Corroles

DOI: 10.1002/anie.200700757

DNA Binding and Catalytic Properties of Positively Charged Corroles**

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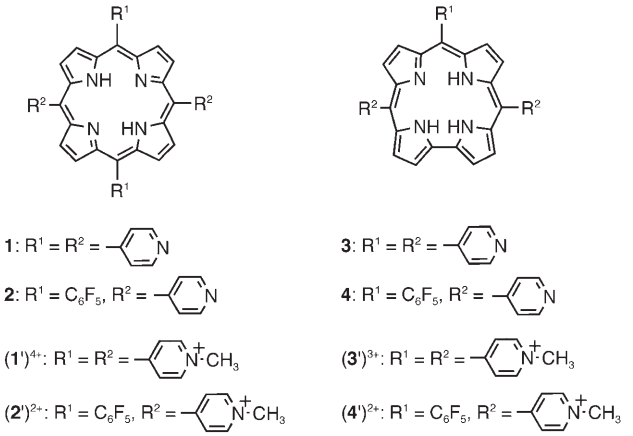
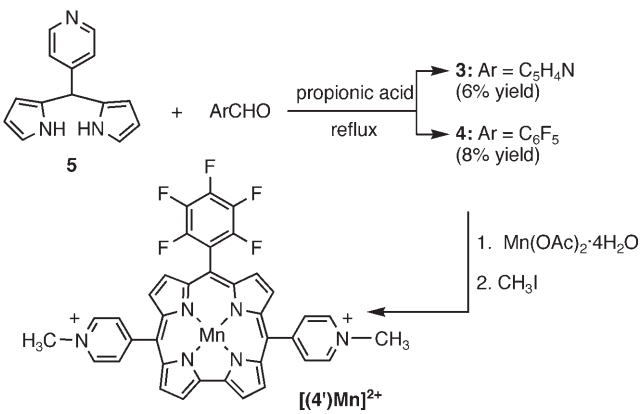
The recent disclosure of practical approaches for the synthesis of triarylcorroles and their selective modifications[1,2] allowed for the utilization of the corresponding metal complexes as key components in catalysis, solar cells, sensors, and medicinal applications.[3,4] Corroles with sulfonate head groups,[2] which induce water-solubility owing to their negative charge, played an important role in many of these cases.[4] On the other hand, there is only a single report about a corrole with positively charged substituents. This particular derivative was used in what remains the only reported medicinal investigation in vivo with corroles.[5] The corrole with three remote positive charges displayed significantly better efficacy in inhibiting tumor progression and metastasis in animal models than analogous porphyrins. The main and probably sole reason for no other reports regarding positively charged corroles appears to be the synthetic challenge. The trispyridylium-substituted corrole ($(\mathbf{3}')^{3+}$ in Scheme 1) has not yet been reported, whereas the corresponding 5,10,15,20-tetrakis(4-*N*-methylpyridyl)porphyrin (TMPyP; $(\mathbf{1}')^{4+}$ in Scheme 1) is the most intensively investigated porphyrin for medicinal and biological applications. Specific examples include the interactions between $(\mathbf{1}')^{4+}$ and DNA and utilization of the metal complexes of $(\mathbf{1}')^{4+}$ for site-specific cleavage of DNA and decomposition of reactive oxygen species (ROS).[6,7]

Herein we report a facile route to the tris- and bispyridyl corroles **3** and **4**, respectively. Metalation by manganese and subsequent N-methylation led to the water-soluble manganese(III) corrole $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ (Scheme 2) whose molecular structure was resolved by X-ray crystallography. The comparison of $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ and the manganese(III) complex of the analogous porphyrin $(\mathbf{2}')^{2+}$ ($[(\mathbf{2}')\mathrm{Mn(Cl)}]^{2+}$) revealed unique differences regarding both DNA binding and peroxynitrite decomposition.

Targeting the synthesis of pyridyl-substituted corroles, we have first found that the solvent-free method (best suited for electron-poor aldehydes)[1] failed when applied to condensation of pyrrole with 4-pyridinecarboxaldehyde. Modifications introduced by Gryko and Jadach (trifluoroacetic acid)[8] and Collman and Decreau (microwaves)[9] also did not yield appreciable amounts of the desired compound. Large effort was devoted to further development of the stepwise-approach technique advanced by Gryko and Piechota: condensation of preprepared dipyrromethane with aldehyde followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[10] The utilization of pyridine-substituted dipyrromethane **5**[11,12] and 4-pyridinecarboxaldehyde was not fruitful, but the combination of **5** with the very reactive pentafluorobenzaldehyde was. The bispyridyl corrole **4** was isolated in yields of 2.1–2.4%, accompanied by porphyrin **2**



Scheme 1. Positively charged porphyrins (left) and analogous corroles (right).



