Dynamics of CO Binding to Lacunar Iron(II) Cyclidene Complexes

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Abstract: The kinetics of carbon monoxide binding and dissociation have been studied for a series of lacunar iron(II) cyclidene complexes to elucidate the dependence of dynamic parameters on the various structural features of these versatile compounds. Ligand substituents have large effects on the binding and dissociative rate constants, and remarkably, four distinctly different steric effects have been observed. (1) Changing cavity size alters the rate of CO binding by as much as 4 orders of magnitude, presumably by constraining access to the metal ion. (2) Decreases in cavity size also can increase the rate of CO dissociation by a factor of 10 or so. (3) Placing bulky groups in the path CO must follow to enter the cavity decreases the rate of binding because of steric effect (1), but these same obstructions may also decrease the rate of dissociation by blocking the escape path and, possibly, fostering geminate recombination. (4) Proximal ligand strain both decreases the rate of binding and increases the rate of CO dissociation. In contrast, changes in the iron(III)/(II) redox potential, which accompany ligand substitutions, were found to have only a small impact on CO binding kinetics. The effects on the rate constants of the basicity of the axial base and of solvent polarity were also investigated.

Introduction

Many studies have been performed on the binding of dioxygen to hemoglobin, myoglobin, free hemes, and many chemically synthesized derivatives and models. In the case of iron dioxygen carriers, studies have generally been limited to the prosthetic group of the natural products with the sole exception of the cyclidene complexes reported here. In addition to dioxygen, other physiologically important molecules, such as carbon monoxide, have been studied, and these have played an important role in elucidating the fundamental properties of these compounds. The affinities and kinetic parameters for the binding of small molecules to various dioxygen carriers vary widely. Several recent reviews[1−5] both discuss the fundamental behavior of dioxygen carriers and summarize their known structure−reactivity relationships. Matters of major concern include the thermodynamics and kinetics of binding and dissociation and the tendencies and mechanisms of oxidative destruction by dioxygen (autoxidation) of the dioxygen carriers. Among the many factors that affect dioxygen and carbon monoxide binding are the identity and oxidation state of the metal ion, distal steric hindrance, proximal ligand basicity, proximal base strain, ligand electronic effects, and solvent polarity. Considerable attention has been devoted to studies of the effect of steric hindrance on the process of ligand binding to heme proteins and model compounds.[6−12] Distal side steric effects, generated by the positioning of bulky groups near the active site,[6,8,9] were differentiated from steric effects due to distortion of the porphyrin ring structure−doming and ruffling.[10d,12] The former steric effects are reflected only by changes in the binding rate constants with no alteration in dissociation rates. For several model compounds, the changes observed in dissociation rate constants were attributed to the second phenomenon, i.e., deformation of the porphyrin ring and, ultimately, weakening the bond to the carbonyl ligand. The cyclidene complexes have provided a unique opportunity to examine these and other effects in a family of compounds whose structures are distinctly different from those of the porphyrins.

The lacunar iron(II) cyclidene complexes[13−21] represent a class of synthetic models for the naturally occurring dioxygen carriers that do not contain a porphyrin ring, having a neutral

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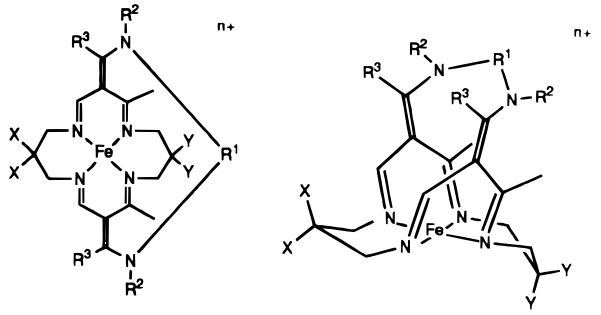

Figure 1. Planar and three-dimensional representation of iron(II) lacunar cyclidene complexes.

