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Axial ligation to low spin iron(II) macrocycles: inorganic and biomimetic applications

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Abstract - The chemistry of FeN_4 complexes analogous to hemes are presented emphasizing the fundamental dissociative mechanism for axial ligation. Implications of kinetic and equilibrium data to our understanding of metal ligand bonding are discussed. Applications of this class of complexes to inorganic photochemistry, biomimetic chemistry, and novel linear chain supermolecules are presented.

A variety of planar macrocyclic tetradentate nitrogen donor ligands (N_4) in conjunction with two monodentate axial ligands generally give relatively inert low spin complexes trans-FeN_4XY. These complexes are distinctly colored, are readily soluble in organic solvents and undergo clean axial ligand substitution reactions. Along with hemes, they comprise a distinct class of inorganic complexes which bridge the gap between classical Werner complexes and generally more inert organometallic or π-acid complexes. Extensive work on FeN_4XY systems in recent years provides a considerable body of systematic quantitative data with which to understand the inorganic chemistry of the heme group as well as considerable insight into fundamental concepts of metal ligand bonding.

Some of the ligand systems which have been investigated are summarized below. The resulting FeN_4XY complexes are electrically neutral (FeP,FePc,$Fe(dioxime)_2$),unpositively $Fe(DOHpn)^+$) or dipositively (FeTIM,FeTAAB, Fe14ane, Fe15ane) charged.

Axial Ligands:	PBu_3	tributylphosphine
	$P(OBu)_3$	tributylphosphite
	BzNC	benzylisocyanide
	TMiC	tosylmethylisocyanide
	DIB	1,4 diisocyanobenzene
	MeIm	methylimidazole
	py	pyridine
	CO	carbon monoxide

N_4 =	TPP	tetraphenylporphyrin[1-3]
	P	protoporphyrin IX dimethyl ester or related porphyrins[4-8]
	Pc	phthalocyanine[9-11]
	$(DMGH)_2$	bis-dimethylglyoximate[12,13]
	$(BQDH)_2$	bis benzoquinonedioximate[14,15]
	$(NPQH)_2$	bis napthoquinone dioximate[15]
	DOHpn	diacetylmonoximeiminodiacetylmonoximato-1,3 propane[16]
	TIM	2,3,9,10 tetramethyl 1,4,8,11 tetraazacyclotetradeca 1,3,8,10 tetraene[16-18]
	14ane	1,4,8,11 tetaazacyclotetradecane[19]
	TAAB	tetrabenzo [b,f,j,n][1,5,9,13]tetraazacyclohexadecine[20]

Spectral features. The visible spectra of iron porphyrins and phthalocyanines are dominated by intense π-π transitions which are only slightly perturbed by the axial ligands (~40nm). The saturated low spin Fe[14ane]$^{+2}$ derivatives give weaker d-d bands. The other systems all display intense MLCT bands. These bands shift much more dramatically with changes in the axial ligands. As shown in table 1 the MLCT band shifts to higher energy as π-acceptor ligands are introduced which lower dxz,yz. The position of the MLCT band is also critically dependent on the N_4 ligand and can be moved at will through the visible region with changes in the π-conjugation of N_4 as demonstrated for $Fe(DMGH)_2$ and $Fe(NPQH)_2$ derivatives. This feature is especially useful in photochemical studies and photochromic applications. Correlations of ligand lability with the MLCT band

TABLE 1 MLCT λ_{max} (nm) for FeN_4XY Complexes

		N_4				
X	Y	$(DMGH)_2$	DOHpn	TIM	$(NPQH)_2$	$(BQDH)_2$
MeIm	MeIm	531	602	667	702	755
	PBu_3	499			642	680
	$P(OBu)_3$	460		580	592	612
	BzNC	445	500	555	567	582
	CO	385	418	450	474	485
PBu_3	PBu_3	468			594	616
	$P(OBu)_3$	436			558	570
	CO	376			470	475
$P(OBu)_3$	$P(OBu)_3$	414		520	527	537
	CO	360			455	
BzNC	BzNC	392	440	490	505	515

TABLE II. Comparison of Lability of Ligands in Iron Complexes: ΔG^{*}_{298} (kcal/mol) Trans to MeIm.[15]

