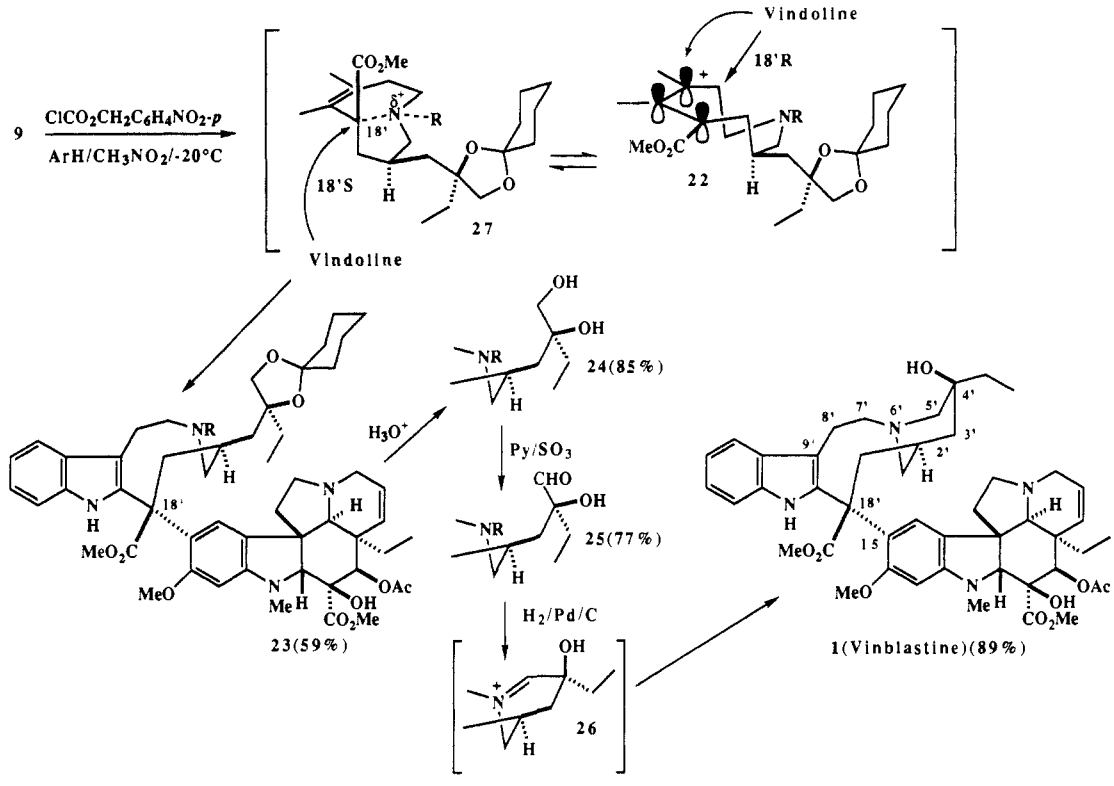
Scheme V[a]



[a] R = $CO_2CH_2C_6H_4NO_2$-*p*.

the balance between the relative rates without resorting to major structural alterations. Classically, increase the solvent polarity and lower the temperature.[9] All the coupling reactions were run in CH_2Cl_2 (ϵ, 8.9) at 25 °C. On the basis of the results shown in Scheme II (retention of configuration at C-18′), we treated **9** with $ClCO_2CH_2C_6H_4NO_2$-*p*/vindoline/CH_3NO_2 (ϵ, 35.9) at −20 °C and obtained the correct 18′*S* stereoisomer **23** (46%) along with **12** (33%) and traces of **13**. Carrying out the same coupling procedure as above but in the presence of 2,6-di-*tert*-butyl-4-methylpyridine gave **23** (59%) and **12** (31%). Hydrolysis of **23** gave the diol **24** (85%), which was oxidized, by using pyridine/SO_3, to the α-hydroxy aldehyde **25** (77%). Hydrogenolysis of **25** (Pd/C/MeOH) gave vinblastine (**1**) (89%), Scheme V. This last transformation presumably proceeds via the iminium ion **26**, which is the intermediate in Kutney's biomimetic conversion of 3′,4′-anhydrovinblastine (**3**) into vinblastine (**1**).[10]