tetraaza macrocyclic ligand instead. Because of their unique structures, these complexes (Figure 1) have a hydrophobic cavity into which small ligands may enter and bind to the metal atom, at what is called an axial site. A second axial position, opposite to the one in the cavity, is usually occupied by a bulky nitrogenous base, commonly present in large excess. A particular strength of this family of complexes arises from the broad variations in structural parameters that are readily accessed. To study the influence of varying these ligand parameters, cyclidene ligands have been prepared with variations involving the substituents R^1, R^2, R^3, X, and Y (Figure 1**)**. The abbreviations used throughout this paper for the metal cyclidene complexes list the metal ion with the X and Y substituents, if different from hydrogen, on each side of the metal ion, followed by the substituents R^3, R^2, and R^1 according to the following scheme: $(X)Fe(Y)R^3R^2R^1$. Changes in R^1 directly alter the cavity size, a change that is expected to generate steric effects, while all three R groups may contribute to electronic effects. X and Y are also expected to exert steric effects.

For the lacunar cobalt(II) and iron(II) cyclidene complexes the equilibrium constants for O_2 binding and the resistance of the O_2 carrier to autoxidation depend strongly on the ligand substituents. Further, like the heme-based dioxygen carriers, carbon monoxide adducts of several lacunar iron(II) cyclidene complexes have previously been prepared, and characterized, and an X-ray crystal structure determination has been reported.[16] In summary, the cyclidene family of complexes is particularly useful for the exploration of the fundamental structure−function relationships of dioxygen carriers for the following reasons. (1) Small molecule binding depends strongly on ligand substituents.[15,19,21−23] (2) Cyclidene structures are easily varied in several appropriate ways. (3) Much highly detailed structural information is available on cyclidene complexes.[24,25] (4) And because of its preferred conformation, the 16-membered cyclidene ring is especially facilitative of formation of a lacuna[26] within which the small molecule can bind.

In our studies, this special structural feature, the cavity, and the modification of its dimensions have been demonstrated to be very sensitive tools for distinguishing among different steric effects. Very small changes in the cavity size, produced by variations of the substituent groups on the distal side of the macrocycle, have been proven to influence the affinity for carbon monoxide binding and the rates of both the association and dissociation processes. By increasing steric hindrance near the active site we are able to observe distinctive changes, not only in the association process, as observed in the porphyrin chemistry, but also in the reverse process of carbon monoxide dissociation.

In this paper, we report systematic equilibrium and kinetic studies of carbon monoxide binding to iron(II) cyclidene complexes. This work provides an evaluation of the influence of steric and electronic factors, the basicity of the axial ligand, and solvent properties on carbon monoxide binding and dissociation rates and on CO affinity.

Experimental Section

Iron(II) cyclidene complexes were synthesized as described elsewhere.[15,18−20] All chemicals used in this work were of analytical grade or better. Solvents were purified by recommended procedures,[27] and were degassed prior to use. Liquid reagents were treated similarly. Carbon monoxide and nitrogen gases were passed through Ridox (Fischer) in order to remove residual traces of dioxygen and water.

Solutions of the iron(II) cyclidene complexes were all freshly prepared in a glovebox under nitrogen atmosphere prior to the kinetic and equilibrium studies. The concentration of the complex was usually in the range of $(1-5) \times 10^{-5}$ M, and measurements were performed in acetonitrile in the presence of 1.5 M 1-methylimidazole, with the exception of the investigations directed at the influence of solvent and axial ligand. To the best of our knowledge, the solubility of carbon monoxide in acetonitrile has not been reported, and an estimated value of 6.6 mM at 25 °C and 1 atm was used in our calculations.[28a]

Equilibrium Measurements. Equilibrium constants, K^{CO}, were determined by spectrophotometric titrations. Absorbance changes in the spectral region from 300 to 550 nm were recorded with a Varian-Cary 2300 spectrophotometer connected to an IBM PC. This configuration allows automated data collection and instrument control. Equilibrium constants for axial base coordination were determined by spectrophotometric titration on a Shimadzu UV 2100 spectrophotometer, using a Hamilton microliter syringe.

