-1-oxa-4,10-dithia-7-azacyclododecane (AT$_2$12C4, **2**) into a nitrobenzhydrol scaffold (Scheme 1).[8] Rurack et al. explored the coordination chemistry of AT$_2$12C4 in a fluorescent sensor for Fe^{3+}.[9] FC-DMNB utilizes a 4,5-dimethoxy-2-nitrobenzyl (DMNB) caging chromophore and exhibits modest photolysis quantum yields ($\Phi = 0.05$, $\varepsilon_{350} = 5700\ \text{cm}^{-1}\ \text{M}^{-1}$) like other nitrobenzhydrol-based photocages. In contrast, a nitrodibenzofuran-based (NDBF) Ca^{2+} photocage possesses $\Phi \sim 0.7$ and a high molar absorptivity ($\varepsilon = 18\,400\ \text{cm}^{-1}\ \text{M}^{-1}$) but uses chelator fragmentation as the uncaging strategy.[10] We hypothesized that replacing the DMNB group with a NDBF chromophore also would improve the uncaging efficiency of FerriCast and related nitrobenzhydrol photocages, but no practical route to useful NDBF precursors had been reported.

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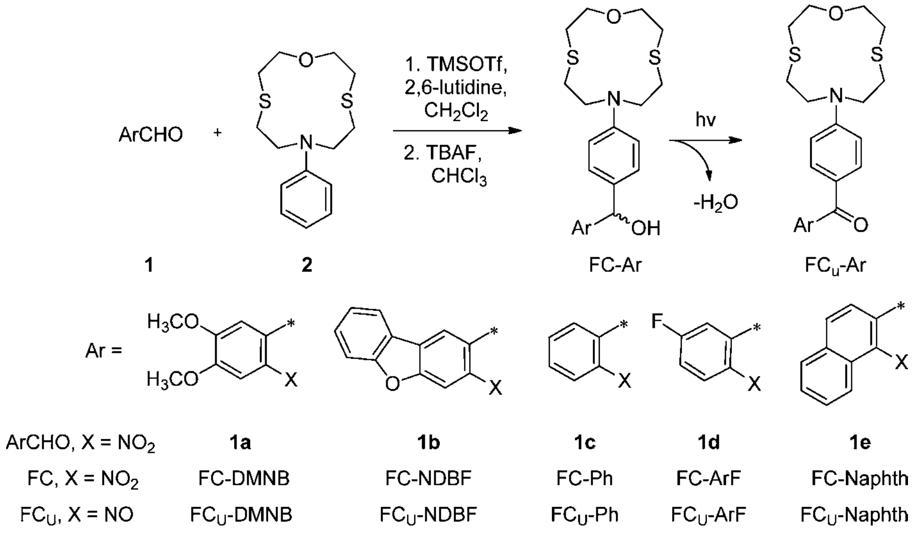
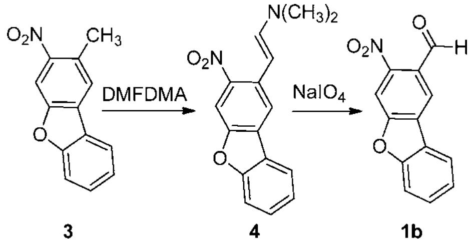
Scheme 1. Synthesis of FerriCast Derivatives and Photolysis to the Corresponding Photoproducts



The 2-methyl-3-nitrodibenzofuran **3** intermediate was synthesized in five steps,[11] and the methyl group was converted to an aldehyde (Scheme 2).[12] Extended reaction times with dimethylformamide dimethylacetal (DMFDMA) were required to convert **3** to **4**. Electron-donating groups, such as the ether in compound **3**, often inhibit these reactions.[13] Oxidative cleavage of **4** with sodium periodate afforded 3-nitro-2-dibenzofurancarboxaldehyde (**1b**). FerriCast-nitrodibenzofuran (FC-NDBF) was prepared from **2** and **1b** using a two-step, one-pot trimethylsilyl trifluoromethanesulfonate (TMSOTf) assisted electrophilic aromatic substitution reaction.[4] To characterize the metal binding properties of the new photocage completely, the photoproduct FerriUnc-NDBF (FC_U-NDBF) was prepared by the bulk photolysis of FC-NDBF (Scheme 1).