The pronounced favorable solvent effect in reversing the stereochemistry at C-18′ could be attributed to preferential solvation of the "closed" iminium ion **27** versus the more delocalized "open" iminium ion **22**. Trapping of the "closed" ion leads to the correct C-18′ *S* stereochemistry with overall retention of configuration.[11] The overall yield from **9** to vinblastine is 34% (four steps).[12] Finally it should be noted that coupling of the C-18′ epimer **10** to vindoline using the above conditions gave none of the correct C-18′ *S* stereochemistry.

Acknowledgment. The National Institutes of Health (GM 29801) are thanked for their support of this research. Dr. Vince Lynch (X-ray lab, Department of Chemistry and Biochemistry, The University of Texas at Austin) is thanked for the X-ray structure determinations of **17** and **19**. Dr. Homer Pearce (Eli Lilly) is gratefully thanked for supplies of vindoline and vinblastine. Dr. J. P. Kutney is thanked for FAB mass spectra.

Supplementary Material Available: Spectral data for compounds **9–15**, **17**, **19–21**, **23–25**, **1**, and the C-4′ epimers of **12** and **13** and details of the X-ray determination of **17** and **19** (48 pages). Ordering information is given on any current masthead page.

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(11) Assignment of the absolute configuration at C-18′ is made by comparison of the CD curves with **1**. These correlations can only be used with any reliability if the alkaloids are very similar to the natural bis alkaloids. Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670. Kutney, J. P.; Gregonis, D. E.; Imhof, R.; Itoh, I.; Jahngen, E.; Scott, A. I.; Chan, W. K. *J. Am. Chem. Soc.* **1975**, *97*, 5013.

(12) Coupling 4′-epi **9** (leurosidine series) to vindoline using the described procedure with CH_3NO_2 gave the corresponding 18′*S* bis alkaloid in 77% yield, clearly suggesting that there is ample room for improvement in the vinblastine series. We are currently investigating the optimization of this reaction.

Activation of Dioxygen by Bis[(2-carboxy-6-carboxylato)pyridine]iron(II) for the Bromination (via $BrCCl_3$) and Monooxygenation (via PhNHNHPh) of Saturated Hydrocarbons: Reaction Mimic for the Methane Monooxygenase Proteins

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The activation of dioxygen for the monooxygenation of saturated hydrocarbons by the methane monooxygenase (MMO, μ-oxo-

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Table I. Activation of O_2 by $Fe^{II}(DPAH)_2$ via $BrCCl_3$ and PhNHNHPh for the Oxidation and Oxygenation of Hydrocarbons[a]

