References and Notes

(1) H. H. Storch, N. Golumbic, and R. B. Anderson, "The Fischer-Tropsch and Related Synthesis", Wiley, New York, N.Y., 1951; H. Pichler, *Adv. Catal.*, **4**, 271 (1952); G. A. Mills and F. W. Seffgen, *Catal. Rev. Sci. Eng.*, **8**, 159 (1973); M. A. Vannice, *ibid.*, **14**, 153 (1976).

(2) F. Basolo and R. L. Burwell, Ed., "Catalysis, Progress in Research," Plenum Press, New York, N.Y., 1973; M. A. Vannice, *J. Catal.*, **37**, 449, 462 (1975); G. Henrici-Olive and S. Olive, *Angew. Chem., Int. Ed. Engl.*, **15**, 136 (1976); P. H. Spitz, *Chemtech*, 294 (1977); G. A. Mills, *ibid.*, 418 (1977); and references cited therein.

(3) J. M. Manriquez, D. R. McAlister, R. D. Sinner, and J. E. Bercaw, *J. Am. Chem. Soc.*, **98**, 6733 (1976); **100**, 2716 (1978); L. I. Shoer and J. Schwartz, *ibid.*, **99**, 5831 (1977); J. C. Huffman, J. G. Stone, W. C. Krusell, and K. G. Caulton, *ibid.*, **99**, 5829 (1977); G. Fachinetti, C. Floriani, A. Roselli, and S. Pucci, *J. Chem. Soc., Chem. Commun.*, 269 (1978); J. A. Labinger, K. S. Wong, and W. R. Scheidt, *J. Am. Chem. Soc.*, **100**, 3254 (1978).

(4) A recent report on the homogeneous hydrogenation of CO by mononuclear hydridocarbonyl complexes of Mn and Co does not involve formyl complexes: J. W. Rathke and H. M. Feder, *J. Am. Chem. Soc.*, **100**, 3623 (1978). Several metal cluster systems also hydrogenate CO: M. G. Thomas, B. F. Beier, and E. L. Muetterties, *ibid.*, **98**, 1296 (1976); G. C. Demitras and E. L. Muetterties, *ibid.*, **99**, 2796 (1977); A. K. Smith, A. Theolier, J. M. Basset, R. Ugo, D. Commereuc, and Y. Chauvin, *ibid.*, **100**, 2590 (1978).

(5) (a) P. M. Treichel and R. L. Shubkin, *Inorg. Chem.*, **6**, 1329 (1967); R. P. Stewart, N. Okamoto, and W. A. G. Graham, *J. Organomet. Chem.*, **42**, C32 (1972). (b) A. N. Nesmeyanov, K. N. Anisimov, N. E. Kolobova, and L. L. Krasnoslobodskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 860 (1970).

(6) C. P. Casey and S. M. Neumann, *J. Am. Chem. Soc.*, **98**, 5395 (1976); **100**, 2544 (1978); S. R. Winter, G. W. Cornett, and E. A. Thompson, *J. Organomet. Chem.*, **133**, 339 (1977); J. A. Gladysz, G. M. Williams, W. Tam, and D. L. Johnson, *ibid.*, **140**, Cl (1977); J. A. Gladysz and J. C. Selover, *Tetrahedron Lett.*, 319 (1978); J. A. Gladysz and W. Tam, *J. Am. Chem. Soc.*, **100**, 2545 (1978); *J. Org. Chem.*, **43**, 2279 (1978).

(7) The only characterized neutral η^1-formyl complex was prepared by hydrolysis of a Os(II) thioformyl complex: T. J. Collins and W. R. Roper, *J. Chem. Soc., Chem. Commun.*, 1044 (1976). A neutral Ru(II) formyl compound was tentatively identified as a decomposition product of a methoxide complex: B. N. Chaudret, D. J. Cole-Hamilton, R. S. Nohr, and G. Wilkinson, *J. Chem. Soc., Dalton Trans.*, 1546 (1977).

(8) (a) The reverse of intramolecular hydride transfer to a coordinated carbonyl ligand, CO "deinsertion" of a formyl group to a hydride ligand, represents an established decomposition pathway for η^1-formyl complexes: D. A. Slack, D. L. Egglestone, and M. C. Baird, *J. Organomet. Chem.*, **146**, 71 (1978), and references cited therein. (b) Intramolecular hydride transfer to coordinated thiocarbonyl and isocyanide ligands gives isolable η^1-thioformyl[7] and η^1-formimidoyl complexes with several group 8 metals: D. F. Christian, G. R. Clark, W. R. Roper, J. M. Waters, and K. R. Whittle, *J. Chem. Soc., Chem. Commun.*, 458 (1972); D. F. Christian and W. R. Roper, *J. Organomet. Chem.*, **80**, C35 (1974); D. F. Christian, H. C. Clark, and R. F. Stepaniak, *ibid.*, **112**, 209 (1976).

(9) (a) One secondary mercaptocarbene complex[7] and several secondary aminocarbene complexes are known heteroatom-stabilized secondary carbene complexes: G. R. Clark, *J. Organomet. Chem.*, **134**, 51 (1977); A. J. Hartshorn, M. F. Lappert, and K. Turner, *J. Chem. Soc., Dalton Trans.*, 348 (1978), and references cited therein. (b) For reviews on metal carbene complexes see D. J. Cardin, B. Cetinkaya, and M. F. Lappert, *Chem. Rev.*, **72**, 545 (1972); F. A. Cotton and C. M. Lukehart, *Prog. Inorg. Chem.*, **16**, 487 (1972).

(10) (a) P. W. Jolly and R. Pettit, *J. Am. Chem. Soc.*, **88**, 5044 (1966); (b) M. L. H. Green, M. Ishaq, and R. N. Whiteley, *J. Chem. Soc. A*, 1508 (1967); (c) A. Davison, W. C. Krusell, and R. C. Michaelson, *J. Organomet. Chem.*, **72**, C7 (1974); (d) T. C. Flood, F. J. DiSanti, and D. L. Miles, *Inorg. Chem.*, **15**, 1910 (1976); (e) P. E. Riley, C. E. Capshew, R. Pettit, and R. E. Davis, *ibid.*, 17, 408 (1978); (f) A. E. Stevens and J. L. Beauchamp, *J. Am. Chem. Soc.*, **100**, 2584 (1978).

