with H_2O (2×75 mL). The organic phase was dried ($MgSO_4$) and solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, CH_2Cl_2, 2% MeOH) gave the desired product (0.41 g, 27%) as a pale green powder, m.p. 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.84$ (t, 4H, OCH_2), 4.24 (t, 4H, OCH_2), 4.74 (s, 4H, CH_2), 7.36–7.41 (m, 10H, ArH), 7.95 (d, 4H, ArH), 8.17 (m, 4H, ArH), 8.28 (d, 4H, ArH), 8.63 (dd, 2H, ArH), FAB-MS calcd for $C_{44}H_{36}N_2O_4$: 657.2753 [M+H$^+$]; found: 657.2781. Compounds **2** and **5** were prepared and characterized by similar methods.

Mercury complexes: The $HgCl_2$ complexes of **1**, **2**, and **5** were prepared by a slight adaptation of a literature method.[5a] Complexation at the bipy unit was evidenced by shifts of the resonances corresponding to the bipy protons in the NMR spectra in $CDCl_3$ and CD_3CN.[5a]

Photochemical studies: Photocycloaddition reactions were carried out using a Xenon lamp (see Table 1 for conditions). The ^{1}H NMR spectra of **3** and **4** in CD_3CN revealed no ethylenic proton resonances, and in the case of **3** a clear singlet peak at 4.51 ppm (2H) was evident, which indicated the formation of the 9,9′–10,10′ photoproducts. The quantum yields of fluorescence of **1** and **2** in MeCN were largely unaffected by the presence of Group 1 cations and Hg^{II}, with only Na^+ ions inducing any enhancement when bound to ligand **2** and its $HgCl_2$ complex (**1**, $\Phi_F = 0.04$, **1**+Na^+, $\Phi_F = 0.03$, **2**, $\Phi_F = 0.05$, **2**+Na^+, $\Phi_F = 0.10$).

Received: January 31, 2000 [Z14624]

[1] a) *Photochromism—Molecules and Systems* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **1990**; b) *Organic Photochromic and Thermochromic Compounds*, *Vol. 2* (Eds: J. C. Crano, R. J. Guglielmetti), Kluwer Academic/Plenum, New York, **1999**.

[2] a) J. M. Lehn, *Supramolecular Chemistry—Concepts and Perspectives*, VCH, Weinheim, **1995**; b) A. P. de Silva, I. M. Dixon, H. Q. N. Gunaratne, T. Gunnlaugsson, P. R. S. Maxwell, T. E. Rice, *J. Am. Chem. Soc.* **1999**, *121*, 1393, and references therein; c) M. Asakawa, P. R. Ashton, V. Balzani, A. Credi, G. Mattersteig, O. A. Matthews, M. Montalti, N. Spencer, J. F. Stoddart, M. Venturi, *Chem. Eur. J.* **1997**, *3*, 1992, and references therein; d) T. Gunnlaugsson, D. A. Mac Dónail, D. Parker, *Chem. Commun.* **2000**, 93, and references therein; e) F. Pina, M. Maestri, V. Balzani, *Chem. Commun.* **1999**, 107, and references therein; f) M. Inouye, K. Akamatsu, H. Nakazumi, *J. Am. Chem. Soc.* **1997**, *119*, 9160.

[3] a) J. H. R. Tucker, H. Bouas-Laurent, P. Marsau, S. W. Riley, J. P. Desvergne, *Chem. Commun.* **1997**, 1165; b) D. Marquis, J. P. Desvergne, H. Bouas-Laurent, *J. Org. Chem*. **1995**, *60*, 7984; c) J. P. Desvergne, H. Bouas-Laurent, *J. Chem. Soc. Chem. Commun.* **1978**, 403.

[4] a) G. Deng, T. Sakaki, K. Nakashima, S. Shinkai, *Chem. Lett.* **1992**, 1287; b) A. Beyeler, P. Belser, L. De Cola, *Angew. Chem.* **1997**, *109*, 2878; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 2779.