$[Fe^{II}(DPAH)_2]$, mM	activator (concn, M)	substrate (1 M)	products (concn, mM)[b]
		A. 1.8:1 py/HOAc; O_2 (1 atm, 3.4 mM); 10 h	
32		c-C_6H_{12}	c-C_6H_{10}(O) (4.4)
32	$BrCCl_3$ (1.0)		py(Br) (3.0)
32	$BrCCl_3$ (1.0)	c-C_6H_{12}	c-C_6H_{11}Br (3.2)
32	$BrCCl_3$ (0.01)	c-C_6H_{12}	c-C_6H_{11}Br (1.5), c-C_6H_{10}(O) (1.8)
3	$BrCCl_3$ (1.0)	c-C_6H_{12}	c-C_6H_{11}Br (1.2)
32	PhNHNHPh (1.0)	c-C_6H_{12}	c-C_6H_{10}(O) (21.2)
3	PhNHNHPh (0.1)	c-C_6H_{12}	c-C_6H_{10}(O) (20.9)
		B. 3:1 MeCN/py; O_2 (1 atm, 7 mM); 22 h	
28		c-C_6H_{12}	$(DPAH)_2Fe^{III}OFe^{III}(DPAH)_2$ (14)
5	PhNHNHPh (0.2)	c-C_6H_{12}[c]	c-C_6H_{11}OH (35), c-C_6H_{10}(O) (5.6)
5	PhNHNHPh (0.2)	c-C_6H_{11}OH	c-C_6H_{10}(O) (24)
5	PhNHNHPh (0.2)	*n*-C_6H_{14}	2-C_6H_{13}OH (19), *n*-C_6H_{13}OH (1.5), 2-C_6H_{12}(O) (7.6)
5	PhNHNHPh (0.2)	Me_2CHCH_2Me	C_5H_{11}OH (17) [1°/2°/3°, 21:29:50],[d] $Me_2CHC(O)Me$ (2.5)
5	PhNHNHPh (0.2)	$PhCH_2Me$	PhCH(OH)Me (1.5), PhC(O)Me (13)
5	PhNHNHPh (0.2)	$PhCH_3$	MePhOH (3), PhCH(O) (3)
5	PhNHNHPh (0.2)	PhH	PhOH (3)

[a] Substrate, activating agent, and $Fe^{II}(DPAH)_2$ [$Fe(MeCN)_4(ClO_4)_2$ added to 2 equiv of $(Me_4N)_2DPA$] were combined in 3.5 mL of solvent, followed by the addition of 1 atm of O_2 in a reaction cell with 18 mL of head space. Reaction temperature: 24 ± 2 °C. [b] The product solutions were analyzed by capillary gas chromatography and GC–MS. [c] Combination of 5 mM $Fe^{II}(DPAH)_2$, 1 M c-C_6H_{12}, and 100 mM HOOH in MeCN yields an ol/one product ratio of 2.3. [d] Product profile for R· in a Fenton system; 2-methylbutane (25:35:40), ref 5.

binuclear iron center) enzyme systems has fascinated chemists and biologists for the past decade.[1-3] The basic process involves the insertion of an oxygen atom into the C–H bond of the hydrocarbon via the concerted reduction of O_2 by the MMO hydroxylase/reductase cofactors. A recent communication[4] discusses

$$CH_4 + O_2 \xrightarrow{MMO/(H)_2} CH_3OH + H_2O \qquad (1)$$

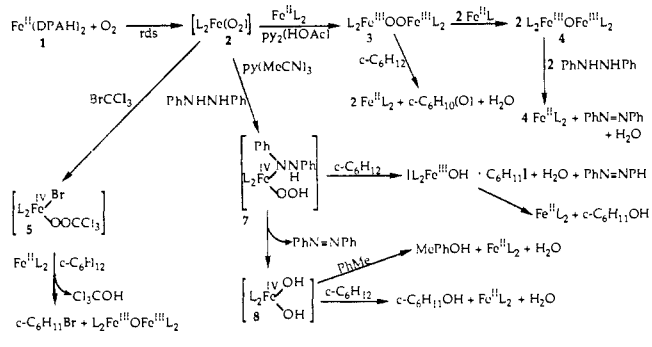
the selective ketonization of methylenic carbons via activation of O_2 by bis[(2-carboxy-6-carboxylato)pyridine]iron(II) [**1**, $Fe^{II}(DPAH)_2$] to give $(DPAH)_2Fe^{III}OOFe^{III}(DPAH)_2$ (**3**) as the reactive intermediate. Here we report that the presence of $BrCCl_3$ (equimolar to substrate, c-C_6H_{12}) causes the system to yield c-C_6H_{11}Br as the sole product [in the absence of $BrCCl_3$, the only product is c-C_6H_{10}(O)] (Table I). With equimolar BuI present, the yield of c-C_6H_{10}(O) is reduced and bipyridine is formed from oxidation of the solvent.