(11) The more stable secondary benzylidene complexes $CpFe(CO)L(CHPh)^+$ have been prepared by protonation of the requisite α-methoxybenzyl iron complexes: M. Brookhart and G. O. Nelson, *J. Am. Chem. Soc.*, **99**, 6099 (1977).

(12) Hydride abstraction from the α position of an alkyl complex and generation of a stabilized metal carbene complex is precedented: A. Sanders, T. Bauch, C. V. Magatti, C. Lorenic, and W. P. Giering, *J. Organomet. Chem.*, **107**, 359 (1976).

(13) The ion $CpFe(CO)_2(CHOCH_3)^+$ has been detected in the gas phase by ion cyclotron resonance spectroscopy. It was evidently generated by hydride abstraction from $CpFe(CO)_2(CH_2OCH_3)$ with the ion $CpFe(CO)_2(CH_2)^+$.[10f]

(14) **2a:** IR (CH_3NO_2) $\nu_{C\equiv O}$ 2085, 2043 cm^{-1}; ^{1}H NMR (CF_3CO_2H) δ 12.88 (s, 1, FeCH), 5.55 (s, 5, Cp), 4.73 (s, 3, CH_3). **2b:** IR (CH_2Cl_2) $\nu_{C\equiv O}$ 2082, 2042 cm^{-1}; ^{1}H NMR (CD_3NO_2) δ 13.24 (s, 1, FeCH), 5.65 (s, 5, Cp), 4.97 (q, J = 7.0 Hz, 2, CH_2), 1.59 (t, J = 7.0 Hz, 3, CH_3). Anal. Calcd for $C_{10}H_{11}O_3FePF_6$: C, 31.61; H, 2.92. Found: C, 31.82; H, 3.12. **2c:** IR (CH_2Cl_2) $\nu_{C\equiv O}$ 1995 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 13.50 (br s, 1, FeCH), 7.65 (s, 15, Ph_3P, 5.28 (d, J = 1.5 Hz, 5, Cp), 4.09 (s, 3, CH_3). Anal. Calcd for etherate $C_{30}H_{34}O_3F_6P_2$: C, 53.43; H, 5.08. Found: C, 53.13; H, 4.81. **2d:** IR (CH_2Cl_2) $\nu_{C\equiv O}$ 1990 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 13.67 (d, J = 1.5 Hz, 1, FeCH), 7.70 (s, 15, Ph_3P), 5.32 (d, J = 1.5 Hz, 5, Cp), 4.40 (m, 2, CH_2), 1.06 (t, J = 7.0 Hz, 3, CH_3). Anal. Calcd for $C_{27}H_{26}O_2FeF_6P_2$: C, 52.79; H, 4.27. Found: C, 53.02; H, 4.49.

(15) Sterically less demanding trans isomers are depicted for **2:** W. K. Dean and W. A. G. Graham, *Inorg. Chem.*, **16,** 1061 (1977). We found no evidence for restricted rotation about either the (carbene) C–O bond (cis–trans isomerization) or the Fe–C(carbene) bond (conformational isomerization).

(16) (a) M. L. H. Green and C. R. Hurley, *J. Organomet. Chem.*, **10**, 188 (1967); (b) M. L. H. Green, L. Mitchard, and M. Swanwick, *J. Chem. Soc. A*, 794 (1971); (c) A. Davison and D. Reger, *J. Am. Chem. Soc.*, **94**, 9237 (1972); (d) P. M. Treichel and K. P. Wagner, *J. Organomet. Chem.*, **88**, 199 (1975).

(17) R. K. Kochhar and R. Pettit, *J. Organomet. Chem.*, **6**, 272 (1966).

(18) Anionic formyl complexes transfer hydride to organic and inorganic substrates.[6] In addition, these formyl complexes may also act as hydride acceptors, with methanol as the ultimate product.

(19) J. A. Van Doorn, C. Masters, and H. C. Volger, *J. Organomet. Chem.*, **105**, 245 (1976).

(20) A. Davison, M. L. H. Green, and G. Wilkinson, *J. Chem. Soc.*, 3172 (1961).

Water-Soluble Polyphosphazenes as Carrier Molecules for Iron(III) and Iron(II) Porphyrins[1,2]

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Abstract: The water-soluble poly(aminophosphazenes) $[NP(NHCH_3)_2]_n$ (**1**) and $[NP(NHCH_3)_x(NHCH_2CH_2CH_2C_3N_2H_3)_y]_n$ (**2**) (containing the 3-(1-imidazolyl)propylamino group) have been investigated as polymeric "carrier" ligands for iron(III) and iron(II) protoporphyrin IX. In the presence of aqueous polymer **1**, hemin or heme exists as hematin–hemin hydroxide or bisaquoheme, respectively, with only weak (probably acid-base) binding between the polymer and the metalloporphyrin. However, polymer **2** binds strongly to both heme and hemin via the imidazole residues. In aqueous solution or as solid films, the presence of the polymeric ligands did not prevent the irreversible oxidation of heme on contact with oxygen. Polymer–heme complexes of polymers **1** and **2**, including the CO and oxidized complexes, were characterized by electronic absorption and Mössbauer spectroscopy. Although the Mössbauer data confirmed that Fe(II) oxidation occurred on contact with O_2, the electronic spectra were compatible with reversible dioxygen binding. The apparent "dioxygen cycling" in the solid state was attributed to oxidation of Fe(II) by dioxygen, followed by reduction of the Fe(III) by the polymer or, in some cases, by residual reducing agent.

In this paper we report the synthesis of a new, high polymeric, water-soluble carrier molecule (**2**) for the binding of metalloporphyrins, and the behavior of this polymer as a coordination ligand for hemin and heme in aqueous solution and in the solid state. The behavior of polymer **2** as a ligand is compared to that of the related macromolecule, **1**. The re-

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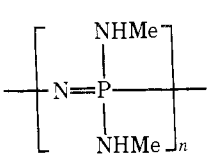

$[-N{=}P(NHMe)_2-]_n$

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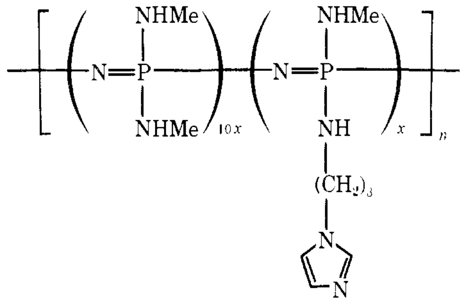


2

$n \simeq 15\,000$

sponse of heme complexes of **1** or **2** to carbon monoxide and dioxygen has also been examined.