The solutions of the complexes were placed in a gas-tight quartz cell of 1 cm path length and equilibrated to a temperature of (25.0 ± 0.3) °C. Carbon monoxide/nitrogen mixtures of known composition were generated with use of a Tylan TO-28 controller with model FC-260 mass flow controllers and compressed gas cylinders of the pure gases.

Electrochemical Measurements. Cyclic voltammetry experiments were performed with use of a single-compartment cell. The working

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electrode was a 3 mm diameter glassy carbon Kel-F electrode (Bioanalytical systems), the secondary electrode a platinum wire, and the pseudo-reference electrode was a silver wire. The experiments were performed with a Princeton Applied Research (PAR) programmer model 175, PAR potentiostat model 173 and the output was directly recorded on paper with a Houston Instruments model 200 XY recorder. Redox potentials for the Fe(III)/Fe(II) couples were determined under nitrogen atmosphere in an acetonitrile solution of 0.1 M tetrabutylammonium hexafluorophosphate, using ferrocene as an internal standard.

Kinetic Measurements. Rapid kinetic experiments were undertaken on a modified Durrum Dionex Stopped Flow Spectrophotometer Model D-110, interfaced with a Northstar Horizon computer. Software for the data collecting and processing was provided by On Line Instrument Systems, Inc. Kinetic data were acquired under pseudo-first-order conditions ([FeL] ≪ [CO]) after in situ photodissociation of the CO adduct of the iron(II) complexes with a flash gun (Achiever model 260AF) interconnected with a triggering mechanism, providing a dead time of 10 ms. The solutions were placed in a 1-cm quartz cell, and the temperature was maintained at (25.0 ± 0.5) °C. The change of absorbance was followed as a function of time for at least two wavelengths in the visible region of the spectrum.

A cryo-stopped flow instrument from Hi-Tech Scientific, Model SF-41, was used to determine the dissociation rate constants for some complexes according to the procedure described by Traylor et al.[6] In this experiment, a solution of the carbon monoxide adduct of the iron cyclidene complex was mixed with a solution of tosylmethyl isocyanide, and the change of absorbance was followed in a 1-cm optical cell at a temperature of (25.0 ± 0.1) °C.

In the studies of the base concentration dependencies, the stopped flow experiments were performed with the Bio Sequential SX-18 MV Stopped Flow Reaction Analyzer from Applied Photophysics Ltd. adapted for anaerobic conditions. An observation optical pathlength of 10 mm was selected for our experiments. The solutions of known CO concentrations in these studies were prepared by mixing liquid solutions (saturated with CO and Ar/N_2), using Hamilton gas-tight syringes.

Results and Discussion

Lacunar cyclidene complexes of the formula $Fe^{II}(R^3R^2R^1$-[16]Cyc) have been shown previously[14,15] to exist in a solution as 5-coordinate, high-spin species. Like other complexes with tetraazamacrocycles, the spin state of iron(II) cyclidene complexes depends on coordination at both axial positions. Whereas the 5-coordinate complexes are high spin, binding of a sixth ligand produces the related low-spin species. The process is usually accompanied by UV−vis spectral changes and can also be observed in ^{1}H NMR spectra that are characteristic of the spin state. Magnetic moment data determined[15a] for a series of cyclidene derivatives in a variety of solvents indicate the presence of only high-spin, 5-coordinate complexes. In addition to four nitrogen donors from the cyclidene ligand, the external axial position is occupied by the base molecule present in solution. Presumably, the bis(hexafluorophosphate) salts of iron(II) cyclidenes in acetonitrile solution have a solvent molecule coordinated at the external axial site as the fifth ligand. This is readily displaced by a stronger nitrogen donor base molecule, (equation 1).

$$Fe^{II}L(CH_3CN) + MeIm \overset{K_{Fe}^{MeIm}}{\leftrightarrow} Fe^{II}L(MeIm) + CH_3CN \quad (1)$$

The process is accompanied by isosbestic UV−vis spectral changes with no indication of the formation of a third species, such as the 6-coordinate B−Fe−B hemochrome. Thus the spectral changes accompanying the addition of 1-methylimidazole (MeIm) to $Fe^{II}PhBzXy(PF_6)_2$ in acetonitrile solution are characterized by the disappearance of an absorbance maximum at 420 nm. Well-defined isosbestic points show the formation of the 5-coordinate 1-methylimidazole species and the value of $K_{Fe}^{MeIm} = (2.9 \pm 0.1) \times 10^3\ M^{-1}$ was obtained from a plot of $1/(A - A_0)$ vs 1/[MeIm].