When the 1.8:1 py/HOAc solvent is replaced with MeCN or 3:1 MeCN/py, the $Fe^{II}(DPAH)_2/O_2$ combination does not react with hydrocarbon substrates, but undergoes autoxidation to give $(DPAH)_2Fe^{III}OFe^{III}(DPAH)_2$. However, the presence of PhNHNHPh causes the system to become a hydrocarbon monooxygenase (c-C_6H_{12} → c-C_6H_{11}OH). The products and reaction efficiencies for various concentrations of $Fe^{II}(DPAH)_2$ and PhNHNHPh with several substrates are summarized in Table I.

The maximum efficiency and monooxygenase selectivity are achieved with 5 mM $Fe^{II}(DPAH)_2$, 200 mM PhNHNHPh, and 1 atm of O_2 in 3:1 MeCN/py. The distribution of ROH isomers from 2-methylbutane indicates a selectivity in the order >CH > $>CH_2$ > $-CH_3$; the relative reactivities per C–H bond are 1.00, 0.29, and 0.05, respectively. A recent study[5] of $Fe^{II}(PA)_2$/HOOH Fenton chemistry in 1.8:1 py/HOAc gave relative reactivities of 1.00, 0.43, and 0.07, and the values for aqueous •OH are 1.00, 0.48, and 0.10.[6] Thus, the reactive intermediate from the $Fe^{II}(DPAH)_2/O_2$/PhNHNHPh system is more selective than Fenton-derived and free •OH.

In the absence of an activating agent ($BrCCl_3$, BuI, or PhNHNHPh), combination of $Fe^{II}(DPAH)_2$ and O_2 leads to the formation of $(DPAH)_2Fe^{III}OFe^{III}(DPAH)_2$ (**4**) via the transient formation of $(DPAH)_2Fe^{III}OOFe^{III}(DPAH)_2$ (**3**) (ketonizes methylenic carbons),[4] which prompts the conclusion that a 1:1 adduct [$(DPAH)_2Fe(O_2)$ (**2**)] is initially formed via a rate-limiting step (Scheme I). In the presence of activating agents, **2** is trapped, especially when the $[Fe^{II}(DPAH)_2]/[O_2]$ ratio is less than unity. This conclusion and the results of Table I are the basis for the proposed reaction pathways of Scheme I. The hydroxylation of alkanes via a $Fe(py)_4Cl_2/O_2$/PhNHNHPh/PhC(O)OH/Me_2C(O) system[10] has been rationalized to involve an intermediate that is analogous to species **7**.

Scheme I. Activation of Dioxygen by $Fe^{II}(DPAH)_2$



The ability of the $Fe^{II}(DPAH)_2/O_2$/PhNHNHPh system (where PhNHNHPh is a mimic for flavin reductases)[7,8] to monooxygenate saturated hydrocarbons closely parallels the chemistry of the methane monooxygenase proteins.[1-3] However, the enzyme oxygenates 2-methylbutane with an isomer distribution of 82% primary alcohol, 10% secondary, and 8% tertiary.[9] The present model gives a distribution of 21% primary, 29% secondary, and 50% tertiary. Clearly the protein affords a cavity that is selective for CH_4 and CH_3 groups. Although the likely reactive intermediates (**7** and **8**, Scheme I) of the model are less reactive than free •OH, they are able to oxygenate CH_3 groups and benzene (Table I).

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Cobalt-Induced Activation of Hydrogen Peroxide for the Direct Ketonization of Methylenic Carbons [c-C_6H_{12} → c-C_6H_{10}(O)], the Oxidation of Alcohols and Aldehydes, and the Dioxygenation of Aryl Olefins and Acetylenes

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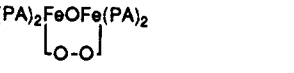
A recent study[1] has described the catalytic activation of excess hydrogen peroxide by bis(picolinato)iron(II) [$Fe^{II}(PA)_2$] for the efficient, selective ketonization of methylenic carbons and the dioxygenation of aryl olefins and acetylenes; the reactive intermediate has been postulated to be



Independent studies[2,3] report similar results, but attribute the selectivity toward methylenic carbon to an $X_3Fe^{V}{=}O$ intermediate (from $Fe^{III}X_3$ plus HOOH). The suggestion is that the hypervalent iron attacks methylenic carbon to form iron–carbon single or double bonds with subsequent reaction with a second HOOH to yield primarily ketone. Both groups agree that iron–picolinate complexes in a pyridine/acetic acid solvent matrix represent an optimal system in terms of efficiency and selectivity.