[5] a) J. Rebek Jr., J. E. Trend, R. V. Wattley, S. Chakravorti, *J. Am. Chem. Soc.* **1979**, *101*, 4333; b) P. D. Beer, A. S. Rothin, *J. Chem. Soc. Chem. Commun*. **1988**, 52.

[6] For clarity, the photoproducts are depicted in a planar cisoid conformation.

[7] K. T. Potts, K. A. Gheyson Raiford, M. Keshavarz-K, *J. Am. Chem. Soc.* **1993**, *115*, 2793.

[8] For examples of photochromic logic devices in which one input is light and the output is absorbance or fluorescence, see references [2e] and [2f].

[9] J. P. Desvergne, M. Gotta, J. C. Soulignac, H. Bouas-Laurent, *Tetrahedron Lett*. **1995**, *36*, 1259.

Evidence for Cooperativity in the Disproportionation of H_2O_2 Efficiently Catalyzed by a Tetranuclear Manganese Complex**

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Dedicated to Professor Stephen J. Lippard on the occasion of his 60th birthday

Intracellular hydrogen peroxide produced during O_2 metabolism in cells is an indiscriminate oxidizer of cellular components and its toxicity has been associated with oxidative stress,[1] cancer,[2] and aging.[3, 4] Disproportionation of intracellular hydrogen peroxide [Eq. (1)] by catalase provides a vital biological defense against this toxic oxygen metabolite.[5]

$$2\,H_2O_2 \longrightarrow O_2 + 2\,H_2O \qquad (1)$$

In addition to intracellular sources, the photochemical generation of hydrogen peroxide is well established.[6] Furthermore, in light of the possible health risks associated with halogenated byproducts produced by chlorination,[7, 8] the industrial consumption of hydrogen peroxide is expected to increase as it replaces chlorine as a bleaching and sterilizing agent.[9] It has been proposed that the residual hydrogen peroxide used in industrial processes can be decomposed before disposal through the application of transition metal complexes or catalases.[10]

Due to the toxicity of hydrogen peroxide and its pervasiveness in biological and industrial settings, the structure and function of catalases and catalase mimics is of considerable interest. While the majority of catalases contain a heme cofactor,[11] a number of nonheme catalases require manganese as a cofactor.[11–13] The synthesis, characterization, and reactivity studies of polynuclear manganese model systems have contributed significantly to our understanding of the structure and function of manganese catalases.[14–27] We have an ongoing effort in the synthesis and isolation of well defined, oxo-bridged multinuclear manganese species and we report herein that the adamantane-shaped mixed-valence

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[**] We thank the U.S. National Institutes of Health (GM38275) for financial support of this research.

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$Mn^{III}(Mn^{IV})_3$ complex $[Mn_4O_6(bpea)_4]^{3+}$ [28] (**1**; bpea = *N*,*N*-bis(2-pyridylmethyl)ethylamine) is an extremely efficient H_2O_2 disproportionation catalyst in the presence of the base $Me_3(tacn)$ ($Me_3(tacn)$ = 1,4,7-trimethyl-1,4,7-triazacyclononane; aqueous $pK_a = 11.7$), with the highest catalytic constant, k_{cat}, reported to date for any synthetic manganese complex. A base-mediated switch from Michaelis–Menten kinetics to cooperative kinetics also distinguishes the oxygen evolution promoted by **1**. The data presented herein for complex **1** reveal a novel biomimetic catalytic system exhibiting cooperative behavior.[29–35]