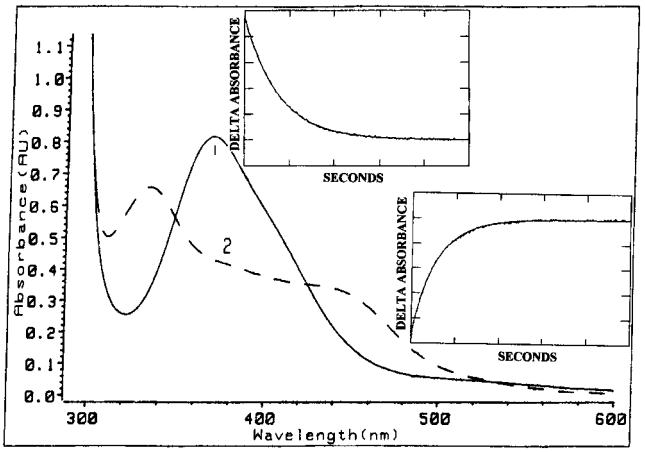

Figure 2. UV−vis spectral changes upon carbon monoxide binding to $[Fe^{II}(PhMeC_5[16]Cyc)Cl]PF_6$ in a 1.5 M 1-methylimidazole/acetonitrile mixture at 25 °C: (1) $P_{CO} = 0$ Torr; (2) $P_{CO} = 766$ Torr. Inserts show kinetic curves observed over 5 s at $P_{CO} = 766$ Torr and 380 (top) and 460 nm (bottom).

The second class of iron(II) cyclidenes are chlorohexafluorophosphate salts. These complexes exist in acetonitrile solution with the chloride anion coordinated to the iron. The equilibrium constants for chloride binding were found[15a] to be very large, in the range of 10^4 to $10^5\ M^{-1}$. In the presence of 1-methylimidazole, the existence of axial base equilibria between the chloro and 1-methylimidazole species has been established.[15b] In our studies, we found that a 1.5 M concentration of 1-methylimidazole (see below) is sufficiently high for the 5-coordinate, 1-methylimidazole complex to constitute 99.99% of the iron species. The isosbestic behavior observed for the binding of CO, and the base concentration independent kinetic traces are indicative of a simple equilibrium between the 5-coordinate MeIm complex and the CO. Detailed study of the equilibria in systems containing chloride and 1-methylimidazole support these conclusions.

The equilibrium constant for chloride binding was determined by titration of $Fe^{II}PhBzXy(PF_6)_2$ with tetrabutylammonium chloride, according to eq 2.

$$Fe^{II}L(CH_3CN) + Cl^- \overset{K_{Fe}^{Cl}}{\leftrightarrow} Fe^{II}L(Cl^-) + CH_3CN \quad (2)$$

The titration was monitored at the wavelength used to determine K_{Fe}^{MeIm}, 420 nm, and also showed isosbestic behavior, giving $K_{Fe}^{Cl} = (1.3 \pm 0.3) \times 10^4\ M^{-1}$. Combining eqs 1 and 2 provides an estimate of the equilibrium constant for the reaction of 1-methylimidazole with $[Fe^{II}(PhBzXy)Cl]PF_6$ to replace the chloride ligand; the value of $K_{FeCl}^{MeIm} = K_{Fe}^{MeIm}/K_{Fe}^{Cl} = (0.22 \pm 0.03)$. Thus, as stated above, a large excess of 1-methylimidazole is required in order to assure that only a single 5-coordinate species is present in solution.

In the presence of carbon monoxide, CO binds at the second axial site of the metal. Typical spectral changes occurring during CO binding to the iron(II) cyclidene complexes are shown in Figure 2, with the corresponding kinetic curves as insets.