Scheme 2. Synthesis of the water-soluble manganese(III) corrole with two pyridinium groups.

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[**] This work was supported by the German Israel Cooperation (Z.G.) and by the Israel Science Foundation under Grants No. 254/04 (I.G.) and 330/04 (Z.G.).

(Scheme 1). Much better results were obtained by combining the stepwise approach with Adler–Longo conditions (Scheme 2): the heating of dipyrromethane **5** with pentafluorobenzaldehyde in propionic acid yielded 8% of corrole **4** without the aid of DDQ (relying on air as oxidant).[13] Encouraged by this result, the same procedure was also performed with 4-pyridinecarboxaldehyde; a 6% yield of the desired corrole **3** was obtained after separation from **1**.[14]

Manganese was inserted into the bispyridyl-substituted corrole and porphyrin derivatives **4** and **2**, respectively,[15] which were subsequently N-methylated to afford the water-soluble manganese(III) complexes $[(\mathbf{4}')Mn]^{2+}$ (Scheme 2) and $[(\mathbf{2}')Mn(Cl)]^{2+}$ (Scheme 1).[16] Crystallization of the bispyridinium-substituted derivative $[(\mathbf{4}')Mn]^{2+}$ from a diethyl ether/hexane/methanol mixture ($\approx$2:3:1) yielded crystals suitable for X-ray crystallography analysis.[17] It represents the first crystal structure determination of such a corrole; notably, only two structures of positively charged manganese porphyrins have been reported in the literature.[18,19]

The molecular structure of $[(\mathbf{4}')Mn]^{2+}$ in the respective crystal (Figure 1) is slightly domed in shape owing to an additional molecule of methanol (from the crystallization

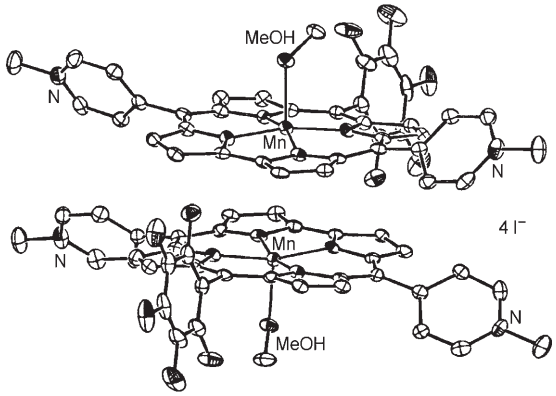


Figure 1. Molecular structure of $[(\mathbf{4}')Mn(MeOH]^{2+}\cdot 2I^-$. The thermal ellipsoids are shown at 50% probability.

solvent) that ligates axially to the central Mn^{III} ion at Mn···O(methanol) = 2.19 Å. The five-coordinate Mn^{III} ion deviates slightly from the mean plane of the inner pyrrole N atoms towards the axial ligand by 0.20–0.21 Å, and all equatorial Mn···N bonds are within 1.90–1.92 Å. This is characteristic of manganese(III) corrole complexes, whereas in analogous porphyrin complexes, these bond distances are considerably longer, 1.99–2.02 Å, owing to the larger size of the porphyrin macrocycle. Also noteworthy is that the $[(\mathbf{4}')Mn]^{2+}$ moieties form dimers in the crystal with relatively close contacts between the concave sides of the two species, which face one another (an entire dimer also comprises the asymmetric unit of the structure). Thus, the nonbonding distances between the nearly overlapping C atoms of the macrocyclic core in the two units are within 3.4–3.6 Å, and the distance between the corresponding Mn ion centers is 4.17 Å. This close interaction is associated with further significant "saddle"-type distortion of the corrole rings owing to the positively charged *N*-methyl pyridylium groups bending outward to minimize the repulsive interactions between them (Figure 1). The latter observation supports the notion that there is specific attraction between the two corrole complexes. The crystal structure of this material contains additional molecules of methanol and water solvent in the interface between these dimers, which hydrogen bond to the iodine counterions as well as to the axial ligands.