The kinetics of oxygen evolution from the disproportionation of H_2O_2 was studied by a video recording the displacement of mineral oil in a gas buret. Treatment of an acetonitrile solution of $\mathbf{1}\cdot 3ClO_4$[28] (bulk electrolysis, 0.228 mM)[36, 37] with an excess of aqueous H_2O_2 (100 mM) immediately evolved O_2. The total volume of O_2 evolved (2.37 mL, 97.7 μmol) was consistent with disproportionation of H_2O_2 at an initial rate $v_0 = -d[H_2O_2]/dt = 0.57$ mM s^{-1}. Isotope-labeling studies ($H_2{}^{18}O_2$[38]) monitored by GC/MS showed peaks at *m*/*z* 32 and 36 in a 7:93 ratio and no *m*/*z* 34 (O_2) was observed. Together, these results indicate that both oxygen atoms of evolved O_2 originate from the same H_2O_2 molecule.

Initial rate data determined for a range of H_2O_2 concentrations (0.010–0.33 M) and $\mathbf{1}\cdot 3ClO_4$ (method B,[36] $Me_3(tacn) = 3.2\times10^{-5}$–$3.2\times10^{-3}$ M) show, at low concentrations of H_2O_2, that the rate of disproportionation is first order in both tetranuclear complex and H_2O_2 concentration; rate = $k[\mathbf{1}][H_2O_2]$, with an average rate constant k of 114 ± 14 M^{-1} s^{-1}. Complex **1** exhibits saturation kinetics (Figure 1).[39]

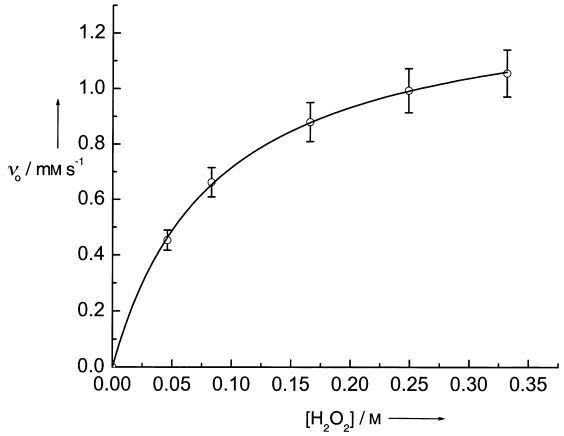


Figure 1. H_2O_2 saturation kinetics for $\mathbf{1}\cdot 3ClO_4$ (0.105 mM, $Me_3(tacn)$ reduction) showing a fit of the Michaelis–Menten equation with K_m = 0.087 M and $V_{max} = 1.34 \pm 0.11$ mM s^{-1}.

These data can be described by the Michaelis–Menten equation [Eq. (2)], where S is the substrate concentration, K_m is the substrate binding constant, and V_{max} is the maximum rate of the reaction.

$$\frac{v_0}{V_{max}} = \frac{S}{K_m + S} \qquad (2)$$

Nonlinear least-squares fitting of the data in Figure 1 to Equation (2) gave $K_m = 0.087$ M and $V_{max} = 1.34 \pm 0.11$ mM s^{-1} with a value of $k_{cat} = 11.1 \pm 0.9$ s^{-1}.[40] For comparison, kinetic measurements of the manganese catalase from *Lactobacillus plantarum*, modeled using Michaelis–Menten kinetics, gave $K_m = 0.35$ M and $k_{cat} = 2.0\times10^5$ s^{-1}.[11]

In contrast to the activity of **1**, solutions of the $(Mn^{IV})_4$ complex $\mathbf{2}\cdot 4ClO_4$ were only slightly active. Addition of hydrogen peroxide (0.234 M) to an acetonitrile solution of $\mathbf{2}\cdot 4ClO_4$ (0.265 mM) exhibited an initial rate $v_0 = 1.6$ μM s^{-1}, in contrast to $v_0 = 1.15$ mM s^{-1} for **1** ($Me_3(tacn)$ reduction)[36] under the same conditions. On the other hand, we observed a substantially faster rate (83.7 mM s^{-1}) for $\mathbf{1}\cdot 3ClO_4$ prepared from $\mathbf{2}\cdot 4ClO_4$ using a large excess (4.8 equivalents) of $Me_3(tacn)$.[36] A number of manganese–oxo complexes were previously shown to exhibit significant rate enhancement for the disproportionation of hydrogen peroxide in the presence of exogenous base.[17, 18, 26, 27, 41–44] It was proposed that at least a part of this effect was the base-facilitated deprotonation of H_2O_2 in the course of the coordination of hydroperoxide to the metal complex.