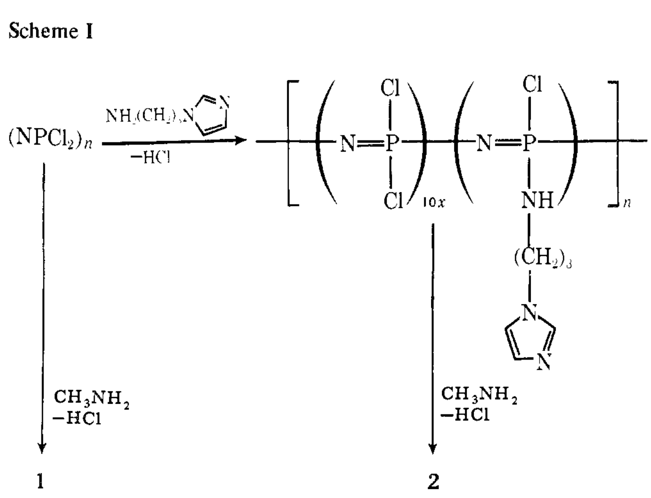
Synthetic metal complexes that bind oxygen reversibly are of interest for a variety of reasons.[5] Such complexes provide information about the mechanism of oxygen transport in living systems or offer the long-range biomedical prospect of hemoglobin substitutes.[6-16] Alternatively, complexes of this type could, in theory, function as catalysts for the conversion of oxygen to water.

The ability of hemoglobin or myoglobin to bind dioxygen reversibly constitutes a well-known anomaly when compared with the oxidative instability of simple ferrous compounds in the presence of oxygen and water. This phenomenon has been ascribed to a number of factors. These include (a) the existence of a hydrophobic pocket around the iron porphyrin site which retards oxidative electron transfer from iron to oxygen in the nonpolar environment, (b) the inability of the iron-porphyrin units to approach closely enough in the metalloprotein system to permit μ-oxo bridged dimer formation—an apparent prerequisite for oxidation to the Fe(III) species, and (c) the existence of an environment of low acidity, since acids facilitate the oxidation of hemoglobin and myoglobin.[10]

Several model systems have been described in which metalloporphyrin structures have been designed to mimic the environment of the prosthetic group in hemoglobin. The "picket fence" structure of Collman[6] and the capped porphyrin of Baldwin[7] provide hydrophobic environments for the metal and also retard dimerization. Model porphyrins synthesized by Traylor[8] have been used to examine the role played by the fifth and sixth ligands attached to Fe(II), and Basolo[9] has studied the behavior of iron(II) porphyrin structures physically separated from each other on the surface of particles of silica gel. All of these systems bind oxygen in organic media, often at low temperature. The effect of physical separation was also studied earlier by Wang,[10] who embedded a heme ester in a solid hydrophobic polystyrene matrix and observed reversible dioxygen binding. However, the free heme carboxylic acid was irreversibly oxidized under the same conditions. None of these small molecule model systems reversibly bound oxygen in aqueous media at ambient temperatures.

The reasoning behind our work is as follows. A polymer molecule in solution generally occupies a random coiled conformation in which parts of the molecule may be shielded from other parts. Moreover, a metalloporphyrin bound strongly to one polymer molecule may be shielded from similar units attached to other chains or to distal parts of the same chain. A finite probability exists that metalloporphyrin dimerization may occur under such circumstances especially at the extreme of high dilutions, but that probability is expected to be lower than in the absence of polymer. In very concentrated polymer solutions or in the solid state, this shielding should be highly effective even when the matrix is comprised of a hydrophilic polymer, perhaps containing water molecules trapped in the lattice. During the course of our investigation, two reports have appeared of similar approaches taken by other groups. Tsuchida and co-workers[11] utilized solutions of iron(II) protoporphyrin IX in aqueous poly(4-vinylpyridine) or poly(*N*-vinyl-2-methylimidazole) for oxygenation-deoxygenation experiments. Electronic spectral evidence was obtained for the formation of a dioxygen complex, but oxygen could only be removed by displacement with carbon monoxide. Bayer and Holzbach[12] reported that an imidazolyl-heme analogue, bound covalently to poly(ethylene oxide) or a poly(ethylene oxide)-urethane copolymer, absorbed and released dioxygen readily at 25 °C in dilute aqueous media. Our observations differ markedly from these reports.

Scheme I



$n \approx 15\,000$

Our aim was to devise a synthetic polymer system that would bind metalloporphyrins and solubilize them in aqueous media. An additional objective was to provide a coordinative binding site attached to the polymer that might function as a model for the binding sites in naturally occurring metalloproteins. For the reasons discussed above, the selection of a basic polymer was seen to be a distinct advantage over an acidic one. An ideal carrier polymer should also be capable of subtle structural modification to optimize the coordinate solvation and conformational characteristics. In a long-range practical sense, the carrier polymer chosen should be biologically compatible and capable of retarding the excretion of small molecules bound to it. Polymer **2** fulfills many of these requirements.

Results and Discussion

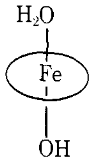
Synthesis and Characteristics of the Carrier Polymers. Polymer **2** was synthesized by the route shown in Scheme I. The synthesis of poly[bis(methylamino)phosphazene] (polymer **1**) was described earlier.[17] Polymer **1** is a hydrolytically stable macromolecule that is soluble in water, alcohols, and chloroform. Aqueous solutions are basic (pH 8-9 for a 1% w/v solution) and hydrogen chloride is bound strongly as a salt. This polymer has recently been shown to possess donor coordination sites for transition metals such as platinum, and X-ray cyrstallographic work with the model compound, $[NP(NHCH_3)_2]_4{\cdot}PtCl_2$, showed that the *skeletal* nitrogen atoms coordinate to the metal.[1] This is compatible with other studies which suggest that the skeletal nitrogen atoms in aminophosphazenes are more basic than those in the side groups.[18]

Polymer **2** was synthesized to provide a water-soluble macromolecule with a stronger, more accessible coordination binding site for iron than that provided by polymer **1**. This polymer was expected to form complexes that could be compared spectroscopically with hemoglobin and myoglobin. In the synthesis of polymer **2**, the 3-(1-imidazolyl)propylamino groups were introduced first in order to favor the maximum separation of these units along each chain. The remaining phosphorus-chlorine bonds were then removed by reaction with methylamine. The resultant polymer was both water soluble and hydrolytically stable. Approximately one repeating group in 11 bore a pendant imidazole group.