The corrole and porphyrin complexes with two pyridinium substituents, $[(\mathbf{4}')Mn]^{2+}$ and $[(\mathbf{2}')Mn(Cl)]^{2+}$, respectively, were investigated with respect to two important aspects: interaction with DNA and the catalytic decomposition of peroxynitrite. The method chosen for investigating the former aspect was induced circular dichroism (ICD), which is the most straightforward indication for noncovalent binding of such molecules to chiral hosts.[6] The ICD spectra of $[(\mathbf{4}')Mn]^{2+}$ and $[(\mathbf{2}')Mn(Cl)]^{2+}$ shown in Figure 2a,b provide

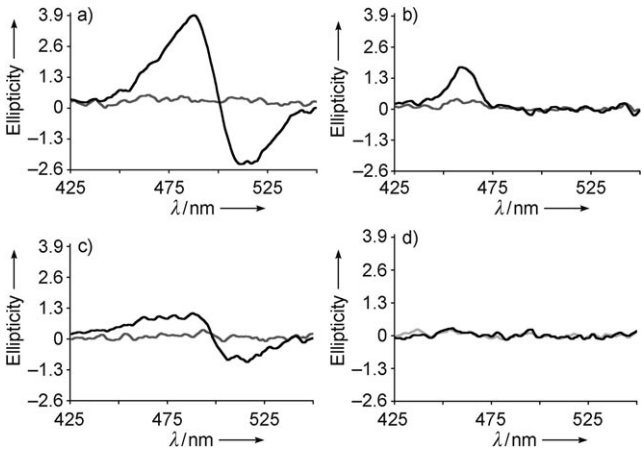


Figure 2. The visible CD spectra obtained before (gray line) and after (black line) addition of 27 μM calf-thymus DNA to 6 μM aqueous solutions of the manganese complexes at two ionic strengths (*I*). a) $[(\mathbf{4}')Mn]^{2+}$, $I = 0.01$ M; b) $[(\mathbf{2}')Mn(Cl)]^{2+}$, $I = 0.01$ M; c) $[(\mathbf{4}')Mn]^{2+}$, $I = 0.2$ M; d) $[(\mathbf{2}')Mn(Cl)]^{2+}$, $I = 0.2$ M. Note: Identical results were obtained at a 200:6 DNA/chromophore ratio.

clear-cut evidence for the chromophores residing within the chiral pocket provided by the macromolecule:[20] both DNA (no absorbance in the visible) and the chromophore (achiral) otherwise display no CD signals in that part of the spectrum (Figure 2, gray lines). The difference is that although the spectrum of $[(\mathbf{4}')Mn]^{2+}$ is composed of both negative and positive components (Figure 2a), that of the analogous porphyrin derivative $[(\mathbf{2}')Mn(Cl)]^{2+}$ displays only a positive CD band that is also of much lower ellipticity (Figure 2b). These phenomena may be analyzed with the aid of empirical rules that were developed regarding porphyrin binding modes to DNA: intercalation is characterized by a negative CD band, whereas a positive CD band is indicative of outside (groove) binding.[21,22] Assuming that the same rules hold for corroles as well, the results suggest that the corrole is capable of intercalation into DNA, whereas the analogous porphyrin is only capable of outside binding. This may be attributed to

differences in the coordination chemistry of the manganese(III) ion chelated by dianionic porphyrins and trianionic corroles. Four nitrogen atoms define the equatorial plane in both complexes, but a full charge balance exists in the latter case only. Manganese porphyrin complexese require at least one strongly bound axial ligand,[18,19] which is considered the main obstacle for intercalation.[21] On the other hand, the molecular structure of $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ reveals only one axially coordinated solvent molecule; four-coordinated manganese(III) corroles have been reported as well.[23] Accordingly, the probability of forming a four-coordinated manganese(III) complex, which is required for DNA intercalation, may safely be concluded to be much larger for corroles than for porphyrins. We further note that the earlier discussed intermolecular interactions evident in the solid-state structure of $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ hint at π-stacking interactions with DNA base pairs as an additional driving force for intercalation. The importance of this aspect will be addressed in future investigations with the metal-free derivatives.