Substrate conversion rates were determined for several concentrations of $\mathbf{1}\cdot 3ClO_4$ and $Me_3(tacn)$ and these results are shown in Figure 2. We propose that the sigmoidal shape of the O_2 evolution rate versus the number of base equivalents of

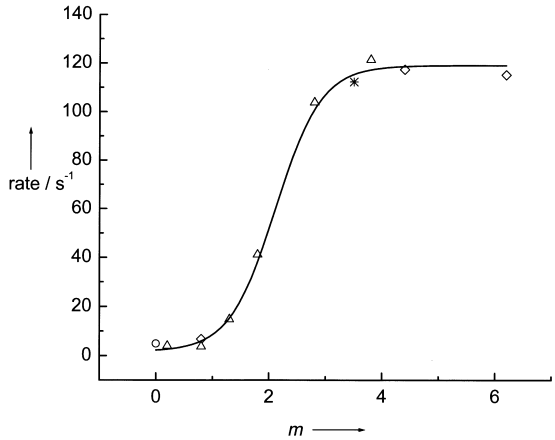


Figure 2. A composite of substrate conversion rate versus the number of base equivalents (*m*) of $Me_3(tacn)$.[45] Experimental conditions: 100 mM H_2O_2 and $\mathbf{1}\cdot 3ClO_4$ [○: **1** = 0.228 mM, bulk electrolysis; ∗: **1** = 0.096 mM, $Me_3(tacn)$ reduction; ◇: **1** = 0.105 mM, $Me_3(tacn)$ reduction; △: **1** = 0.245 mM, $Me_3(tacn)$ reduction]. The curve is a nonlinear least-squares fit of a Boltzman function to all of the data.

$Me_3(tacn)$[45] is consistent with a base-activated switch in the mechanism of hydrogen peroxide disproportionation. Additional experimental evidence of such a switch is revealed by the saturation kinetics of **1** in the presence of excess base (Figure 3).[39] These data reveal a dramatic deviation from the Michaelis–Menten kinetics observed for **1** with little or no excess base (Figure 1). The sigmoidal shape of the substrate conversion profile at this higher base concentration is indicative of cooperativity in the disproportionation reaction (vide infra).[46–48] These data can be described with the Hill equation [Eq. (3)], where n is the Hill coefficient.[49]

$$\frac{v_0}{V_{max}} = \frac{S^n}{K_m{}^n + S^n} \qquad (3)$$

  0570-0833/00/3912-2170 $ 17.50+.50/0

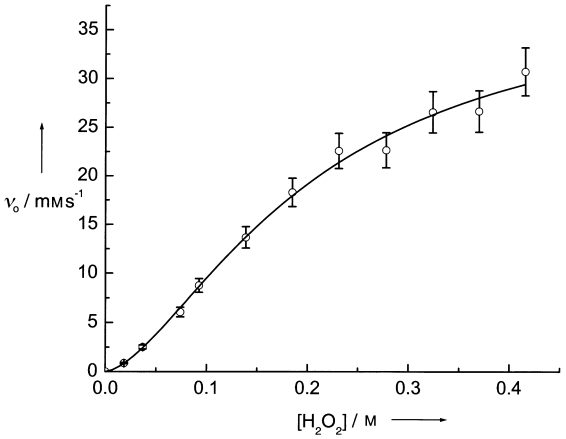
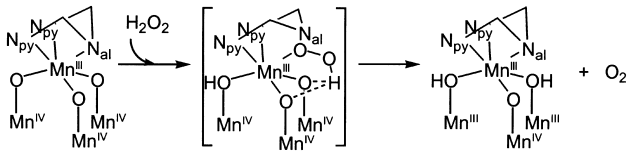


Figure 3. H_2O_2 saturation kinetics for $\mathbf{1}\cdot 3ClO_4$ (0.096 mM, Me_3(tacn) reduction, 4.2 equiv) showing the fit of the Hill equation [Eq. (3)].