Overall Approach. The overall approach used in this work was as follows. Hemin chloride (iron(III) protoporphyrin IX chloride) was dissolved in aqueous solutions or aqueous ethanolic solutions of polymer **1** or **2**. Initial experiments were carried out to establish whether or not the iron porphyrin was bound to the polymer in solution and to determine the nature of the binding. The polymer-iron(III) porphyrin systems were then reduced to the polymer-iron(II) porphyrin state with the use of dithionite ion. The resultant solutions, or films made from them, were subsequently exposed to atmospheric oxygen, and the nature of the products was determined by electronic and Mössbauer spectroscopy. Removal of bound oxygen was attempted at reduced pressures. The binding of carbon monoxide was also examined. Each of these aspects will be discussed in turn.

Mode of Binding of Polymers 1 and 2 to Hemin Chloride. Hemin chloride dissolved in aqueous solutions of **2** to form red polymer-bisimidazole hemin complexes. This mode of binding was indicated by the typical hemichrome electronic spectra and by Mössbauer spectra of frozen solutions or films at the same temperature (see Table I). However, the Mössbauer spectra also indicated the presence of some unbound hematin and hemin hydroxide (**3**), especially in the frozen aqueous medium.

By contrast, aqueous solutions of hemin chloride with polymer **1** contained hematin or hemin hydroxide only, with no evidence for a direct coordination binding (**4**) between polymer **1** and Fe(III). In fact, the binding between polymer **1** and hemin appeared to be mainly through acid-base interactions between the carboxylic acid residues of hemin and the basic nitrogen atoms of the polymer (**5**). These conclusions are based on the following observations.



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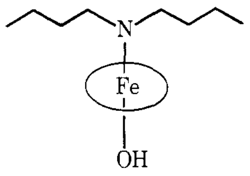

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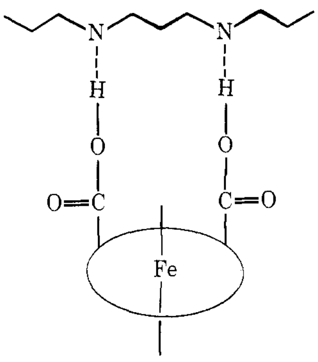

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First, hemin chloride dissolves in aqueous solutions of polymer **1** (either unbuffered or buffered to pH 7) to yield green solutions. Hemin chloride is insoluble in water at pH 7, but dissolves at pH >9.6 to form hematin (hemin hydroxide). The visible and Mössbauer spectra of the hemin-polymer **1** system were identical with those of hematin. Second, low molecular weight metal complexes can penetrate semipermeable membranes, whereas high polymers cannot. This difference may be used as a tentative criterion of binding between a small molecule and a high polymer. For example, polymer **2** inhibited the dialysis of hemin in ethanol solution. In 100% ethanol or 60% ethanolic water, polymer **1** retarded but did not prevent the dialysis of hemin through a cellulose dialysis tube. When added imidazole or pyridine was also present, the rate of dialysis was completely independent of the presence or absence of polymer **1**. This indicates only a weak form of binding between hemin and polymer **1**, and one that can readily be broken by an added small molecule organic base. A carboxylic acid-polymer base interaction would be compatible with this observation. In aqueous solutions of polymer **1**, as well as in the films obtained by evaporation of the aqueous solvent, the iron(III) protoporphyrin IX is present as hematin.

Table I. Electronic and Mössbauer Spectral Data

system	electronic spectral peaks, nm	Mössbauer spectra δ, mm/s[a]	Mössbauer spectra Δ, mm/s
hemin + **1** + H_2O	395,[b] ~585 (broad)	0.40	0.59
heme + **1** + H_2O	415,[b] 526, 557 (broad)	0.62	1.47
heme + **1** + H_2O + CO	411,[b] 535, 565	0.26	0.31
heme + **1** as film	430,[b] 520-600 (broad)	0.58[c] 1.00	1.47[c] 4.60
heme + **1** film + O_2	400,[b,e] 520-600 (broad)[e]	0.40	0.60
hematin-hemin hydroxide in H_2O	395,[b] ~585 (broad)	0.33	0.62
bisaquoheme[19]		0.57[c] 0.98	1.30[c] 4.41
hemin + **2** + H_2O	407,[b] 532, 562	0.25 0.40	2.10[d] 0.60
heme + **2** + H_2O and as a film	420,[b] 530,[d] 560[d]	0.45	1.0
heme + **2** + H_2O + CO	412,[b] 540, 572	0.26	0.33
heme + **2** as a film + CO[f]	412,[b] 520-570 (broad)	0.26	0.33
heme + **2** as film + O_2	412,[b,e] 520-570 (broad)[e]	0.20	2.0

[a] Relative to metallic iron. [b] Soret band. [c] Main peaks. [d] Sharp peaks. [e] These peaks appeared with oxygenation and disappeared when the system was evacuated: the process could be recycled. [f] Prepared by treatment of heme + **2** + O_2 or heme + **2** as film with CO.

Mode of Binding of Polymers 1 or 2 to Iron(II) Protoporphyrin IX. Solutions of hemin in aqueous polymer **1** and **2** were reduced by treatment with aqueous sodium dithionite. The hemin-polymer **1** system underwent a color change from green to brown during this step, and the hemin-polymer **2** system changed from red to cherry red. Dithionite addition to the deoxygenated solutions was usually continued until no further change was observed in the Soret region of the spectrum. As discussed in the Experimental Section, an excess of dithionite was invariably required in order to effect complete reduction. Excess dithionite could, in principle, reduce oxidized iron, formed by the irreversible reaction with dioxygen, and this could give the appearance of reversible oxygen binding.[21] For this reason, Mössbauer evidence for an iron-dioxygen complex as well as *multiple* reversible oxygen binding cycles is needed to ensure that the effect is not spurious.