Leaving Group	N_4				
	heme	BQDH	NPQH	DMGH	Pc
MeIm	13.1	17.7	21.2	20.5	21.0
$P(OBu)_3$	15.1	20.9	24.2	23.3	22.5
PBu_3	15.9	22.4	25.6	25	23.5
BzNC	17.9	22.2	25.5	25	23.1
CO	19.6	20.0	22.1	24.7	19.8

are observed pointing to an important role of π-bonding. The effects of the N_4 ligand on the axial π-bonding properties of iron are apparent in ν_{CO} for the carbonyl derivatives which range from 1970 cm^{-1} in hemes and $Fe(DMGH)_2(MeIm)(CO)$ up to 2028 cm^{-1} in neutral $Fe(BQDH)_2(MeIm)(CO)$ and even higher for +2 charged complexes. The ν_{CO} does not generally correlate with the lability of CO except for systematic variations:

with π-conjugation: $Fe(BQDH)_2 > Fe(NPQH)_2 > Fe(DMGH)_2$

with charge: $Fe\ TIM^{+2} > FeDOHpn^{+} > Fe(DMGH)_2$

AXIAL LIGATION REACTIONS

An overwhelming body of evidence (which we won't present here) exists for a simple dissociative mechanism for axial ligand substitution in all FeN_4XY systems. Since ligand binding and release are mechanistically simple, both the kinetics (lability) and thermodynamics (stability) can be understood in terms of the same basic concepts. The nature of the N_4 ligands generally limits reactivity to the axial sites, minimizes structural distortion of the pentacoordinate species, and prevents isomerization. For hemes, pentacoordinate complexes (the reactive intermediate in ligand substitution reactions of the six coordinate species) can be detected spectrophotometrically through synthetic tricks [6,21,22] or via flash photolysis[4-7] and in some cases may be isolated and structurally characterized[23,24]. Few, if any reactive intermediates, are this well characterized in all of inorganic chemistry.

Equilibrium constants for ligation to iron (e.g. 1-4) are related to corresponding on (k+) and off (k-) rate constants. These fundamental parameters are now known for a vast array of ligands providing a comprehensive data base with which to understand the mutual effects of ligands on the substitutional reactivity of coordination complexes.

$$FeN_4X_2 \underset{k_{+x}}{\overset{k_{-x}}{\rightleftharpoons}} FeN_4X \underset{k_{-y}}{\overset{k_{+y}}{\rightleftharpoons}} FeN_4XY \qquad (1)$$

$$FeN_4 + X \longrightarrow FeN_4X \qquad K_x = k_{+x}/k_{-x} \qquad (2)$$

$$FeN_4X + X \longrightarrow FeN_4X_2 \qquad K_x^X = k_{+x}^X/k_{-x}^X \qquad (3)$$

$$FeN_4X_2 + Y \longrightarrow FeN_4XY + X \qquad (4)$$

$$K_{x,y} = (k_{+y}^X/k_{+x}^X)(k_{-x}^X/k_{-y}^X)$$

Off rates. Table 2 shows the range of labilities found as a function of N_4, and the leaving ligand, L. The values of ΔG^{*} shown correspond to rate constants from 10^3 to 10^{-6} s^{-1}. In addition, the lability of ligands in these systems are dramatically dependent on the trans ligand. For example MeIm lability spans six orders of magnitude in

$Fe(DMGH)_2(MeIm)T$ T = MeIm, py > PBu_3 > $P(OBu)_3$ ≥ BzNC;CO. The delabilizing effect of π-acceptors is explained in terms of a loss of synergistic π bonding as the good donor (MeIm) is removed. The trans effect series has been explored in some depth for hemes, FePc, $Fe(DMGH)_2$, $Fe(BQDH)_2$, and $Fe(NPQH)_2$. The trans effect differs as a function of both the nature of the leaving ligand and the N_4 macrocycle. What emerges is a strong case for a delocalized bonding picture in which every ligand in a complex has an effect on the

bonding of every other ligand. Rate constants, k_{-X} or the corresponding $\Delta H^{\ddagger}_{-X}$ provide a good measure of metal ligand bond strengths since the on-rate constants k_{+X} are nearly diffusion controlled. The use of this data to better understand the deceptively simple notion of a metal ligand bond strength has been presented elsewhere.[8]