Another difference is evident in the effect of ionic strength (I) on the ICD of the two complexes (Figure 2c,d): an increase in I from 0.01 to 0.2 M completely eliminated the signal for the porphyrin complex, whereas that of the corrole analogue only diminished in intensity (to about one third). Both the positive and the negative CD bands remained quite intense, suggesting that both intercalation (the negative band) and groove binding (the positive band) play an important role for $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ even at $I = 0.2$ M. High ionic strength may be expected to affect all binding modes of positively charged macrocycles to DNA owing to the competition of chromophore molecules and electrolyte cations for the negatively charged moieties on the DNA superstructure.[6] The larger ratio of [positive charges]/[molecular size] of the corrole (owing to the "missing" C_6F_5 group) could well be the reason for what appears as an overall larger affinity for DNA of the $[(\mathbf{4}')\mathrm{Mn}]^{2+}$ ion relative to the $[(\mathbf{2}')\mathrm{Mn(Cl)}]^{2+}$ ion.

The structurally related corrole and porphyrin manganese complexes were also investigated as catalysts for decomposition of peroxynitrite (HOONO),[7,24] a cytotoxic agent that allegedly plays a major role in many pathological conditions.[25–29] HOONO, produced by the combination of nitric oxide and the superoxide anion, decomposes at physiological pH values by two distinct pathways (Scheme 3): isomerization to nitrate (route a) and homolytic bond cleavage (route b) into the most-reactive oxygen and nitrogen species $^{\bullet}OH$ and $^{\bullet}NO_2$.[30] The urgent need to develop synthetic catalysts as a means for protecting cells and tissues from peroxynitrite formed in situ is highlighted by the absence of a specific enzyme capable of transforming it into biologically benign products. We have recently demonstrated that manganese and iron complexes of negatively charged corroles are potent catalysts for that purpose.[31] The former was identified as the first manganese complex displaying catalytic activity without the aid of sacrificial agents and it did so by a genuine disproportionation process forming only NO_2^- and O_2 (Scheme 3, route c). One limitation is that the catalytic rate ($k_{cat} = 4.0 \times 10^4\ \mathrm{M^{-1}s^{-1}}$ at 25 °C) is quite close to that of the oxidation of biological targets by peroxynitrite (10^3–$10^4\ \mathrm{M^{-1}s^{-1}}$)[29b] and is significantly slower than that obtained by the combination of manganese(III) porphyrins and reducing agents.[32–34] Our motivation for examining the new compounds relied on literature data that showed that metal complexes of positively charged porphyrins are faster-performing catalysts than negatively charged analogues.[34]

The rate constants for decomposition of peroxynitrite at pH 7.4 and 25 °C were determined with and without the presence of the potential catalyst by following the decay of 385 μM peroxynitrite at its characteristic λ_{max} (302 nm) by using a stopped-flow spectrophotometer.[36] Importantly, the iodide counterions in the complexes were first exchanged by

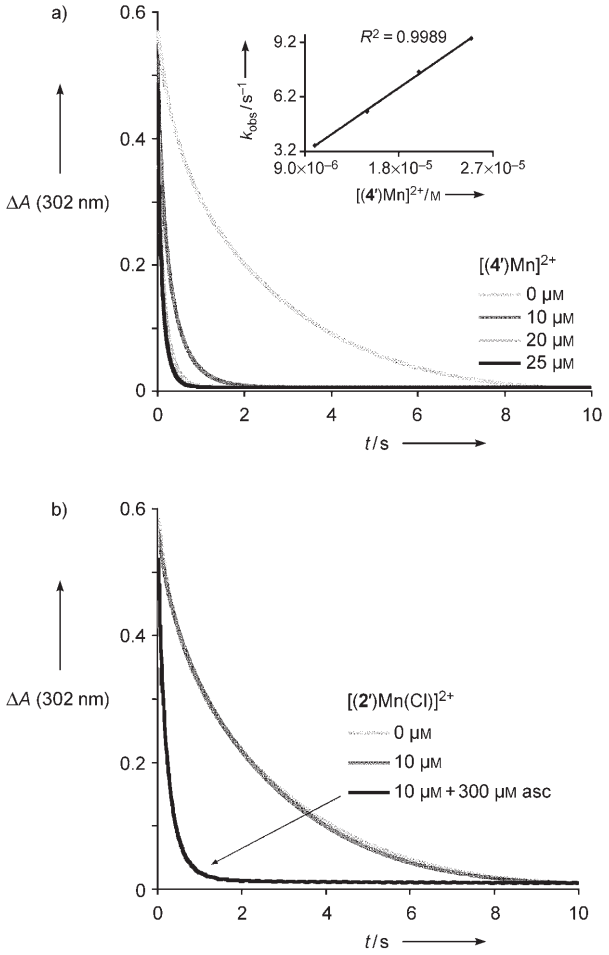
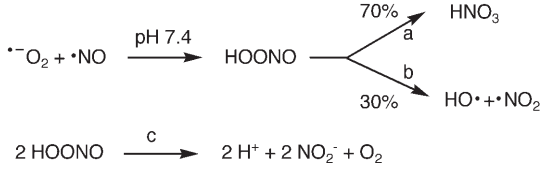