A least-squares fit of the data in Figure 3 with Equation (3) gave $V_{max} = 38.9 \pm 3.1$ mM s^{-1}, $K_m = 0.204$ M, and $n = 1.58$, with a value of $k_{cat} = 405$ s^{-1}. It is noteworthy that the crossover from an efficient, yet unremarkable, catalytic system exhibiting Michaelis–Menten kinetics to an extremely efficient one exhibiting cooperative kinetics renders a catalyst which has the highest k_{cat} reported for any synthetic manganese complex to date.[14–22] Substitution of $n = 1$ in Equation (3) reduces the Hill equation to the Michaelis–Menten equation [Eq. (2)] and values of $n > 1$ indicates the extent of cooperativity.[46–48] By comparison, data for hydrogen peroxide disproportionation with only a slight excess Me_3(tacn) (Figure 1) which were fit with the Michaelis–Menten equation fits equally well with the Hill equation with $n = 1.03$.

We propose that the observed cooperativity in the disproportionation of hydrogen peroxide by **1** at the higher base concentrations originates in cooperative binding or cooperative kinetics. A plausible initial reaction of **1** with H_2O_2 and one that is consistent with our previous studies (vide infra) is illustrated in Scheme 1.[50] Reaction of **1** with H_2O_2 most likely



Scheme 1. Initial reaction of **1** with H_2O_2. For the polydentate, Mn^{III}-coordinated bpea ligand, N_{py} and N_{al} represent the nitrogen atoms of the pyridyl and ethylamine moieties, respectively.

occurs via coordination of hydroperoxide to the more labile Mn^{III} site. The enhanced lability of **1** at the Mn^{III} site arises from elongation along the Mn^{III}-N_{al}-O_{oxo} axis due to Jahn–Teller distortion of the d_3 Mn^{III} center.[28] Lability of the amine nitrogen atom and flexibility of the bpea ligand at the Mn^{III} site of the dimeric complex $[Mn_2O_2(OAc)(bpea)_2](ClO_4)_2$ (**3**) has previously been proposed as a basis for the its reactivity with water or the hydroxide ion.[51] Similar distortion of the Mn^{III} site of **1** could facilitate attack by H_2O_2.

The oxo bridges of **1** are nucleophilic, as demonstrated by the enhanced oxo-bridge basicity of **1** by approximately 17 pK_a units following one-electron reduction of **2** and by the observation that **2** readily undergoes coupled e^-/H^+ and $e^-/2H^+$ processes.[28] Hence, the reaction of **1** with H_2O_2 could lead to oxidation to yield O_2 and a $(Mn^{III})_3(Mn^{IV})$ tetramer (**3**; Scheme 1) in a net $2e^-/2H^+$ process. The $(Mn^{III})_3(Mn^{IV})$ tetramer could subsequently bind a second equivalent of hydroperoxide followed by reduction of H_2O_2 and restoration of **1** (Scheme 1).

The rate of H_2O_2 disproportionation in our studies was significantly affected by addition of the strong base Me_3(tacn). In control experiments, however, we observed that addition of Me_3(tacn) to H_2O_2 in acetonitrile in the absence of **1** resulted in only a very slow disproportionation of H_2O_2. Slow base-catalyzed disproportionation of H_2O_2 in the absence of a transition metal complex is similar to that reported by others.[52, 53] It is possible that a part of the effect of Me_3(tacn) in the present system could be base-facilitated deprotonation of H_2O_2, similar to the effect noted above for other catalytic manganese systems. The striking difference in our system, however, is the sigmoidal behavior of rate with increasing base concentration, which leads to catalytic cooperativity.