On-rates. Addition rates to pentacoordinate hemes are quite rapid[4-6] ($k=10^7$-10^8 m^{-1} s^{-1}). While directly determined on-rates for other FeN_4 systems are not currently known, competitive methods show that these pentacoordinate species are similarly weakly discriminating[9,11,13] and are likely to have similar rate constants. Addition of a ligand to a vacant coordination site is one of the most fundamental processes imaginable yet only a handful of rate contants for such reactions are currently known.[25-27]

One expects that this reaction would be complicated for iron (II) hemes since the spin state of the 5 and 6 coordinate species are different. Theoretical work for thermal reactions requiring electronically forbidden surface crossings is not highly developed.[28] Rates for spin equilibrating iron complexes involving only expansion but not breakage of metal ligand bonds seem to depend primarily on Franck-Condon factors[29] and are typically much faster than Fe-X bond making in hemes. Known on-rates to hemes and related complexes do not reveal any important spin effects other than those associated with Franck-Condon factors. For example triplet oxygen adds to either quintet hemes or doublet cobalt porphyrins[30] with comparable rates. Imidazoles, isocyanides, and O_2 add to hemes with similar rates but CO adds about 10x slower. The somewhat greater rates for CO or imidazole addition to flat (triplet) hemes compared to high spin pentacoordinate hemes is likely due to barriers associated with movement of the iron visa-vi the heme plane. The slower rates for CO addition to T-state pentacoordinate hemes[31] is a clear example of how the on-rate barrier may be increased by strain associated with movement of the iron into the heme plane. Steric effects which block access to the vacant site have been shown to have profound effects on addition rates.[6,32,3] This feature found in capped hemes and hemoproteins has been clearly documented for a variety of bulky and diatomic ligands in cyclophane hemes.[6]

PHOTOCHEMISTRY

FeN_4XY systems provide a rich supply of relatively substitution inert complexes for the investigation of photochemical axial ligand substitution reactions. The photodissociation of CO from hemes is well known. All FeN_4 systems investigated to date show a high quantum yield for CO photolysis and lower values for isocyanides, phosphines, and imidazoles.[34,35,36] The greater thermal inertness of the non-heme systems is a distinct advantage.

Extensive investigations of $Fe(DMGH)_2$ and $Fe(NPQH)_2$ complexes have been carried out involving a variety of axial ligands. Data for the photosubstitution reactions

$$FeN_4LT + E \xrightarrow{h\nu} FeN_4TE + L \qquad (5)$$

are fully consistent with a D mechanism in which the ligand L is lost from a photoactive state generating a pentacoordinate intermediate FeN_4T. The reactivity of the pentacoordinate intermediate is quantitatively probed through competitive trapping studies and the concentration dependence of ϕ. Its reactivity is essentially identical to that of the corresponding intermediate formed in dissociative thermal substitution reactions. Since both thermal and photochemical substitution reactions of FeN_4XY systems proceed via the same dissociative mechanism, they provide an ideal system to investigate the effect of electronic structure on metal ligand bond strength. The temperature dependence of the off-rate constant, k_{-L}, affords $\Delta H^{\ddagger}_{-L}$, a good measure of the ground state Fe-L bond strength.

The corresponding excited state bond activation enthalpy, $\Delta H^{\ddagger}_{-L}$*, is not as easily obtained. The quantum yields for ligand photodissociation are found to be temperature dependent from which an apparent activation energy may be obtained. While ΔEapp may include factors associated with the temperature dependence of competing photophysical processes, the major contribution to ΔEapp is likely the metal ligand bond strength in the excited state. The ΔEapp for $Fe(DMGH)_2(MeIm)X$ for X = CO, $P(OBu)_3$, BzNC and PBu_3 are ~1, 4.3, 4.6, and 8.1 kcal/mole and these correlate with the observed quantum yields. A

common low-lying thermally equlibrated ligand field state probably of picosecond lifetime involving population of d_{z^2} is likely responsible for the gross similarities in the photochemistry of hemes and other FeN_4 systems described here. The ligand field state is apparently populated with high efficiency, from π^* states in the case of hemes and phthalocyanines or from MLCT states for other FeN_4 complexes. This state should have axial ligand bonding comparable to high spin hemes or corresponding cobalt(II) analogues, both of which contain one electron in d_{z^2}. Structural data[21] for these analogues indicates axial ligand bond lengths 0.2 to 0.3A longer than low spin Fe(II). The enthalpy for piperidine binding to (pip)CoTPP is - 1.7 kcal/mole[38,39] and the off-rate constant k-pip may be estimated as a 10^8 - 10^9 s^{-1} for $CoTPP(pip)_2$.