To gain further insight to the chemistry of this unique HOOH-activation system, we have investigated other transition-metal complexes. Here we report that bis(bipyridine)cobalt(II) [$Co^{II}(bpy)_2^{2+}$, **1**] activates HOOH for the selective ketonization of methylenic carbons, the oxidation of alcohols and aldehydes, and the dioxygenation of aryl olefins and acetylenes. Table I summarizes the product distributions for a series of substrates that result from the catalytic activation of HOOH or *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$. The product profiles indicate that oxidase (or monooxygenase) chemistry is favored in pure MeCN solvent (c-C_6H_{12} → c-C_6H_{11}OH), but the ketonization of methylenic carbon and dioxygenase chemistry are favored in MeCN/py (4:1 molar ratio) [c-C_6H_{12} → c-C_6H_{10}(O); c-PhCH=CHPh → 2PhCH(O)]. The selective ketonization of cyclohexene in MeCN/py contrasts with its enhanced monooxygenation in pure MeCN (one/ol ratio, 16:1 vs 1:1) and is compelling evidence for two reactive intermediates. The presence of O_2 inhibits the reactivity of c-C_6H_{12} with HOOH by 10–20%. In pure MeCN, $Co^{II}(bpy)_2^{2+}$ catalyzes HOOH for the stoichiometric transformation of 1,4-cyclohexadiene to benzene.

When *t*-BuOOH is the oxygen source, the reactivity with substrates is about 10 times greater in pure MeCN than in MeCN/py (Table I). With $PhCH_3$ the dominant product is $PhCH_2OOBu$-*t*, which requires two *t*-BuOOH molecules per substrate. When c-C_6H_{12} is the substrate, c-C_6H_{10}(O) and c-C_6H_{11}OOBu-*t* are the major products (both require two *t*-BuOOH molecules per substrate) and the ketone probably results from the decomposition of c-C_6H_{11}OOBu-*t*. In contrast, with $(Me)_2CHCH_2Me$ the major product is $(Me)_2C(OH)CH_2Me$ (one *t*-BuOOH per substrate). The use of *t*-BuOOH precludes (or strongly suppresses) formation of the reactive intermediate for the direct ketonization of methylenic carbons.

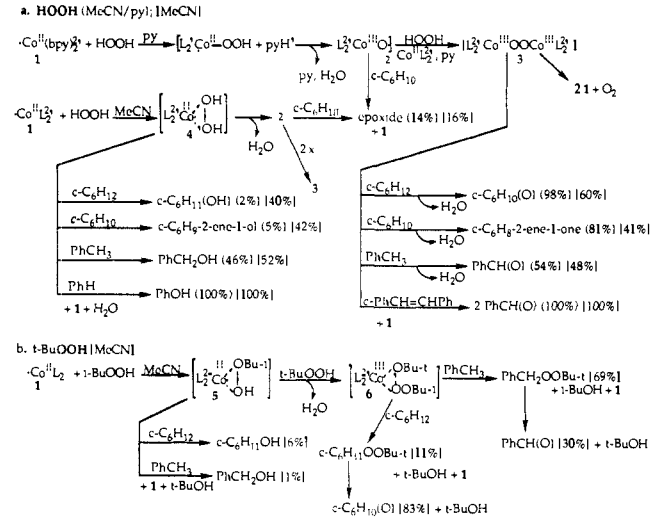
The results of Table I and the close parallels of the product profiles to those for the $Fe^{II}(PA)_2$/HOOH/(py/HOAc) system[1] prompt the conclusion that the combination of $Co^{II}(bpy)_2^{2+}$ (**1**) and HOOH results in the initial formation of an oxene intermediate [$(bpy)_2^{2+}Co^{III}O^{\bullet}$, **2**], which (in MeCN/py) rapidly reacts

