with pH: 64, 26, 8, and 2% for monomer, dimer, trimer, and tetramer in 0.015 M solution. Indeed the average number of molecules in each stack decreases from 2.28 at pD 8, 2.24 at pD 5.4, to 2.16 at pD 1.8 for a 0.015 M solution. Thus it is understandable that the original results fitted the presence of $H(phen)_2^+$ with some suggestion of the presence of $H(phen)_3^+$. More recent measurements[2,3] have used 0.01 M solutions and found only evidence for $H(phen)_2^+$: the average number of molecules in each stack is nearer 2.0 under these conditions. Likewise the variation of the pK_a with pH found in the potentiometric determination of the pK_a by Krumholz[15] and the similar anomalies found in potentiometric titrations in 0.01 M solution observed earlier[16] can also be explained by the presence of short stacks. However, in the much stronger solutions (0.6 M) used by Rund,[10] stacking proceeds further: at the pK_a the average length of stack is 5.0 and at pD 1.8 it is still 4.2, despite the lower stability constant. In the strongest solution obtainable at the pK_a, 3.5 M, there are on an average ten molecules in each stack and 64% of the phenanthroline is present in stacks containing more than ten molecules: only 1.3% is present as the monomer.

Thus the experimental results which led to the suggestion of $H(phen)_2^+$ and $H(phen)_3^+$ are explained better by the stacking of phenanthroline under the conditions used.

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(6) These solutions were prepared by mixing exactly equimolar phenanthroline and $H(phen)^+$ solutions, which were themselves prepared from analytical reagent quality phenanthroline and phenanthrolinium chloride.

(7) Analysis of second-order NMR spectra and calculation of the stability constants for self-stacking were performed using a Hewlett-Packard 9821A calculator. The variation of chemical shift with concentration was fitted using the isodesmic[8] model of indefinite noncooperative stacking to the relationship $\delta_{obsd} = \delta_\infty + (\delta_\infty - \delta_0)[1 - (4KC + 1)^{1/2}]/2KC$ between the observed chemical shift δ_{obsd} in a solution of total phenanthroline concentration C, the chemical shifts at infinite dilution δ_0 and of a molecule within a stack δ_∞ and the stability constant K.

(8) The isodesmic model of indefinite noncooperative stacking (Schimmack, W.; Sapper, H.; Lohmann, W. *Biophys. Struct. Mechanism* **1975**, *1*, 113–120) assumes that the equilibrium constants for the equilibria

$$(A)_n + A \rightleftharpoons (A)_{n+1}$$

$$K = [(A)_{n+1}]/[(A)_n][A]$$

are all equal [A = phenanthroline, half-protonated phenanthroline (pD 5.4), or monoprotonated phenanthroline (pD 1.8)].

(9) Effectively using one resonance of phenanthroline as a reference for another which is shifted more, to exclude the possibility of any interaction with the internal reference which was $(CH_3)_4N^+$. Use of an external reference, together with an estimated susceptibility correction, for the strongest solutions of phenanthroline at pD 5.4 (0.6–3.5 M) showed that, with [phen] $\geqslant$ 2 M, no internal reference could be reliable.

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Metal–Ligand Synergism in the Chemistry of Macrocyclic Complexes. Base-Induced Reduction of a Cobalt(III) Complex[1]

Sir:

Base-induced, oxidation–reduction reactions of transition metal complexes are reasonably common,[2-6] but almost always mechanistically obscure. In many of these reactions, reduction of the metal in a coordination complex is accompanied by oxidation of a basic species. These reactions may be very roughly classified into two groups depending on whether the base oxidized is a ligand or solvent species. However, it seems unlikely that a similar dichotomous classification will be useful at a mechanistic level since these reactions frequently appear to involve facile electron transfer from a coordinated ligand to the metal. Even the oxidations involving solvent species frequently proceed through intermediates formed from nucleophilic additions of the base to an unsaturated ligand.[3,4,7] Thus, the frequently proposed, but rarely observed, key intermediates in these reactions contain reduced metal centers and coordinated radical ligands. While most of these reactions are very complicated in detail, their potential significance is illustrated in proposals that they mediate base hydrolyses,[8] could be the basis for catalytic oxidations of organic substrates,[9] and could play a key role in the use of transition metal substrates to mediate the light-induced oxidation of water.[4]