The catalytic cooperativity observed in the present system could be due to either cooperative binding of hydroperoxide or cooperative kinetics of disproportionation. A two-electron reduction of the $\{Mn_4O_6\}^{3+}$ core of **1** leads to two additional Mn^{III} ions (**3**; Scheme 1). Reduction of Mn^{IV} to Mn^{III} leads to elongation of both the Mn–N bonds[54] as well as along the Jahn–Teller axis. In the absence of excess base, the proposed final step in H_2O_2 disproportionation involves H_2O_2 reduction and oxidation of the core to **1**. This step must be accompanied by contraction of the Mn–N bonds as well as the Jahn–Teller axis. We propose that the higher Me_3(tacn) concentration could favor binding of two hydroperoxide ions in the $(Mn^{III})_3(Mn^{IV})$ oxidation states and the possibility of a subsequent concerted reduction and oxidation of hydrogen peroxide. In this proposal, the kinetically cooperative disproportionation cycle maintains the $(Mn^{III})_3(Mn^{IV})$ oxidation state throughout and thus avoids the energetic hurdles associated with expansion and contraction of the $\{Mn_4O_6\}$ core.

In conclusion, we have shown that one-electron reduction of the tetranuclear complex **2**, which exhibits very little reactivity toward H_2O_2, leads to the more catalytically active complex **1**. The sigmoidal dependence of the disproportionation rate for **1** on Me_3(tacn) concentration is consistent with a base-mediated mechanism such as the one proposed. Addition of the Me_3(tacn) promotes crossover from a system exhibiting Michaelis–Menten kinetics to a catalytically cooperative kinetic system, to render a greatly more efficient catalyst. This proposal also incorporates the principal feature that we feel makes **1** catalytically active while **2** is relatively inert: a labile Mn^{III} site for the initial binding of hydroperoxo anion.

Received: January 13, 2000 [Z14536]