Figure 3. a) Decomposition of 385 μM peroxynitrite at pH 7.4 and 25 °C monitored at $\lambda = 302$ nm as a function of the concentration of $[(\mathbf{4}')\mathrm{Mn}]^{2+}$. Inset: Plot used for determination of the catalytic rate constant. b) The same experiments with catalytic amounts of $[(\mathbf{2}')\mathrm{Mn(Cl)}]^{2+}$, with and without 300 μM ascorbate (asc).



Scheme 3. Spontaneous (a and b) and desired (c) pathways for decomposition of peroxynitrite.

chlorides to eliminate possible reduction of peroxynitrite by the former ions.[35]

The results uncovered large differences between the two complexes: the $[(\mathbf{4}')Mn]^{2+}$ ion displayed the characteristics of a true catalyst (Figure 3a), but the $[(\mathbf{2}')Mn(Cl)]^{2+}$ ion had absolutely no effect on peroxynitrite unless used in combination with ascorbate as a coreductant (Figure 3b). A catalytic rate constant of $4.0\times10^5\,M^{-1}s^{-1}$ for decomposition of peroxynitrite by $[(\mathbf{4}')Mn]^{2+}$ was elucidated from the linear relationship shown in the inset of Figure 3a; one order of magnitude larger than that of negatively charged manganese corrole.[31] What is more, it is as large as the one we obtained for $[(\mathbf{2}')Mn(Cl)]^{2+}$ ($k_{cat}=4.3\times10^5\,M^{-1}s^{-1}$) in the presence of ascorbate. Without a sacrificial agent, this derivative (similar to all other non-corrole manganese complexes) displayed no catalytic activity.

We report the synthesis and molecular structure of a novel positively charged water-soluble manganese(III) corrole as well as its utilization for DNA binding and for catalyzing peroxynitrite decomposition. Relying on the characteristics that were developed for CD analysis of porphyrin/DNA binding, we conclude that the interaction of the manganese corrole with DNA is strong enough to be observed even at high ionic strengths with the possibility of intercalation into DNA. Both phenomena are unique and not observed for the analogous porphyrin. The positively charged $[(\mathbf{4}')Mn]^{2+}$ complex also appears to be a ten-times-faster catalyst for decomposition of peroxynitrite than a negatively charged manganese corrole: it actually reacts with peroxynitrite as fast as ascorbate-aided manganese porphyrin and faster than biological targets. Taken together, positively charged corroles may be very useful for therapeutic approaches that rely on specific interactions with DNA and as decomposition catalysts of reactive oxygen and nitrogen species (the manganese or other transition metal complexes).

Received: February 19, 2007
Published online: May 4, 2007

Keywords: corroles · DNA · manganese · peroxynitrite · porphyrinoids · structure elucidation

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[12] Synthesis of **5**: The required dipyrromethane (1.03 g) was prepared as in Ref. 15 (yield = 49%), but purified by two chromatographic treatments (alumina, dichloromethane/ethyl acetate 5:1, followed by silica gel, dichloromethane/ethyl acetate 10:0→10:1).