We have found a substantial number of base-induced oxidation–reduction reactions of tetraaza macrocyclic complexes of cobalt. These reactions are mechanistically very interesting since the coupling of ligand and metal redox chemistry seems to provide a means for circumventing the very large reorganizational barriers associated with cobalt(III)–(II) couples.[10] Some of these reactions (e.g., with the $Me_4[14]tetraeneN_4$[11] ligand) appear to result in ligand degradation and difficult-to-characterize products.[10c] In contrast we have found the base-induced redox chemistry of ($Me_2[14]1,11$-dieneN_4)-cobalt[11] complexes to be very extensive, but reasonably straightforward. The key to this system has been the discovery that a major product of the base-induced redox chemistry is a C–C-coupled, bis macrocyclic, binuclear complex.

When rigorously deaerated, aqueous $Co(Me_2[14]1,11\text{-dieneN}_4)Cl_2^+$ (perchlorate media) and NaOH are mixed, a sparingly soluble, yellow precipitate (A) is formed immediately in ~90% yield. The new compound is a low-spin cobalt(II) complex [$\mu_{eff} = 2.12\ \mu_B$/Co; λ_{max} 345 nm (ϵ 5.7×10^2/Co)]. The elemental analysis of this compound is not distinguishable from that of $[Co(Me_2[14]1,11\text{-dieneN}_4)(OH_2)_2](ClO_4)_2$; however, the physical properties differ considerably. The most immediate difference is the very limited solubility of the new compound. Under conditions of high pH (>3) in aerated solutions, we have found that A is formed in competition with the previously reported oxygenation product, $Co(Me_2[14]\text{-}1,11\text{-dieneN}_4\text{-}13\text{-one})(OH_2)_2^{2+}$.[10c] In acidic chloride solutions A may be air oxidized to a cobalt(III) complex, B. This latter complex is also obtained from the stoichiometric (1:1) $FeCl_3$ oxidation of $Co(Me[14]1,11\text{-dieneN}_4)Cl_2^+$ in deaerated, acidic solutions. The methods of generation (summarized above) and the physical characterization (summarized below) indicate that products A and B are binuclear complexes coupled through the bridgehead carbons of the β-diimine moieties of the macrocyclic ligand.

The infrared spectra of B and $Co(Me_2[14]1,11\text{-dieneN}_4)\text{-}Cl_2^+$ differ principally in the C=N region, with the strong absorptions at 1667 and 1691 cm^{-1}, respectively. A very similar shift is observed for the analogous monomeric complex methylated at the bridgehead carbon (C-13). In the ^{1}H NMR spectra, the resonance for the bridgehead protons (integrated intensity equivalent to one ^{1}H per macrocycle) of compound B were 5.9 ppm downfield from Me_4Si ($Me_2SO\text{-}d_6$ solvent),

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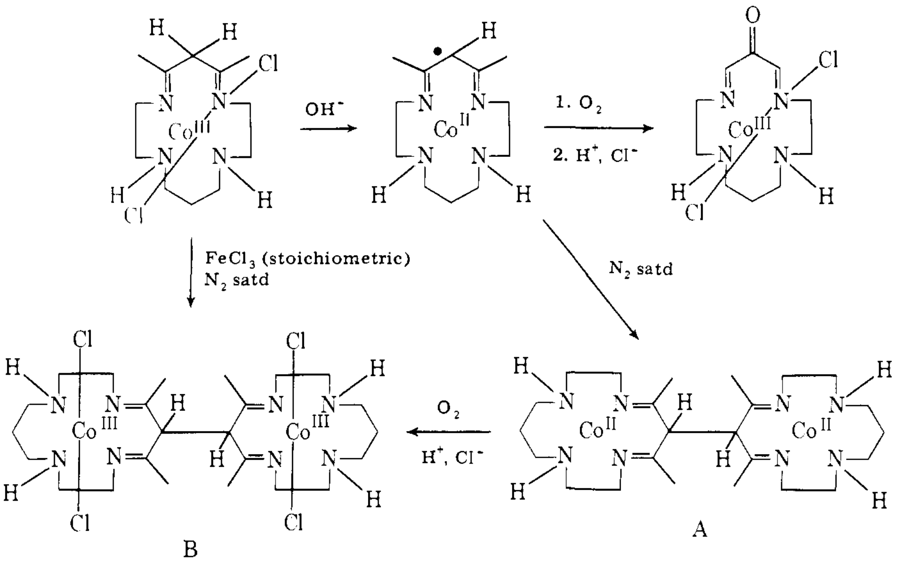
Table I. Cyclic Voltammetry of β-Diimine Complexes