[1] H. Sies in *Oxidative Stress, Oxidants, and Antioxidants* (Ed.: H. Sies), Academic Press, London, **1991**, pp. xv – xxii.
[2] B. Halliwell, J. M. C. Gutteridge in *Methods in Enzymology, Vol. 186* (Eds.: L. Packer, A. N. Glazer), Academic Press, San Diego, **1990**, pp. 1 – 85.
[3] S. J. Stohs, *J. Basic Clin. Physiol. Pharmacol.* **1995**, *6*, 205 – 228.
[4] V. Usmar-Darley, B. Halliwell, *Pharm. Res.* **1996**, *13*, 649 – 662.
[5] W. F. Beyer, Jr., I. Fridovich in *Basic Life Sciences, Vol. 49* (Ed.: M. G. Simic), Plenum, New York, **1988**, pp. 651 – 661.
[6] W. J. Cooper, E. S. Saltzman, R. G. Zika, *J. Geophys. Res.* **1987**, *92*, 2970 – 2980.
[7] G. A. Boorman, V. Dellarco, J. K. Dunnick, R. E. Chapin, S. Hunter, F. Hauchman, H. Gardner, M. Cox, R. C. Sills, *Environ. Health Perspect.* **1999**, *107*, 207 – 217.
[8] Chlorination agents include elemental chlorine, sodium hypochlorite, sodium chlorate, and sodium chlorite.
[9] M. McCoy, *Chem. Eng. News* **1999**, *77*, 18 – 19.
[10] P. Dhaese, *Chem. Today* **1996**, Jan./Feb., 19 – 21.
[11] J. E. Penner-Hahn in *Manganese Redox Enzymes* (Ed.: V. L. Pecoraro), VCH, New York, **1992**, pp. 29 – 45.
[12] J. E. Penner-Hahn in *Comprehensive Biological Catalysis, Vol. III* (Ed.: M. Sinnott), Academic Press, San Diego, **1998**, pp. 439 – 459.
[13] G. C. Dismukes, *Chem. Rev.* **1996**, *96*, 2909 – 2926.
[14] P. J. Pessiki, G. C. Dismukes, *J. Am. Chem. Soc.* **1994**, *116*, 898 – 903.
[15] A. Gelasco, V. L. Pecoraro, *J. Am. Chem. Soc.* **1993**, *115*, 7928 – 7929.
[16] T. Tanase, S. J. Lippard, *Inorg. Chem.* **1995**, *34*, 4682 – 4690.
[17] M.-a. Sasayama, Y. Naruta, *Chem. Lett.* **1995**, 63 – 64.
[18] Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1991**, *113*, 3595 – 3596.
[19] M. Delroisse, A. Rabion, F. Chardac, D. Tétard, J.-B. Verlhac, L. Fraisse, J.-L. Séris, *J. Chem. Soc. Chem. Commun.* **1995**, 949 – 950.
[20] P. Mathur, M. Crowder, G. C. Dismukes, *J. Am. Chem. Soc.* **1987**, *109*, 5227 – 5233.
[21] R. T. Stibrany, S. M. Gorun, *Angew. Chem.* **1990**, *102*, 1195 – 1197; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1156 – 1158.
[22] A. Gelasco, A. Askenas, V. L. Pecoraro, *Inorg. Chem.* **1996**, *35*, 1419 – 1420.
[23] Y. Naruta, M.-a. Sasayama, K. Ichihara, *J. Mol. Catal. A* **1997**, *117*, 115 – 121.
[24] T. C. Brunold, D. R. Gamelin, T. L. Stemmler, S. K. Mandal, W. H. Armstrong, J. E. Penner-Hahn, E. I. Solomon, *J. Am. Chem. Soc.* **1998**, *120*, 8724 – 8738.
[25] A. Gelasco, S. Bensiek, V. L. Pecoraro, *Inorg. Chem.* **1998**, *37*, 3301 – 3309.
[26] D. M. Hong, H. H. Wei, Y. Wang, *J. Chin. Chem. Soc.* **1998**, *45*, 701 – 706.
[27] N. N. Gerasimchuk, A. Gerges, T. Clifford, A. Danby, K. Bowman-James, *Inorg. Chem.* **1999**, *38*, 5633 – 5636.
[28] C. E. Dubé, D. W. Wright, S. Pal, P. J. Bonitatebus, Jr., W. H. Armstrong, *J. Am. Chem. Soc.* **1998**, *120*, 3704 – 3716.
[29] K. D. Karlin, *Science* **1993**, *261*, 701 – 708.
[30] D. H. Vance, A. W. Czarnik, *J. Am. Chem. Soc.* **1993**, *115*, 12165 – 12166.
[31] D. Wahnon, A.-M. Lebuis, J. Chin, *Angew. Chem.* **1995**, *107*, 2594 – 2597; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2412 – 2414.
[32] W. H. Chapman, Jr., R. Breslow, *J. Am. Chem. Soc.* **1995**, *117*, 5462 – 5469.
[33] T. Koike, M. Inoue, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 3091 – 3099.
[34] K. G. Ragunathan, H.-J. Schneider, *Angew. Chem.* **1996**, *108*, 1314 – 1316; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1219 – 1221.
[35] J. Suh, S. H. Hong, *J. Am. Chem. Soc.* **1998**, *120*, 12545 – 12552.