[13] Synthesis of **4**: Pentafluorobenzaldehyde (50 μL, 0,4 mmol) was added to a 10-mL solution of **5** (178 mg, 0.8 mmol) in propionic acid and the mixture was heated to reflux for 50 min. The residue obtained after solvent evaporation was washed with hot water, neutralized with ammonium hydroxide (25%), and washed again with hot water. The solid material was dissolved in methanol, basic alumina was added, and the solvent was evaporated. Separation between **4** and the analogous porphyrin **2** was achieved by column chromatography (silica, CH_2Cl_2 followed by 0.5% methanol) followed by separation by preparative thin-layer chromatography (silica plate, $CHCl_3$/MeOH 50:1) affording pure **4** (18 mg, 8%). **4**: $R_f=0.15$ (CH_2Cl_2/ethyl acetate 1:1). UV/Vis (CH_2Cl_2/MeOH (2:1)): λ_{max} ($\varepsilon10^{-3}$) = 416 (104.99), 576 (16.14), 610 (9.40), 640 (5.34). MS (MALDI-TOF): *m/z* (%): 619 (100) [M^+]. ^{1}H NMR (200 MHz, C_6D_6): $\delta=8.93$ (br s, 4H), 8.67 (d, $J=4$ Hz, 4H), 8.26 (m, 4H), 7.90 ppm (br. s, 4H). ^{19}F (188 MHz): $\delta=-138.79$ (d, $J=23.5$ Hz, 2F), −153.22 (t, $J=21.9$ Hz, 1F), −162.37 ppm (t, $J=22.5$ Hz, 1F). **2:** $R_f=0.37$ (CH_2Cl_2/ethyl acetate 1:1). UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon10^{-3}$) = 414 (233.34), 510 (15.51), 542 (3.17), 586 (4.69). MS (MALDI-TOF LD$^+$): *m/z* (%): 796 (100) [M^+]. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=9.05$ (d, $J=5.2$ Hz, 4H), 8.87 (m, 8H), 8.15 (d, $J=5.4$ Hz, 4H), −2.94 ppm (s, 2H). ^{19}F (188 MHz): $\delta=-137.22$ (dd, $^3J=23.3$ Hz, $^4J=7.9$ Hz, 4F), 151.96 (t, $J=20.9$ Hz, 2F), −161.88 ppm (td, $^3J=22.6$ Hz, $^4J=8.3$ Hz, 4F).

[14] **3**: 4-Pyridinecarboxaldehyde (38 μL, 0.40 mmol) was added to a 10-mL solution of **5** (178 mg, 0.8 mmol) in propionic acid, and the mixture was heated at reflux for 70 min. The residue obtained after solvent evaporation was washed with hot water, neutralized with ammonium hydroxide (25% ammonia), and washed again with hot water. The solid material was dissolved in methanol, basic alumina was added, and the solvent was evaporated. Separation of **3** was achieved by column chromatography (silica, CH_2Cl_2 followed by 0.5% methanol) followed by separation on PTLC (silica plate, $CHCl_3$/MeOH 100:1). The faster eluting fraction was comprised of the brownish red porphyrin (**1**) and the next slightly fluorescent dark-green-colored fraction afforded the desired corrole **3** (6%, 12 mg). Alternatively, good chromatographic separation could be achieved by eluting with ethyl acetate to which methanol was gradually added. $R_f=0.73$ (CH_2Cl_2/MeOH 5:1). UV/Vis (CH_2Cl_2): λ_{max} ($\varepsilon10^{-3}$) = 418 (61.15), 576 (9.85), 614 (5.62); MS (MALDI-TOF LD$^+$): *m/z* (%): 530 (100) [*M*+H]. ^{1}H NMR (300 MHz), (C_6D_6): $\delta=7.87$ (d, $J=5.1$ Hz, 2H), 7.99 (d, $J=5.1$ Hz, 4H), 8.35 (d, $J=4.8$ Hz, 2H), 8.43 (d, $J=4.2$ Hz, 2H),

8.66 (d, $J = 4.8$ Hz, 2H), 8.78 (d, $J = 4.2$ Hz, 2H), 9.02 ppm (br s, 6H).