The hemin to heme reduction process was monitored by the change in electronic absorption spectra, by Mössbauer spectroscopy, and by formation of the carbon monoxide complexes (Table I). The Mössbauer and electronic spectra of the heme-polymer **2** system were compatible with that of a six-coordinate bisimidazole-heme complex, and this structure persisted when water was removed to form a solid film. The presence of the Fe(II) form in solution and in the solid polymer was also confirmed by the formation of a complex with carbon monoxide. Thus, the evidence indicates that the metalloporphyrin remains coordinatively bound to polymer **2** after reduction. No evidence was found for the five-coordinate structure that is characteristic of the deoxy hemoglobin or deoxy myoglobin systems.

Reduction of hemin in the presence of polymer **1** yielded bisaquoheme, which was detected by both Mössbauer spectroscopy and electronic spectroscopy. This species also formed a red carbon monoxide complex. The addition of imidazole or pyridine to the heme-polymer **1** solution converted the brown color to red as bisimidazole heme and bispyridine heme were formed. This behavior is also compatible with the presence of bisaquoheme. Removal of water from the heme-polymer **1** system yielded films and freeze-dried solids that contained monomeric bisaquoheme, although slight shifts in the Mössbauer spectrum (Table I) raised the possibility that four-coordinate (deaquo) heme might be present. Specifically, a heme-polymer **1** film showed a very similar Mössbauer spectrum (δ 0.58, Δ 1.47, and δ 1.0, Δ 4.60 in mm/s) to that of an authentic sample of monomeric heme[19] formed in aqueous detergent (δ 0.57, Δ 1.30, and δ 0.98, Δ 4.41 mm/s). The slight spectral shifts could be compatible with the loss of two water molecules, a process that appears reasonable in view of the facile loss of pyridine from bispyridine heme under vacuum.[20] The Mössbauer spectrum of heme-polymer **1** did not resemble those of bishydroxyheme (δ 0.62 mm/s, Δ 1.70 mm/s) or dimeric heme (δ 0.63 mm/s, Δ 1.51 mm/s). Thus, the evidence indicates that the metalloporphyrin remains essentially unbound to polymer **1** after reduction. Presumably, in solid films of polymer **1**, the heme is isolated in interstices or vacuoles within the polymer matrix.

Interaction of Heme-Polymer Systems with O_2 and CO. After reduction of hemin to heme in the presence of polymer **1** or **2**, dioxygen or carbon monoxide was admitted to the system, and the reaction products were examined. The presence of polymer **1** or **2** did not prevent the rapid, irreversible oxidation of heme to hemin in dilute aqueous solution at 25 °C. However, the solid films obtained by removal of water from both of these systems underwent apparent reversible changes when exposed to oxygen or carbon monoxide. Specifically, when thin films of heme-polymer **2** were exposed for 24 h, the Soret absorbance underwent a shift from 420 to 412 nm. Subsequent storage of the film under vacuum for 1 week reversed this change, and the process could be recycled for at least three or four times, although the amount of Fe(II) which participated in this reversible reaction decreased with each cycle. Similarly, exposure of the film to carbon monoxide induced a reversible Soret absorbance shift to 412 nm.

The reaction of heme-polymer films with carbon monoxide resulted in the formation of a reversible carbon monoxide complex as indicated by both Mössbauer and electronic spectra (Table I). However, because the iron can be *oxidized* by contact with dioxygen and then reduced by excess dithionite[21] or the polymer itself, it was necessary to specifically identify a heme-O_2 complex to confirm that the observed cycling was in fact the result of reversible dioxygen binding. Thus, similar experiments were carried out with freeze-dried solid samples of heme-polymer **1** and heme-polymer **2** samples, and the products were monitored by Mössbauer spectroscopy. Although the reaction with dioxygen was slow, probably because of a low permeability of oxygen through the polymer films, the change in the Mössbauer spectrum of the solid heme-polymer was consistent with the formation of *oxidized* complexes (Table I). The reaction of the oxygen with heme embedded in the polymer films occurred faster when the films were plasticized with water or ethanol. The Mössbauer spectra of the heme-polymer solid never indicated complete oxidation. Instead, mixtures of the oxidized and reduced complexes were present even after 1 month exposure to O_2 (1 atm). It appears, therefore, that the visible spectra of the heme-polymer complexes generated after reaction with dioxygen were mixtures of Fe(II) and Fe(III) and *not* Fe(II)-O_2 complexes. The apparent cycling that was observed was due to "reversible" oxidation-reduction caused by the presence of excess reducing agent.

The hemin-polymer **2** complex yields a Mössbauer spectrum which is similar to that of oxymyoglobin or oxyhemoglobin (oxyhemoglobin δ 0.26, Δ 2.19,[23] hemin-polymer **2** δ 0.25, Δ 2.10 at 77 K). Although the similarities may be somewhat misleading, the product formed from heme-polymer **2** in the presence of dioxygen was definitely shown by Mössbauer spectroscopy to be the *oxidized* complex because the spectrum was highly sensitive to temperature changes. Thus, the peaks were broadened considerably at 4.2 K compared to the spectrum at 77 K. This temperature dependence is consistent with a low-spin Fe(III) complex. The Mössbauer spectrum of oxyhemoglobin does not exhibit this extreme temperature sensitivity.[23]

A sample of the freeze-dried heme-polymer **2** solid, which had been partially oxidized by exposure to oxygen, was treated with carbon monoxide. The Mössbauer spectrum revealed a decrease of both the reduced and oxidized absorbance bands as the characteristic peaks of the CO complex became evident. Thus rereduction of any oxidized material by excess reducing agent appears to be a more facile process in a CO atmosphere. The generation of a CO complex from the reaction product of heme with dioxygen constitutes proof of the oxygen complex only *in the absence of excess reducing agent.* because only an Fe^{II}-O_2 complex, but not an Fe(III) complex, would react with CO.