[36] Complexes $\mathbf{1}\cdot 3\,ClO_4$ and $\mathbf{2}\cdot 4\,ClO_4$ were prepared as previously described.[28] The $Mn^{III}(Mn^{IV})_3$ complex $\mathbf{1}\cdot 3\,ClO_4$ was prepared by one-electron reduction of the $(Mn^{IV})_4$ complex $\mathbf{2}\cdot 4\,ClO_4$ by either its bulk electrolysis in acetonitrile (method A) or by its reaction with 1.2 equiv of Me_3(tacn) (method B).[28]
[37] All reactions were run in 2 mL solutions of CH_3CN/H_2O at 22 °C. All chemicals were of reagent-grade quality and used as received. Aqueous H_2O_2 stock solution (50% w/w, Aldrich) was standardized with $KMnO_4$ and used directly or as diluted with acetonitrile.
[38] 2% $H_2{}^{18}O_2$ (91 ± 1% ^{18}O, 9 ± 1% ^{16}O) was purchased from ICON, Inc.
[39] The error bars in Figures 1 and 3 are based on an estimated initial rate uncertainty of 8%.
[40] The catalytic constant, or turnover number, is defined as $k_{cat} = V_{max}/[cat]$.
[41] P. N. Balasubramanian, E. S. Schmidt, T. C. Bruice, *J. Am. Chem. Soc.* **1987**, *109*, 7865 – 7873.
[42] E. J. Larson, V. L. Pecoraro, *J. Am. Chem. Soc.* **1991**, *113*, 3810 – 3818.
[43] Y. Naruta, M.-a. Sasayama, *Chem. Lett.* **1994**, 2411 – 2414.
[44] M. Kimura, T. Nishigaki, T. Koyama, K. Hanabusa, H. Shirai, *Macromol. Chem. Phys.* **1994**, *195*, 3499 – 3508.
[45] One equivalent of Me_3(tacn) is required to reduce $\mathbf{2}\cdot 4\,ClO_4$ to $\mathbf{1}\cdot 3\,ClO_4$ (ref. [28]), hence the effective number of base equivalents of Me_3tacn (*m*) is one less than the total number of equivalents added to the reaction mixture.
[46] K. E. Neet, *Methods Enzymol.* **1995**, *249*, 519 – 567.
[47] K. E. Neet, *Methods Enzymol.* **1980**, *64*, 139 – 192.
[48] E. Zeffren, P. L. Hall, *The Study of Enzyme Mechanisms*, Wiley, New York, **1973**.
[49] A. V. Hill, *J. Physiol.* **1910**, *40*, iv – vii.
[50] We cannot rule out an alternative Scheme in which a N_{pyr}, rather than N_{al}, dissociates at the Mn^{III} site.
[51] S. Pal, M. M. Olmstead, W. H. Armstrong, *Inorg. Chem.* **1995**, *34*, 4708 – 4715.
[52] J. L. Roberts, Jr., H. Sugimoto, W. C. Barrette, D. T. Sawyer, *J. Am. Chem. Soc.* **1985**, *107*, 4556 – 4557.
[53] G. Rábai, *J. Chem. Soc. Chem. Commun.* **1991**, 1083 – 1084.
[54] H. H. Thorp, G. W. Brudvig, *New J. Chem.* **1991**, *15*, 479 – 490.

A Practical Asymmetric Synthesis of Enantiomerically Pure 3-Substituted Pyroglutamic Acids and Related Compounds**

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In recent years, tailor-made χ-constrained amino acids have emerged as critically important key structural units in the de novo design of peptide-based drugs with enhanced receptor selectivity and stability to metabolic degradation.[1, 2] Incorporation of these amino acids in strategic positions of a peptide chain allows rational design of the three-dimensional topographical structure of the peptide and, thus, opens a new avenue for exploration of the fundamental chemical – physical basis for peptide-mediated biological information transfer.[2] In particular, to explore the topographical requirements of the recently discovered human melanocortin receptors,[3] we need a series of hitherto unknown conformationally con-

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[**] This work was supported by grants from the U.S. Public Health Service (Grant DK 17420) and the National Institute of Drug Abuse (DA 06284 and DA 04248). The views expressed are those of the authors and not necessarily those of the USPHS.

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