Because it is critically important to the mission of gaining control over the system in order to limit CO binding to a simple system involving only the gaseous component and a single predominant iron species, initial experiments were directed at competing axial base equilibria and the CO binding process.

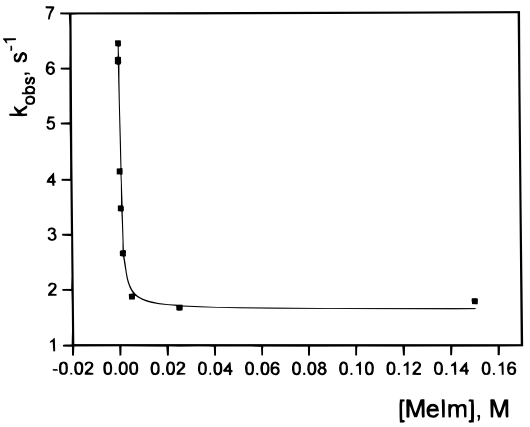

Figure 3. The 1-methylimidazole concentration dependence of the observed rate constant for the CO binding to Fe^{II}(PhBzXy[16]Cyc)-$(PF_6)_2$ in acetonitrile 25 °C. $[Fe^{II}] = 2.6 \times 10^{-5}$ M, [CO] = 0.66 mM, $\lambda = 370$ nm.

Scheme 1

$$Fe^{II}L(CH_3CN) + MeIm + CO \underset{}{\overset{K_{Fe}^{MeIm}}{\Longleftrightarrow}} Fe^{II}L(MeIm) + CH_3CN + CO$$

$$\downarrow k_1 \qquad\qquad \downarrow k_2$$

$$Fe^{II}L(CH_3CN)(CO) \qquad\qquad Fe^{II}L(MeIm)(CO)$$

The process of carbon monoxide binding in the presence of increasing concentrations of 1-methylimidazole was investigated for both the chloro complex, $[Fe^{II}(PhBzXy)Cl]PF_6$, and the acetonitrile complex, $[Fe^{II}(PhBzXy)(CH_3CN)](PF_6)_2$. Stopped flow spectrophotometry showed that $[Fe^{II}(PhBzXy)(CH_3CN)](PF_6)_2$ binds CO in acetonitrile with a second order rate constant of $k_{on} = 9.9 \times 10^3$ M^{-1} s^{-1} (flash photolysis value $k = 6.4 \times 10^3$ M^{-1} s^{-1}). With increasing 1-methylimidazole concentration the observed rate constant for carbon monoxide binding decreases toward a limiting value (Figure 3). This is attributed to the preequilibrium between the solvent- and base-coordinated species, according to Scheme 1. The observed rate constant is given by eq 3

$$k_{obs} = \frac{k_1 + k_2 K_{Fe}^{MeIm}[MeIm]}{1 + K_{Fe}^{MeIm}[MeIm]} \tag{3}$$

Fitting the experimental data to eq 3 provides $K_{Fe}^{MeIm} = (2.5 \pm 0.2) \times 10^3$ M^{-1}, in reasonable agreement with the value of $K_{Fe}^{MeIm} = 2.9 \times 10^3$ M^{-1} determined from the equilibrium studies. The fitted values of $k_1 = (9.77 \pm 0.09) \times 10^3$ M^{-1} s^{-1} and $k_2 = (2.48 \pm 0.09) \times 10^3$ M^{-1} s^{-1} are in very good agreement with the experimentally observed values of 9.9×10^3 and 2.4×10^3 M^{-1} s^{-1}, respectively. Closely similar measurements were carried out beginning with $[Fe^{II}(PhBzXy)Cl]PF_6$.[29] At higher 1-methylimidazole concentrations (approaching 1.5 M), both complexes reach the same limiting rate constant. Therefore, 1.5 M 1-methylimidazole was found to overwhelm the competitive binding by both the solvent and the chloride anion, and can eliminate them from further consideration during studies on the dynamics of carbon monoxide binding. These studies facilitated the determination of reaction conditions such that a single iron complex was present for the various rate measurements.