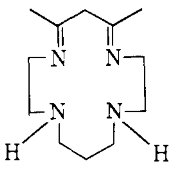
complex	solvent	electrolyte	electrode	$E_{pa} - E_{pc}$, mV[a]	$E_{1/2}$, V vs. NHE[b]	assignment
$Co(Me_2[14]1.11\text{-diene}N_4)(OH_2)_2^{3+}$	H_2O	1.0 M $LiClO_4$	Pt	80	+0.382	Co^{III}-Co^{II}
			HMD	92	+0.385	
$Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$	H_2O	1.0 M HCl	Pt	69	+0.278	Co^{III}-Co^{II}
$Co(Me_2[14]1,11\text{-diene}N_4)(NCS)_2^+$	H_2O	1.0 M NaNCS	Pt	120	−0.079	Co^{III}-Co^{II}
			HMD	73	−0.078	
$Co(Me_2[14]1,11\text{-diene}N_4\text{-13-one})(OH_2)_2^{3+}$	H_2O	1.0 M $LiClO_4$	Pt	79	+0.596	Co^{III}-Co^{II}
	H_2O	1.0 M $HClO_4$	HMD	35[c]	+0.116	ligand
$Co(Me_2[14]1,11\text{-diene}N_4\text{-13-one})Cl_2^+$	H_2O	1.0 M HCl	Pt	76	+0.370	Co^{III}-Co^{II}
$Co(Me_2[14]1,11\text{-diene}N_4\text{-13-one})(NCS)_2^+$	H_2O	1.0 M NaNCS	Pt	74	+0.073	Co^{III}-Co^{II}
$Co(Me_2[14]1,11\text{-dieno}(-1)N_4)(NCS)_2$	H_2O	1.0 M NaNCS	Pt	190	−0.2	Co^{III}-Co^{II}
	H_2O	1.0 M NaNCS	Pt	70	+0.45[c]	$L^- \rightarrow \cdot L$
	DMF	0.10 M $NaClO_4$	Pt	145	(+0.63)[c]	$L^- \rightarrow \cdot L$
$Cu(Me_2[14]1,11\text{-dieno}(-1)N_4)^+$	DMF	0.10 M $NaClO_4$	Pt	125	(+0.65)[c]	$L^- \rightarrow \cdot L$
$Ni(Me_2[14]1,11\text{-dieno}(-1)N_4)^+$	DMF	0.10 M $NaClO_4$	Pt	112	(+0.67)[c]	$L^- \rightarrow \cdot L$

[a] Scan rate typically 0.1 V s^{-1}. [b] Potentials were measured vs. SCE (NaCl). $E_{1/2}$ vs. NHE = $0.236 + (E_{pc} + E_{pa})/2$. The same convention was employed for studies in DMF (values in parentheses) to provide some approximate comparisons. [c] Two-electron wave.

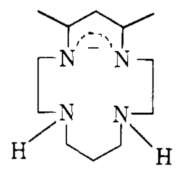
Scheme I



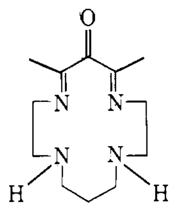
but 4.8 ppm downfield for $Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$ (two bridgehead protons per macrocycle). Similar shifts were observed by Dabrowiak and McElroy in the ^1H NMR behavior of an oxidatively coupled nickel(II) β-diimine complex.[13]