Scheme 2. Synthesis of 3-Nitro-2-dibenzofurancarboxaldehyde



Spectrophotometric titrations of FC-NDBF in CH_3CN with $Fe(ClO_4)_3$ revealed metal binding behavior similar to the first-generation FC-DMNB compound.[8] A conditional binding constant of log $\beta_{12} = 8.0 \pm 0.3$ ($K_d = 11$ nM) was found by fitting titration data with the nonlinear least-squares program HypSpec.[14,15] Titration of FC_U-NDBF revealed a conditional binding constant of $K_d = 8.7 \pm 0.9$ μM when fitting the absorbance changes at 354 nm to a 1:1 binding isotherm. The decrease in binding strength upon photolysis (ΔK_d = 791-fold) indicates that FC-NDBF binds Fe^{3+} more tightly than FC_U-NDBF, which is consistent with the expected uncaging mechanism. To demonstrate Fe^{3+} release from FC-NDBF, a solution of $[Fe(FC\text{-}NDBF)]^{3+}$ was photolyzed in the presence of the Fe^{3+}-selective fluorescent sensor **8** (Figure 1).[8,9]

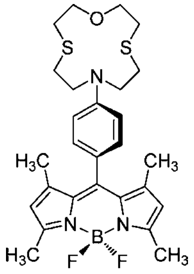

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Figure 1. The structure of fluorescent sensor **8**.[9]

Spectroscopic interrogation of the photolyzed solution shows amplified luminescence corresponding to $[Fe(\mathbf{8})]^{3+}$ with the concomitant development of a charge transfer band at 354 nm characteristic of FC_U-NDBF (Figure 2).

Both the molar absorptivity and the quantum yield of photolysis dictate the uncaging efficiency.[10] While there are two prior reports of NDBF-derived cages, the Φ value reported by Ellis−Davies is independent of metal concentration,[10] and no Φ value is provided for the other.[16] FC-NDBF exhibits a large molar absorptivity (ε_{270} = 12 300 cm^{-1} M^{-1}) in agreement with these compounds (ε ∼ 18 400 cm^{-1} M^{-1});[10] however, the Φ measured by HPLC (0.04 ± 0.01) is significantly smaller than the

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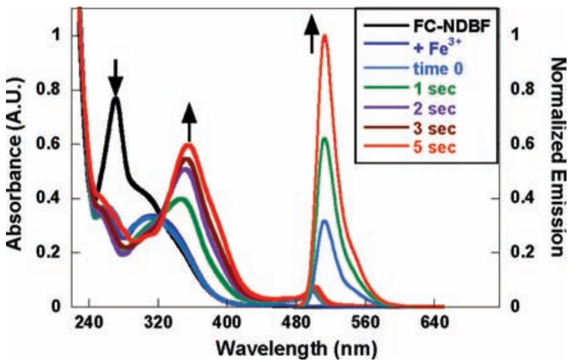


Figure 2. Photolysis of 25 μM $[Fe(FC\text{-}NDBF)]^{3+}$ with a 1000 W Xe source in CH_3CN in the presence of 1.0 μM fluorescent sensor **8** ($\lambda_{ex} = 470$ nm, $\lambda_{em} = 513$ nm, log $\beta_{12} = 12.1$). The thick lines represent the absorbance spectra, and the thin lines represent the emission spectra. Spectra also show the apo ligand (black) and the complex (dark blue). Spectra were recorded after 1, 2, 3, and 5 s of exposure. The CT band at 354 nm corresponds to the photoproduct FC_U-NDBF.

Ellis–Davies photocage ($\Phi \sim 0.70$).[10] The quantum yield of FC-NDBF increases when the cage was saturated with Fe^{3+} ($\Phi = 0.22 \pm 0.09$).

To understand the variance in quantum yield of Cast compounds, the nitrobenzyl chromophore was changed systematically, and the Φ values were correlated with structure, analogous to previous studies on caged esters.[17,18] Using TMSOTf chemistry, the NDBF group was substituted with 2-nitrophenyl (FC-Ph), 5-fluoro-2-nitrophenyl (FC-ArF), and 1-nitronaphthyl (FC-Naphth) groups (Scheme 2). All the measured quantum yields of the apo-cages were small ($\Phi = 0.02-0.06$, $\varepsilon = 840-1450$ cm^{-1} M^{-1}) and in accord with the measured values for apo-FerriCast (Table 1).[8] Metalation of FerriCast with Fe^{3+} leads to a modest enhancement in quantum yield ($\Phi = 0.18 \pm 0.01$, $\varepsilon_{350} = 11\,890$ cm^{-1} M^{-1}), presumably in large part because of the increased molar absorptivity of the $[Fe(FerriCast)]^{3+}$ complex. The Fe^{3+}-induced enhancement of Φ suggests that the aniline receptor inflluences the uncaging efficiency more than substituents on the nitrobenzyl group.