Table I. Activation of HOOH and *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$ for the Oxygenation of Hydrocarbons, the Oxidation of Alcohols and Aldehydes, and the Dioxygenation of Aryl Olefins and Acetylenes in 4:1 MeCN/py[a]

substrate (1 M)	oxidant (200 mM)	products (concn, mM)[b]
c-C_6H_{12}	HOOH	c-C_6H_{10}(O) (61), c-C_6H_{11}OH (1)
c-C_6H_{12} (MeCN)	HOOH	c-C_6H_{10}(O) (14), c-C_6H_{11}OH (9)
c-C_6H_{12}	*t*-BuOOH	c-C_6H_{11}OOBu-*t* (1.5)
c-C_6H_{12} (MeCN)	*t*-BuOOH	c-C_6H_{10}(O) (15), c-C_6H_{11}OOBu-*t* (2), c-C_6H_{11}OH(1)
Me_2CHCH_2Me	HOOH	$Me_2CHC(O)Me$ (12), $Me_2C(OH)CH_2Me$ (5)
Me_2CHCH_2Me (MeCN)	*t*-BuOOH	$Me_2C(OH)CH_2Me$ (9), $Me_2CHC(O)Me$ (1)
$PhCH_2CH_3$	HOOH	PhC(O)Me (30), $PhCH_2CH_2OH$ (11)
$PhCH_3$	HOOH	PhCH(O) (20), $PhCH_2OH$ (17)
$PhCH_3$ (MeCN)	*t*-BuOOH	$PhCH_2OOBu$-*t* (28), PhCH(O) (12)
c-C_6H_{10}	HOOH	R-one (50),[c] epoxide (8), ROH (3)[d]
c-C_6H_{10} (MeCN)	HOOH	ROH (31), R-one (30), epoxide (12), RR (1)
c-C_6H_{10} (MeCN)	*t*-BuOOH	ROOBu-*t* (41), R-one (6), ROH (3), RR (1)
PhH (MeCN)	HOOH	PhOH (34)
c-C_6H_{11}OH (MeCN)	HOOH	c-C_6H_{10}(O) (28)
$PhCH_2OH$ (MeCN)	HOOH	PhCH(O) (40)
PhCH(O) (MeCN)	HOOH	PhC(O)OH (108)
c-PhCH=CHPh (0.65 M)	HOOH	PhCH(O) (87), epoxide (4)
PhC≡CPh	HOOH	PhC(O)C(O)Ph (24)
2,6-$(Me)_2$PhOH	HOOH	2,6-$(Me)_2$Ph(O)$_2$ (5),[e] ROOR (3)
2,6-$(Me)_2$PhOH (MeCN)	*t*-BuOOH	ROOR (9)

[a] Substrates and catalyst [20 mM $Co(bpy)_2^{2+}$] were combined in 7 mL of MeCN/py (4:1 molar ratio) (or MeCN), followed by the slow addition (1–2 min) of either 100 μL of 17.6 M HOOH (50% in H_2O), to give 200 mM HOOH, or 600 μL of 3.0 M *t*-BuOOH (in 2,2,4-trimethylpentane), to give 200 mM *t*-BuOOH. Reaction time and temperature: 6 h at 22 ± 2 °C. [b] The product solutions were analyzed by capillary gas chromatography and GC–MS (either by direct injection of the product solution or by quenching with H_2O and extracting with diethyl ether). [c] Cyclohex-2-ene-1-one. [d] Cyclohex-2-ene-1-ol. [e] 2,6-Dimethyl-*p*-benzoquinone.

Scheme I. Activation of HOOH and *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$



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