$Me_2[14]1,11\text{-diene}N_4$



$Me_2[14]1,11\text{-diene}(-1)N_4$

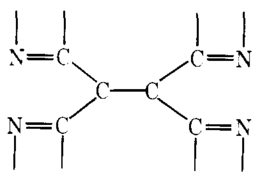


$Me_2[14]1,11\text{-diene}N_4\text{-13-one}$

While the base-induced redox chemistry of $Co(Me_2[14]\text{-}1,11\text{-diene}N_4)Cl_2^+$ proceeds on a preparative scale within the time of mixing, similar additions of base to the diisothiocyanato complex result only in deprotonation of the β-diimine moiety to form $Co(Me_2[14]1,11\text{-dieno}(-1)N_4)(NCS)_2$. This quenching of the internal (β-diiminato(−1) → Co^{III}) electron-transfer reaction on axial substitution of NCS^- for Cl^- is an obvious consequence of the shift in the electrode potential of the Co^{III}-Co^{II} couple from +0.28 V (vs. NHE) for $Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$ to −0.08 V for the diisothiocyanato complex (see Table I). Electrochemical measurements of several metal complexes in DMF and H_2O (Table I) indicate that the potential for the β-diiminato(−1)-β-diiminyl radical couple is ~0.4–0.6 V vs. NHE.[14] The pK_a values of the bridgehead carbons (C-13) in $Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$ and $Co(Me_2[14]1,11\text{-diene}N_2)(NCS)_2^+$ were estimated from acid–base titrations to be ~5 and 7.6, respectively.

On the basis of our observations, we infer a labile, metal-diiminato ligand redox equilibrium as the precursor to formation of the cobalt(II) dimer (A) from the monomeric $Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$ complex as shown in Scheme I.

The extent to which the labile, internal redox equilibrium in these complexes mediates other chemical behavior is under study. It now seems likely that the ligand oxygenation reported earlier[10c] is mediated by such a process. Other rapid reactions, such as the $Fe(phen)_3^{3+}$ oxidations of and the axial substitutions into $Co(Me_2[14]1,11\text{-diene}N_4)Cl_2^+$, are also mediated by the acid–base chemistry of the β-diimine moiety and may involve internal redox reactions. We do have some evidence that moiety J can be further oxidized to a C=C bridge. The resulting dimer would be similar to a nickel(II) complex reported by Cunningham and Sievers.[15] These dimeric com-



J

plexes bear some similarities to quinone-hydroquinone couples and have the potential of functioning as multiequivalent redox reagents. The nickel(II) and copper(II) complexes of Me$_2$[14]1,11-dieneN$_4$ are also easily oxidized and the locus of oxidation in these complexes is being investigated.[16,17]

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(11) Ligand abbreviations are based on conventions reviewed and summarized by Melson:[12] Me$_2$[14]1,11-dieneN$_4$ = 12,14-dimethyl-1,4,8,11-tetraazacyclotetradeca-1,11-diene; Me$_2$[14]1,11-dieno(−1)N$_4$ = 12,14-dimethyl-1,4,8,11-tetraazacyclotetradeca-1,11-dieno(−1); Me$_2$[13]-1,10-dieneN$_4$ = 11,13-dimethyl-1,4,8,11-tetraazacyclotrideca-1,10-diene; Me$_2$[13]1,10-dieno(−1)N$_4$ = 11,13-dimethyl-1,4,8,11-tetraazacyclotrideca-1,10-dieno(−1); [14]aneN$_4$ = 1,4,8,11-tetraazacyclotetradecane; Me$_6$[14]4,11-dieneN$_4$ = 5,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene; Me$_4$[14]tetraeneN$_4$ = 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene; phen = 1,10-phenanthroline.

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(16) Khalifa, M. A.; Endicott, J. F., work in progress. In our hands the previously described[15] "preparation" of the nickel(II) dimer has been very inefficient (yields of less than a few percent); some of the oxidation products may involve ligand dehydrogenation as reported by Busch and co-workers.[17] Such aerial oxidations of β-diiminato complexes may also be complicated by ligand oxygenation. Our preliminary work, as well as the work of others cited above, suggests that the chemistry of these systems couples the properties of metal and ligand in ways that are not always well understood.