To interrogate the influence of the receptor fragment of Cast photocages, the AT_212C4 receptor was replaced with various substituted phenyl groups. The model photocages were synthesized by a Pd-catalyzed coupling reaction between arylboronic acids **5a**–**d** and **1a** (Scheme 3).[19,20] A trend in Φ with the electron-donating capacity of the *para* substituent ($-NMe_2$, $-OMe$, $-H$, $-CF_3$) was revealed (Table 1). With electron-donating groups, such as dimethylamino and methoxy, the Φ is lower (0.03 ± 0.01 and 0.16 ± 0.04, respectively) than photocages with electron-neutral and electron-withdrawing groups like a hydrogen atom or trifluoromethyl group ($\Phi = 0.23 \pm 0.04$ and 0.20 ± 0.01, respectively). In addition, protonation of the dimethylamino group increases Φ to 0.15 ± 0.01 which is similar to the quantum yield of $[Fe(FerriCast)]^{3+}$.

Table 1. Quantum Yields of Photolysis for Nitrobenzhydrols[a]

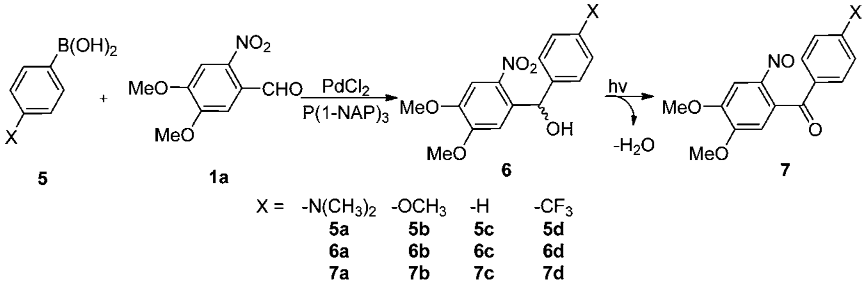
compound	$\Phi_{photolysis}$
FC-DMNB	0.06 ± 0.01
$[Fe(FC\text{-}DMNB)]^{3+}$ [b]	0.18 ± 0.05
FC-NDBF	0.04 ± 0.01
$[Fe(FC\text{-}NDBF)]^{3+}$ [b]	0.22 ± 0.09
FC-Ph	0.05 ± 0.01
FC-ArF	0.02 ± 0.02
FC-Naphth	0.03 ± 0.02
6a $(NCH_3)_2$	0.03 ± 0.01
6a + H^+ [c]	0.15 ± 0.01
6b (OCH_3)	0.16 ± 0.04
6c (H)	0.23 ± 0.04
6d (CF_3)	0.20 ± 0.01

[a] Experiments conducted in CH_3CN, and values were calculated from HPLC data. [b] Photocage and 0.5 equiv of $Fe(ClO_4)_3$. [c] Photocage and 1 equiv of HCl.

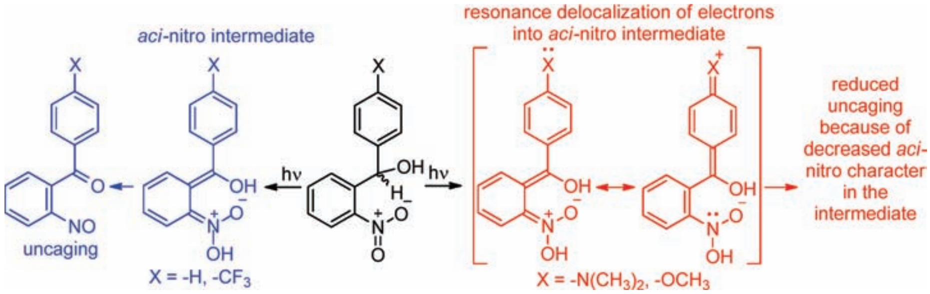
Nitrobenzyl compounds uncage via a Norrish type II mechanism, which involves the formation of a key *aci*-nitro intermediate.[21–23] Electron donation from the aniline in the *para* position of the receptor ring can decrease the *aci*-nitro character of the intermediate, which disfavors uncaging (Scheme 4, red). Conversely, electron-neutral and electron-poor groups cannot interact with the *aci*-nitro intermediate, resulting in larger quantum yields (Scheme 4, blue).

In two prior studies, NDBF-dervied molecules uncage efficiently;[10,16] however, the advantages of the chromophore are less pronounced when incorporated into Cast photocages. The differences in behavior are attributed to the uncaging

Scheme 3. Synthesis and Photolysis of Model Cages



Scheme 4. Resonance with the *aci*-Nitro Intermediate during Photolysis of the Model Cages



mechanism of nitrobenzhydrol photocages. Resonance interactions between photocage components decrease the *aci*-nitro character of the intermediate that is responsible for uncaging. Such interactions are not present in the previously reported NDBF-derived photocages. Since electronic effects can short circuit the benefits of the NDBF chromophore, uncaging mechanisms must be considered when designing photocages. While only partially successful in improving the properties of FerriCast, the new synthesis provides access to 3-nitro-2-dibenzofurancarboxaldehyde, which will assist in the preparation of future NDBF-derived cages that will exploit the unique photochemical properties of the chromophore.

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Supporting Information Available: Experimental details and compound characterization. Additional spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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