BIOMIMETIC STUDIES

The availability of a variety of FeN_4 systems showing chemistry qualitatively similar to hemes but quantitatively quite different provides numerous possibilities for biomimetic studies. An iron phthalocyanine reconstituted myoglobin[41] displays properties which clearly illustrate the delicate balance of chemical interactions which determine a metalloprotein's reactivity. In native hemoglobin and myoglobin the unusual pentacoordinate geometry of the heme is often said to be conferred on the heme by the protein. The vacant sixth coordination site is of course critical to the reversible oxygen binding function of these proteins. The artificial protein, FePcMb, adopts a six coordinate geometry with iron coordinated to both proximal and distal histidines. The relative binding strengths of imidazole to FePc and hemes as indicated by the rate constant k^n_{-n} = 10^{-3} s^{-1} vs 1500 s^{-1} is clearly a determining factor. The precise structure of the metalloprotein is a compromise between conformational factors and metal ligand bonding. In this example, a change in the nature of the N_4 ligand can alter the iron imidazole bonding by ~ 8kcal/mole and dramatically alter the structure. A six coordinate metalloprotein must break an iron histidine bond prior to ligand addition thus retarding ligation of small molecules in both the kinetic and thermodynamic sense. Myoglobin reconstituted with the macrocyclic derivative $FeTAAB^{+2}$ seems to give similar results.[42] Here we see the importance of the unusual lability of hemes. The ready availability of hemes and their well-developed synthetic chemistry is largely responsible for the tremendous attention and success of heme biomimetic studies. Contrast work on cobaloximes vs vitamin B_{12} with that on iron dioximes vs hemes. Yet is is clear that a vast number of unexplored possibilities exist for biomimetic studies of non-heme FeN_4 systems. The lacunar supermolecules of FeN_4 tetraimines developed by Busch are the most prominent examples.[43] The remarkable properties of the glycopeptide antibiotic bleomycin has received considerable attention.[44,45] This molecule is structurally closely related to the macrocyclic iron derivatives described here suggesting that bleomycin like activity might be found in suitably modified FeN_4 systems.[46]

LINEAR CHAIN SUPERMOLECULES

The kinetic and photochemical control of reactivity possible in the more inert FeN_4 systems has led us to explore the synthesis of specifically sequenced chains of FeN_4 units connected via linearly bidentate ligands.[47] Ligands such as pyrazine (pz) 4,4'bipyridine, (bipy), and 1,4-diisocyanobenzene (DIB) may be used to synthesize chains in a systematic fashion much like the synthesis of small segments of biopolymers. The axial ligand bonds serve as both blocking and activating groups.

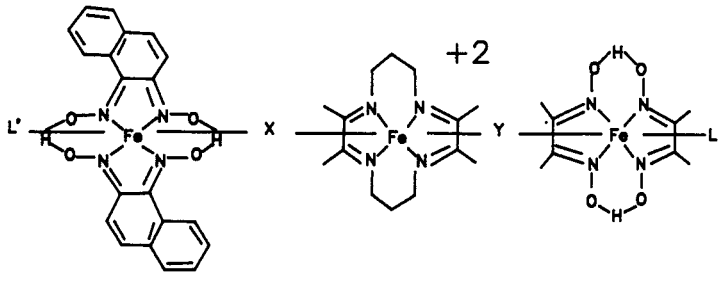

Fig. 1. Linear chain of $Fe(NPQH)_2$, $FeTIM^{+2}$, and $Fe(DMGH)_2$ where linking ligands X or Y may be bipy, pz, or DIB.

Only sufficiently inert systems (certainly not hemes) are suitable for creating viable chains. The kinetic characteristics of a variety of FeN_4 (and some RuN_4)[48-50] systems are now available. This data is especially useful in planning the synthesis of viable linked systems.