The Mössbauer data and the electronic spectral data are consistent with each other if it is assumed that the cycling detected from the electronic spectrum is due to oxidation followed by reduction either by residual $Na_2S_2O_4$ or by the polymer itself. The following experiment was carried out to test this supposition. Hemin chloride was added to a solution of **1** in chloroform or ethanol. A solid film was then prepared of the products, and the Soret absorbance of the hemin was monitored at 403 nm. This absorbance was at a higher wavelength than for the oxidized complex in solution (see Table I). The Soret band shifted to 420 nm when the film was allowed to stand under vacuum for 72 h. The film now contained Fe(II), as indicated both by the electronic absorption spectrum and by the fact that the system reacted with molecular oxygen. The reduction process was more apparent when films were cast from an organic solvent than when they were prepared from aqueous solution. Hydration or protonation of $[NP(NHCH_3)_2]_n$ therefore inhibits this reductive process. Films of **1** that contained tetraphenylporphyrin iron(III) chloride also produced the Fe(II) state when stored under vacuum. A similar (but transient) process occurred when the high polymer, $[NP(OCH_2CF_3)_2]_n$, was used as a matrix, and this suggests that the reduction process may involve the skeletal lone-pair electrons. Polymer **1**-heme films prepared by the reduction of hemin chloride with $Na_2S_2O_4$ in water exhibited a cycling phenomenon when alternately exposed to O_2 and then placed under vacuum. However, this observed cycling is probably due to the presence of dithionite. We have also observed this reversible cycling in *aqueous solution* when the amount of $Na_2S_2O_4$ used was far in excess of that needed for complete reduction.

Structural and Mechanistic Conclusions. Polymers **1** and **2** differ in their capacity to function as carrier molecules for hemin and heme in aqueous solution and in the solid state. Polymer **1** participates mainly by providing an alkaline medium for the generation of hematin–hemin hydroxide or bisaquoheme species and by restricting the free diffusion of the metalloporphyrin molecules by the formation of salt links between basic sites on the polymer and the carboxylic acid groups of the iron porphyrins. On the other hand, polymer **2** binds strongly to the Fe(III) or Fe(II) site via the pendant imidazole side groups and, presumably, also anchors the metalloporphyrin via carboxylic acid–skeletal nitrogen salt linkages. However, this improved anchoring does not significantly retard the oxidation of Fe(II) to Fe(III) in dilute aqueous solution. An oxidative pathway involving charge delocalization, as suggested by Wang,[10] appears to be operative.

This, in itself, is surprising in view of the published report by Bayer and Holzbach[12] that bisimidazole–heme-type complexes that are linked covalently to poly(ethylene glycol) or poly(ethylene glycol urethanes) (polymer **6**) rapidly and reversibly bind dioxygen at 25 °C in aqueous buffer at pH 8.1. The main differences between that system and our own follow: (1) Polymer **2** possesses on the average one imidazolyl group per 11 repeating units, whereas polymer **6** contains one imdiazolyl group per chain. (2) The complexes formed between polymer **2** and heme possess free carboxylic acid groups. Polymer **6** contains only one, and a derivative of this polymer contains no free carboxylic acid groups. (3) The basicity of polymer **2** is higher than that of polymer **6**. However, the visible spectra reported for the complexes of polymer **6** are almost identical with those observed by us for the polymer **2** complexes. In particular, our reduced heme–polymer **2** complex is a six-coordinate bisimidazolyl complex, but polymer **6** was reported to yield a five-coordinate complex. The Soret absorption occurred at 421 nm for the reduced complex of polymer **6**, and the Soret band was at 420 nm for the reduced complex of polymer **2**. Polymer **2**–heme and polymer **6**–heme had identical spectra for the O_2 and CO complex. As discussed, the O_2 complex of polymer **2**–heme really consists of mixtures of the reduced and oxidized complexes.

Another polymer–heme system, prepared by Tsuchida et al.,[11d] was also reported to yield an oxygen complex. The polymer used was poly(4-vinylpyridine). Although the system would not cycle between the oxy and the deoxy forms, it was reported that bound oxygen could be displaced by CO. However, bound oxygen could not be displaced by evacuation or by flushing with an inert gas. Large amounts of reducing agent were present (100-fold molar excess per Fe), and there exists the possibility that here, also, oxidation of Fe(II) occurred on contact with oxygen, followed by reduction by excess reducing agent.

Comparisons with Hemoglobin and Myoglobin. Although heme–polymer **1** and heme–polymer **2** complexes are oxidized in contact with oxygen, both systems bind carbon monoxide. The visible spectra of the polymer–heme–CO complexes are different from those of carbon monoxymyoglobin or carbon monoxyhemoglobin, but the Mössbauer spectra are virtually identical (Table I).

Experimental Section

Equipment and Materials. Electronic absorption spectra were recorded on a Cary 17 spectrophotometer with the use of 1-cm glass cells equipped with Teflon stopcocks. All procedures that involved the use of Fe(II) species were carried out under nitrogen or on a glass high-vacuum line. Mössbauer spectra were recorded at 77 and 4.2 K of the frozen solutions or the dehydrated solids freeze-dried from H_2O, with the samples placed in 3- or 7-mm thick polyethylene containers. ^{57}Fe-enriched porphyrins were synthesized to obtain the maximum spectral sensitivity.

Sodium dithionite, $Na_2S_2O_4$ (J. T. Baker), *N*-(3-bromopropyl)phthalimide (Aldrich), $AgNO_3$ (Fisher), hydrazine hydrate (Mallinckrodt), and hexadecyltrimethylammonium bromide (Eastman) were used as received. Triethylamine (Eastman) was dried and distilled from BaO. Methylamine (Matheson) was dried and distilled from metallic sodium before use, imidazole (Eastman) was recrystallized from benzene and sublimed before use, and pyridine (Eastman) was distilled from KOH. Carbon monoxide and oxygen (Air Products) were used as received. Hexachlorocyclotriphosphazene $(NPCl_2)_3$ (El Monte Chemical Corp.) was separated from the mixture of higher cyclic species by sublimation. It was recrystallized from hot *n*-heptane and resublimed before use (mp 111–113 °C). 3-(1-Imidazolyl)propylamine dihydrochloride was prepared by the method reported by Schwan.[24]

Benzene and *n*-heptane (Fisher) were dried and distilled from CaH_2. Tetrahydrofuran (THF) (Fisher) was dried and distilled from $LiAlH_4$. Water was distilled once before use. The monobasic potassium phosphate-sodium hydroxide buffer (pH 7) was obtained from Fisher.