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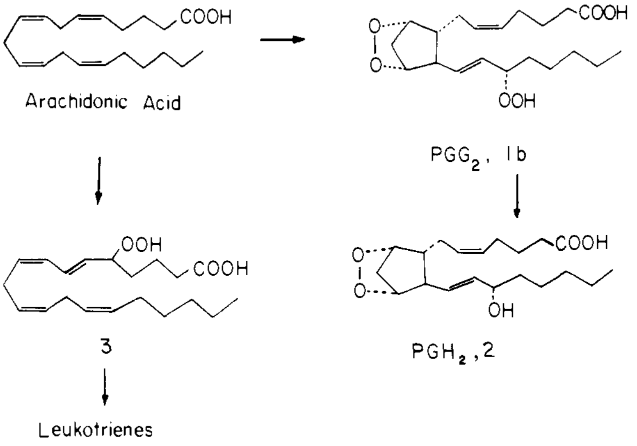
Prostaglandin G$_2$

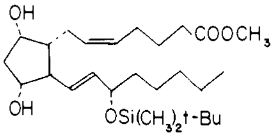
Sir:

The finding that compounds containing the peroxide group are important natural products derived from polyunsaturated fatty acids has resulted in a renewed interest in peroxide synthesis.[1-5] Several methods[1-4] have been developed for the construction of the bicyclo[2.2.1] endoperoxide nucleus of PGH$_2$ (**2**), and syntheses of this compound[6] and its methyl ester[3,7] have been recently reported. The allyl-type hydroperoxide group is also the focus of considerable chemical interest since this functionality is present in a proposed biological intermediate (**3**) to the slow reacting substance of anaphylaxis (SRS-A) as well as in PGG$_2$ (**1b**).



PGG$_2$ is the first isolable intermediate formed in the conversion of arachidonic acid into the prostaglandins and thromboxanes and, as such, it plays a central role in the biochemistry of fatty acids. It is difficult to obtain pure from biological sources and the lability of the 9,11-peroxide linkage and the 15-hydroperoxide group pose a dual threat in any synthetic approach to the compound. In fact, no reports of attempted syntheses of PGG$_2$ have appeared in the literature. The reaction of alkyl halides with hydrogen peroxide and silver trifluoroacetate[9,10] has proven to be a method suitable for the generation of the 9,11-peroxide bridge of PGH$_2$ (**2**),[6,7] and it occurred to us that this method might also be used to introduce the allylic 15-hydroperoxy group of PGG$_2$.[11] We report here the first chemical synthesis of PGG$_2$. In this synthesis, the 9,11-peroxide bridge and the 15-OOH are simultaneously introduced via the silver trifluoroacetate/hydrogen peroxide method in a triple displacement reaction.

The synthesis proceeds from PGF$_{2\alpha}$ methyl ester through the 15-*tert*-butyldimethylsilyl ether[3] (**4**) to **5a**. The crucial 9β,11β-dibromo derivative (**5b**) was previously prepared[3,6] by displacement of 9α,11α-disulfonates with bromide ion. This approach has been criticized[12] because the bromide displacement reaction leads to a mixture of epimeric dibromides and the desired isomer is isolated in only 20% yield after a tedious chromatographic purification. The intermediate **5a** may be prepared in one step from **4** (50% yield) by treatment of **4** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate[13] and tetraethylammonium bromide. No epimers of **5a** are formed by the use of these extremely mild reaction conditions and the preparation of **5** by this route gains not only in terms of overall yield (the sequence **4** → **5b** is shortened by one step and the yield is higher) but also in that the difficult chromatographic separation of isomers is avoided. Thus, 0.1265 g of **4** was treated with 0.9276 g of 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and 1.3854 g of tetraethylammonium bromide in 7 mL of methylene chloride at −15 °C for 20 min. Following an aqueous wash and chromatography on silica with 2% acetone-98% hexane, 0.080 g of pure **5a** was isolated. Hydrolysis



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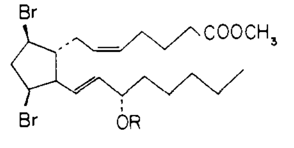

5 a, R = Si(CH$_3$)$_2$t-Bu
b, R = H

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