TABLE 3 SUMMARY OF LINKED COMPLEXES

	L	N_4	N_4'	L'	λ_{max}(nm)[a]
Homobinuclear:	$LFeN_4$-DIB-FeN_4L				
	Py	DMGH			426,376
	MeIm	DMGH			426,381
	Py	NPQH			540,395 sh
	MeIm	NPQH			548,400
	CH_3CN	TIM			500,402,352
	MeIm	TIM			532,422,358
Heterobinuclear:	$LFeN_4$-DIB-FeN_4'L'				
	Py	DMGH	NPQH	Py	540,426,365
	MeIm	DMGH	NPQH	MeIm	548,426,381
	Py	DMGH	TIM	MeIm	532,420
Heterotrinuclear:	$LFeN_4$-DIB-FeN_4'-DIB-FeN_4L				
	Py	DMGH	TIM		468,400 sh
	MeIm	NPQH	DMGH		546,430 sh, 380

a. TIM complexes as PF_6^- salt in CH_3CN, all others in $CHCl_3$.

Homo- and heterobinuclear compounds as well as some trinuclear compounds prepared to date are listed in Table 3.

Simple homobinuclear complexes are obtained in almost quantitative yield by reaction of a labile FeN_4L_2 L = py, MeIm, or CH_3CN with 1/2 equivalent of 1,4-diisocyanobenzene (DIB). The strong trans delabilizing effect of isocyanides renders the resulting complex substitution inert preventing polymerization. Heterobinuclear complexes are obtained by reaction of a labile FeN_4L_2 complex with a pure FeN_4L(DIB) complex. Reactions proceed cleanly and may be readily followed by visible spectroscopy. For example the reaction

$$Fe(NPQH)_2(MeIm)_2 + Fe(DMGH)_2(MeIm)(DIB) \longrightarrow (MeIm)\,Fe(NPQH)_2\text{-DIB-}Fe(DMGH)_2(MeIm) + MeIm \qquad (6)$$

is characterized by a decrease of 702 mn due to $Fe(NPQH)_2(MeIm)_2$ and an increase at 548 nm characteristic of the napthoquinone species coordinated to DIB. The free NC sites in a sample can be spectrophotometrically titrated via equation 6. Products are purified by column chromatography giving isolated materials showing single spot purity by TLC and characteristic nmr spectra, and visible spectra essentially the superposition of those of the corresponding mononuclear chromophores. These linked chromophores have potential for systematic studies of long range electron or energy transfer, as well as for biomimetic studies involving multiple recognition sites arrayed in a linear chain.

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REFERENCES

1. C.J. Weschler, D.L. Anderson, F. Basolo, J. Am. Chem. Soc., 97, 6707 (1975).
2. D. Brault, M. Rougee, Biochemistry, 14, 4100 (1975).
3. J.P. Collman, Accts. Chem. Res. 10, 265 (1977.
4. T.G. Traylor, Accts. Chem. Res. 14, 105 (1981).
5. D.W. Dixon, C. Kirmaier, D. Holten, J. Am. Chem. Soc. 107, 808 (1985).
6. T.G. Traylor, S. Tsuchiya, D. Campbell, M. Mitchell, D.V. Stynes, N. Koga, J. Am. Chem. Soc., 107, 604 (1985).
7. D. Lavalette, C. Tetreau, M. Momenteau, J. Am. Chem. Soc., 101, 5395, 1979.
8. D.V. Stynes, D. Fletcher, X. Chen, Inorg. Chem., 25, 3483, (1986)
9. D.V. Stynes, B.R. James, J. Am. Chem. Soc., 96, 2733 (1974).
10. D.V. Stynes, J. Am. Chem. Soc., 96, 5942 (1974).