The various hemin and heme modifications were obtained as follows. Hemin chloride (Nutritional Biochemical Corp.) was used as received. Monomeric heme was prepared by the published method[19] as was dimeric heme[19] and bishydroxyheme.[25] Tetraphenylporphyrin iron(III) chloride (TPPFeCl) was obtained from Strem Chemicals Inc. Cellulose dialysis tubing was obtained from Fisher.

Polymer 1. Poly(dichlorophosphazene), $(NPCl_2)_n$, was prepared by the thermal polymerization of $(NPCl_2)_3$ (200 g) in an evacuated, sealed glass tube at 250 °C for 8–24 h.[26] The unpolymerized trimer (~120 g) was removed by vacuum sublimation at 50 °C. The polymer was dissolved in benzene to yield a ~3% solution, and this was added slowly with stirring to a fivefold excess of methylamine in THF at 0 °C. After 24-h reaction at 0 → 25 °C, the precipitate was collected, dissolved in water, and purified by dialysis in water for 3 days. Concentration of the dialyzed solution and precipitation into THF yielded polymer **1**.[17]

Polymer 2. 3-(1-Imidazolyl)propylamine dihydrochloride[24] was placed in benzene (250 mL). Triethylamine (10 mL) was added to the amine hydrochloride, and the mixture was boiled at reflux for 3 h under nitrogen. The reaction mixture was added to a solution of $(NPCl_2)_n$ (10 g) in benzene (800 mL), prepared as described above, at 0 °C under nitrogen. Methylamine (100 mL) was added quickly to the polymer solution and the reaction mixture was stirred for 24 h. The precipitate was collected, dissolved in water, and dialyzed against water for 72 h. The aqueous solution was concentrated and the polymer, $\overline{M}_n \sim 2.6 \times 10^6$, was isolated by precipitation into THF.

Hemin and Heme–Polymer Complexes. Hemin chloride (1×10^{-6} mol) was added to aqueous solutions of polymer **1** or **2** (1% w/v) at 25 °C. These solutions were then examined directly by UV–visible spectroscopy and by Mössbauer techniques as frozen solutions or freeze-dried solids. Reduction of hemin to heme was accomplished by the addition of aqueous solutions of sodium dithionite (prepared from freshly opened bottles or evacuated storage vials) until no further change could be detected in the electronic spectrum. As reported by other workers[11d] an appreciable excess of dithionite was often required to achieve complete conversion to heme, even when oxygen was rigorously excluded from the system. A tenfold excess of dithionite frequently resulted in only a 50% reduction to heme, and a ~50-fold excess was occasionally required to achieve 100% reduction. The reduction was carried out in UV–visible cells that were equipped with vacuum-line connectors. Films were prepared directly on the walls of the cell by removal of the water under vacuum. Exposure of these films to oxygen or carbon monoxide took place by the addition of the reactive gases to the evacuated cell. Removal of bound carbon monoxide was accomplished by evacuation of the system at 10^{-2}–10^{-3} Torr via a vacuum line. The spectroscopic changes that accompanied these processes are typified by the spectra shown in Table I.

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References and Notes

(1) Previous related papers on the biological uses of phosphazene polymers: H. R. Allcock, R. W. Allen, and J. P. O'Brien, *J. Am. Chem. Soc.*, **99**, 3984, 3987 (1977).

(2) Previous papers in the series: (a) H. R. Allcock, T. J. Fuller, K. Matsumura, and K. M. Smeltz, *Macromolecules*, **10**, 824 (1977); (b) H. R. Allcock, J. L. Schmutz, and K. M. Kosydar, *ibid.*, **11**, 179 (1978).

(3) Deceased 1974.

(4) Part of this work was taken from the Ph.D. Thesis of J. L. Schmutz, The Pennsylvania State University, 1976.

(5) J. P. Collman, C. M. Elliot, T. R. Halbert, and B. S. Tovrog, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 18 (1977).

(6) (a) J. P. Collman, R. R. Gagne, T. R. Halbert, J. C. Marchon, and C. A. Reed, *J. Am. Chem. Soc.*, **95**, 7868 (1973); (b) J. P. Collman, R. R. Gagne, and C. A. Reed, *ibid.*, **96**, 2629 (1974); (c) J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang, and W. T. Robinson, *ibid.*, **97**, 1427 (1975); (d) J. P. Collman, R. R. Gagne, and C. A. Reed, "Organo-Transition Metal Chemistry", Y. Ishii and M. Tsutsui, Ed., Plenum Press, New York, N.Y., 1975, p 329; (e) J. P. Collman, J. I. Brauman, and K. S. Suslick, *J. Am. Chem. Soc.*, **97**, 7185 (1975); (f) J. P. Collman and C. A. Reed, *ibid.*, **95**, 2048 (1973).

(7) (a) J. Almog, J. E. Baldwin, R. L. Dyer, and M. Peters, *J. Am. Chem. Soc.*, **97**, 226 (1975); (b) J. Almog, J. E. Baldwin, and J. Huff, *ibid.*, **97**, 227 (1975).

(8) (a) C. K. Chang and T. G. Traylor, *J. Am. Chem. Soc.*, **95**, 5810 (1973); (b) *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2647 (1973); (c) W. S. Brinigar and C. K. Chang, *J. Am. Chem. Soc.*, **96**, 5595 (1974); (d) W. S. Brinigar, C. K. Chang, J. Geibel, and T. G. Traylor, *ibid.*, **96**, 5597 (1974); (e) C. K. Chang and T. G. Traylor, *Biochem. Biophys. Res. Commun.*, **62**, 719 (1975).

(9) O. Leal, D. A. Anderson, R. G. Bowman, F. Basolo, and R. L. Burwell, Jr., *J. Am. Chem. Soc.*, **97**, 5125 (1975).

(10) (a) J. H. Wang, *J. Am. Chem. Soc.*, **80**, 3168 (1958); (b) J. H. Wang, *Haematin Enzymes, Symp. Int. Union Biochem.*, **19**, 98 (1961).