[15] Manganese insertion: **2**-Mn and **4**-Mn were prepared by heating the porphyrin/corrole pyridine solution at reflux with 15 equivalents of $Mn(OAc)_2 \cdot 4H_2O$ followed by chromatographic separation (silica, starting with CH_2Cl_2 and gradually adding methanol), affording 92%, and 81% yield, respectively. **2**-Mn: UV/Vis (MeOH): λ_{max} ($\varepsilon 10^{-3}$) = 328 (12.6), 370 (22.5), 392 (19.5), 458 (49.7), 554 (5.2), 766 (0.84). MS (MALDI-TOF LD$^+$): m/z (%): 849 (100) [M^+]. ^{19}F (MeOD) (188 MHz): $\delta = -134.49$ (br s, 4F), -148.20 (s, 2F), -157.08 ppm (s, 4F). **4**-Mn: UV/Vis (MeOH): λ_{max} ($\varepsilon 10^{-3}$) = 368 (16.7), 402 (26.7), 420 (4.8), 458 (18.4), 484 (16.2), 634 (9.4). MS (MALDI-TOF LD$^+$): m/z (%): 670 (100) [M^+]. ^{19}F (C_5D_4N) (188 MHz): $\delta = -136.58$ (br s, 2F), -155.16 (s, 1F), -161.23 ppm (s, 2F)

[16] N-methylation: **2**-Mn and **4**-Mn were dissolved in hot THF and excess methyl iodide was added to the solutions, which were then left at 40 °C until complete precipitation. The solid material was collected by centrifugation and washed with THF and diethyl ether until the solvent was colorless. [(**2′**)Mn(X)]$^{2+}$: UV/Vis (phosphate buffer solution; pH 6.8): λ_{max} ($\varepsilon 10^{-3}$) = 372 (22.4), 394 (19.7), 460 (56.4), 558 (5.7). MS (MALDI-TOF LD$^+$) m/z (%): 879 (10) [M^+], 864 (100) [$M-15$], 849 (50) [$M-30$]. ^{19}F (MeOD) (188 MHz): $\delta = -137.87$ (br s, 4F), -151.28 (s, 2F), -160.04 ppm (s, 4F). [(**4′**)Mn]$^{2+}$: UV/Vis (KH_2PO_4 0.3 M, pH 6.8): λ_{max} ($\varepsilon 10^{-3}$) = 488 (49.4), 556 (8.4), 598 (10.3), 660 (15.9); MS (MALDI-TOF LD$^+$): m/z (%): 700 (10) [M^+], 685 (100) [$M-15$]. ESI (CH_3CN/H_2O, 70/30) m/z (%): 685 (40) [M^+-15], 370.5 (85) [$M^+ + CH_3CN$]/2, 350.0 (100) [M^+]/2. ^{19}F (MeOD) (188 MHz): $\delta = -129.08$ (br s, 2F), -152.51 (s, 1F), -158.68 ppm (s, 2F). The product was crystallized by slow diffusion of an *n*-hexane/diethyl ether mixture into concentrated methanol solution.

[17] [(**4′**)Mn]$^{2+}$ was crystallized as a methanol and water solvate. Crystal data: $2(C_{37}H_{22}F_5MnN_6)^{2+} \cdot 4I^- \cdot 5CH_4O \cdot H_2O$, M = 2086.92, triclinic, space group $P\bar{1}$, $a = 16.1423(4)$, $b = 16.5311(4)$, $c = 16.6329(5)$ Å, $\alpha = 115.329(1)$, $\beta = 90.631(1)$, $\gamma = 94.626(1)°$, $V = 3993.6(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.735$ g cm^{-3}, 45552 reflections measured, 15503 unique ($R_{int} = 0.061$, $2\theta_{max} = 52.0°$), final R = 0.069 ($wR = 0.177$) for 10085 reflections with $I > 2\sigma(I)$ and R = 0.112 ($wR = 0.203$) for all data. CCDC-634668 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[20] Stock solutions were prepared by dissolving calf-thymus DNA (1 mg, Sigma Aldrich) in 1 mL of doubly distilled water and were left overnight at 4 °C. Experiments were carried out at 24 °C and pH 6.8 (5 mM NaH_2PO_4, 2.5 mM Na_2HPO_4, and either 0.01 M or 0.2 M NaCl); DNA concentrations were calculated by using $\varepsilon^{262nm} = 1.32 \times 10^4$ M^{-1} cm^1.[21]

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[35] [(**2′**)Mn(X)]$^{2+}$ and [(**4′**)Mn]$^{2+}$ were dissolved in 10 mL of water (aided by 1 mL of methanol for the latter), 1.5 g of freshly HCl-regenerated ion-exchange resin (Dowex 1:8 chloride form) was added and the vessels were slowly shaken over night. The resin was filtrated and the solvent was lyophilized

[36] Peroxynitrite was prepared according to published procedures,[33] and the experimental procedures were identical to those reported in Ref. [31].