11. J. Martinsen, M. Miller, D. Trojan, D.A. Sweigart, Inorg. Chem., 19, 2162 (1980).
12. I.W. Pang, D.V. Stynes, Inorg. Chem. 16, 2192 (1977).
13. X. Chen, D.V. Stynes, Inorg. Chem. 25, 1173 (1986).
14. F. Pomposo, D.V. Stynes, Inorg. Chem., 22, 569 (1983).
15. N. Siddiqui, D.V. Stynes, Inorg. Chem., 25, 1982 (1986).
16. D.V. Stynes, K. Singh, B. Ng, S. Wilshire, Inorg. Chem. Acta. 58, 197 (1982).
17. A. Butler, Linck, Inorg. Chem. 23, 2227 (1984).
18. N.K. Kildahl, T.J. Lewis, T.J. Antonopoulos, Inorg. Chem. 20, 3952 (1981).
19. D.V. Stynes, Y.S. Hui, V. Chew, Inorg. Chem. 21, 1222 (1983).
20. I.W. Pang, D.V. Stynes, Inorg. Chem. 16, 2192 (1977).
21. W.R. Scheidt, C.A. Reed, Chem. Rev., 81 543 (1981).
22. P.E. Ellis, J.E. Linard, T. Symanski, R.D. Jones, J.R. Budge, F. Basolo, J. Am. Chem. Soc., 102, 1889 (1980).
23. W.R. Scheidt and M.E. Frisse, J. Am. Chem. Soc.., 97, 17 (1975).
D.K Geiger and W.R. Scheidt, Inorg. Chem. 21, 1208 (1982).
24. G.B. Jameson, F.S. Molinaro, J.A. Ibers, J.P. Collman, J.I. Brauman, E. Rose, and K.S. Suslick, J. Am. Chem. Soc. 100 6769 (1978).
25. D. Wink, P.C. Ford, J. Am. Chem. Soc., 107, 1794 (1985).
26. S.P. Church, F.W. Grevels, H. Hermann, K. Schaffner, Inorg. Chem., 24, 418 (1985).
27. T.A. Seder, S.P. Church, A.J. Ovderkirk, E. Weitz, J. Am. Chem. Soc. 107, 1432 (1985).
28. D.C. Doetschman and J. Szumowski, J. Chem. Phys., 84, 2866 (1986).
29. E.V. Dose, M.A. Hoselton, N. Sutin, M.F. Tweedle and L.J. Wilson, J. Am. Chem. Soc., 100, 1141 (1978).
30. B.M. Hoffman and Q.H. Gibson,Proc. Nat. Acad. Sci., USA, 75, 21 (1978).
31. D.K. White, J.B. Cannon, T.G. Traylor, J. Am. Chem. Soc., 101 2443 (1979).
32. J.P. Collman, J.I. Brauman, B.L. Iverson, J.L.Sessler, R.M. Morris, Q.H. Gibson, J. Am. Chem. Soc., 105, 3052 (1983).
33. B. Ward, C. Wang, C.K. Chang, J. Am. Chem. Soc., 103, 3052 (1981).
34. A. Walch and G. Loew, J. Am. Chem. Soc. 104m 2346 (1982).
35. M.J. Incorvia, and J.I. Zink, Inorg. Chem. 16, 3161 (1977).
36. C. Irwin and D.V. Stynes, Inorg. Chem., 17, 2682 (1978).
37. D.V. Stynes and X Chen, Inorg. Chem. in press.
38. F.A. Walker, J. Am. Chem. Soc. 95, 1154 (1973).
39. C.D. Tait, D. Holten, and M. Gouterman, J. Am. Chem. Soc., 106, 6653 (1984).
40. C. Tetreau, D. Lavalette and M. Momenteau, J. Am. Chem. Soc., 105, 1506 (1983).
41. D.V. Stynes, S. Liu, and H. Marcus, Inorg. Chem., 24, 4325 (1985).
42. N. Kildahl, J. Kolis, J. Beckett, G. Holland and M. Patz, J. Coord. Chem. 12, 259 (1983).
43. T.S. Meade and D.H. Busch, "Progress in Inorganic Chemisry", S.J. Lippard, Ed., Wiley, New York, 1985, Vol.33, p.59.
44. H. Sugiyama, R. Kilkuskie, L. Chang, L. Ma and S.M, Hecht, J. Am. Chem. Soc., 108, 3852 (1986).
45. Hecht, S.M. Ed. "Bleomycin: Chemical, Biochemical and Biological Aspects", Springer-Verlag: New York, 1979.
46. P.G. Schultz, J.C. Taylor, and P.B. Dervan, J. Am. Chem. Soc., 104, 661 (1982).
47. P. Lefko and D.V. Stynes, submitted.
48. M.M. Doeff and D.A. Sweigart, Inorg. Chem., 20, 1683 (1981).
49. F. Pomposo, D. Carruthers, D.V. Stynes, Inorg. Chem., 21, 4245 (1982).
50. C. DiFelice and D.V. Stynes, unpublished results.