(11) (a) E. Tsuchida, K. Honda, and H. Sata, *Biopolymers*, **13**, 2147 (1974); (b) E. Tsuchida, K. Honda, and E. Hasegawa, *Biochim. Biophys. Acta*, **393**, 483 (1975); (c) E. Tsuchida, E. Hasegawa, and K. Honda, *Biochem. Biophys. Res. Commun.*, **67**, 846 (1975); (d) E. Tsuchida, K. Honda, and H. Sata, *Inorg. Chem.*, **15**, 352 (1976).

(12) E. Bayer and G. Holzbach, *Angew. Chem., Int. Ed. Engl.*, **16**, 117 (1977).

(13) (a) A. H. Corwin and Z. Reyes, *J. Am. Chem. Soc.*, **78**, 2437 (1956); (b) A. H. Corwin and S. D. Bruck, *ibid.*, **80**, 4736 (1958).

(14) P. L. Anderson, C. J. Weschler, and F. Basolo, *J. Am. Chem. Soc.*, **96**, 5599 (1974).

(15) G. C. Wagner and R. J. Kassner, *J. Am. Chem. Soc.*, **96**, 5593 (1974).

(16) (a) J. E. Baldwin and J. Huff, *J. Am. Chem. Soc.*, **95**, 5757 (1973); (b) J. Almog, J. E. Baldwin, R. C. Dyer, J. Huff, and C. J. Wilkerson, *ibid.*, **96**, 5600 (1974).

(17) H. R. Allcock, W. J. Cook, and D. P. Mack, *Inorg. Chem.*, **11**, 2584 (1972).

(18) (a) D. Feakins, W. A. Last, and R. A. Shaw, *J. Chem. Soc.*, 4464 (1964); (b) D. Feakins, W. A. Last, S. N. Nabi, and R. A. Shaw, *J. Chem. Soc. A*, 1831 (1966).

(19) J. E. Falk, "Porphyrins and Metalloporphyrins", Elsevier, Amsterdam, 1964, p 81.

(20) J. O. Allen, W. H. Fuchsman, C. A. Beaudreau, and W. S. Caughey, *Biochemistry*, **7**, 624 (1968).

(21) M. J. Cowan, J. M. F. Drake, and R. J. P. Williams, *Discuss. Faraday. Soc.*, **27**, 217 (1959).

(22) C. M. Epstein, D. K. Straub, and C. Maricondi, *Inorg. Chem.*, **6**, 1720 (1967).

(23) G. Lang and W. Marshall, *Proc. Phys. Soc., London*, **87**, 3 (1966).

(24) T. S. Schwan, *J. Heterocycl. Chem.*, **4**, 633 (1967).

(25) J. Keilin, *Nature (London)*, **165**, 151 (1950).

(26) H. R. Allcock, R. L. Kugel, and K. J. Valan, *Inorg. Chem.*, **5**, 1709 (1966).

Ligand Exchange in TaX(η^4-naphthalene)($Me_2PC_2H_4PMe_2$)$_2$. The Pentagonal Bipyramid to Monocapped Trigonal Prism Traverse

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Abstract: Treatment of $TaCl_4(dmpe)_2$ (dmpe = 1,2-bis(dimethylphosphino)ethane) with sodium naphthalene affords TaCl(η^4-$C_{10}H_8$)(dmpe)$_2$, which is reduced by additional sodium naphthalene to an unisolated anion, Na[Ta(η^4-$C_{10}H_8$)(dmpe)$_2$]. Protonation or methylation of the anion gives TaH(η^4-$C_{10}H_8$)(dmpe)$_2$ or Ta(CH_3)(η^4-$C_{10}H_8$)(dmpe)$_2$, respectively. Related procedures yield the analogous 1,3-cyclohexadiene adduct, TaCl(η-C_6H_8)(dmpe)$_2$. Exchange experiments suggest that the naphthalene unit and the bidentate phosphine are of similar lability, both being relatively inert. TaH(η^4-$C_{10}H_8$)(dmpe)$_2$ is a poor hydrogenation catalyst. Crystals of the TaCl(η^4-$C_{10}H_8$)(dmpe)$_2$ compound are monoclinic, space group $P2_1/c$, with a = 10.343 (3) Å, b = 10.281 (3) Å, c = 24.642 (7) Å, β = 97.39°. Full-matrix least-squares refinement of positional and thermal parameters for all nonhydrogen atoms (including fixed H atom contributions) with 4019 data for which $F > 3.92\sigma(F)$ led to $R = 0.028$ and $R_w = 0.040$. The molecular structure of the complex may be considered to be an approximate pentagonal bipyramid, with Ta, 2P, Cl, and the midpoints of the η^4-olefin bonds forming the pentagonal plane (deviations $<\sim 0.2$ Å). The dihedral angle between the coordinated and uncoordinated portions of naphthalene is 43.0°. The naphthalene complexes undergo ^{31}P site exchange by a mechanism involving rotation of the diene unit. Formally, this corresponds to a pseudorotation exchanging axial and equatorial sites in the pentagonal bipyramid in a pairwise fashion. Activation parameters for the process in Ta(CH_3)(η^4-$C_{10}H_8$)(dmpe)$_2$ are $\Delta H^{\ddagger} = 13.0 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = 1.0 \pm 0.9$ eu. These values are only approximate as they are based on the assumption that the rate of rotation of the diene over edges of the P_4 plane is the same for all edges.

Although seven-coordination is relatively rare for classical coordination compounds and for organometallic complexes of electron-rich transition metals, it is common for the electron-poor, early transition metals.[2] Since no regular polyhedron with seven vertices exists, a variety of structures are plausible. However, most (but not all) seven-coordinate complexes are derived by major or minor distortion from three idealized geometries—the monocapped octahedron (C_{3v}), the monocapped trigonal prism (C_{2v}), and the pentagonal bipyramid (D_{5h}).[2,3] The properties of seven-coordination (e.g., factors affecting structure, the relative energetics of the various structural types, and rearrangement mechanisms connecting the different geometries) may have consequences for the chemistry of the early transition metals. There is at least one explicit example of the stereochemistry of an octahedral isomerization reaction being controlled by the structure of a seven-coordinate intermediate.[4]

Earlier, in preliminary form, we reported the preparation, structure, and dynamics of TaCl(η^4-$C_{10}H_8$)(dmpe)$_2$ (dmpe = 1,2-bis(dimethylphosphino)ethane), an approximate pen-

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