The binding of carbon monoxide to the iron complex can be represented by eq 4 (simplified by not showing the axial base):

$$FeL^{2+} + CO \underset{k_{off}}{\overset{k_{on}}{\Leftrightarrow}} FeL(CO)^{2+} \tag{4}$$

The carbon monoxide concentration dependence of the observed pseudo-first-order rate may be readily derived for the above kinetic model and is shown in eq 5.

$$k_{obs} = k_{off} + k_{on}[CO] \tag{5}$$

A typical plot of k_{obs} versus the concentration of CO is shown in Figure 4. The slope corresponds to the second-order rate constant for carbon monoxide binding (k_{on}). The dissociation rate constant (k_{off}) is estimated by extrapolating to zero carbon monoxide concentration. Overall, the binding rate constants (k_{on}) were determined with a standard deviation of less than 5%.

The values of the dissociation rate constants (k_{off}) obtained from the intercept have much higher errors. Reliable values of k_{off} could not be obtained for those complexes that bind carbon monoxide very rapidly, since in those cases k_{off} is much smaller than the product k_{on}[CO]. For complexes in which R^1 is either of the polymethylene chains $(CH_2)_6$ or $(CH_2)_8$, k_{off} was determined by an independent method,[6] in which the CO molecule from the carbon monoxide adduct is replaced by tosylmethyl isocyanide. The conditions were chosen such that the dissociation of the carbon monoxide was the rate determining step of the substitution reaction, and the observed rate constant is then equal to the dissociation rate constant for carbon monoxide.

The experimental rate constants were used to calculate the equilibrium constants according to eq 6. The equilibrium

$$K^{CO} = \frac{k_{on}}{k_{off}} \tag{6}$$

constants for carbon monoxide binding for most of the complexes were also determined by direct spectrophotometric titrations. In a given experiment, the carbon monoxide/nitrogen mixture was introduced into the solution, and absorbance changes were recorded after equilibration. Typical spectral changes are shown in Figure 5. The equilibrium constants were calculated by using the Ketelaar equation.[30] The equilibrium constants obtained in these dynamic studies were used to calculate the dissociation rate constants according to eq 6. These calculated values, where available, were compared with the dissociation constants determined from the intercept of the linear concentration dependence (eq 5**)** and found to be in reasonable agreement. The results of the studies reported here are summarized in Tables 1−6.

Distal Steric Effect. Among the principal design considerations for dioxygen carrier models is the positioning of the superstructure in the vicinity of the metal ion binding site. One of the purposes of the superstructure is to control the affinity of the small molecule binding by steric interactions either at the point of entry or subsequent to coordination. The greater the steric hindrance imposed by the superstructure, the more limited is the affinity of the ligand for the metal center. This effect has been demonstrated in recent studies of several porphyrin derivatives[7−12] in which increased steric hindrance around the binding site results in lower carbon monoxide binding rate constants, k_{on}, and lower equilibrium constants, K^{CO}.

For the cyclidene complexes, distal steric hindrance was generated in two different ways: first, by changing the length of the bridging aliphatic groups (R^1) between the outermost

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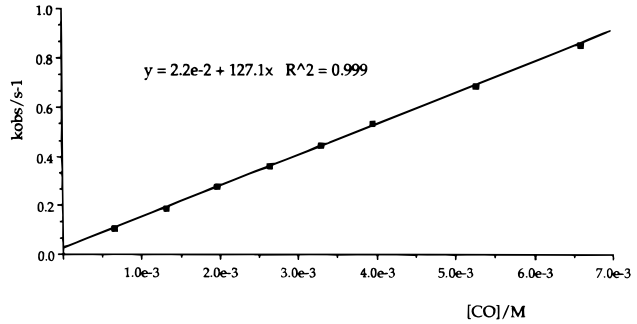

Figure 4. Determination of the second-order rate constants for carbon monoxide binding to $[Fe^{II}(PhMeC_5[16]Cyc)Cl]PF_6$ at 25 °C in a 1.5 M 1-methylimidazole/acetonitrile mixture. Data measured at 380 and 460 nm.

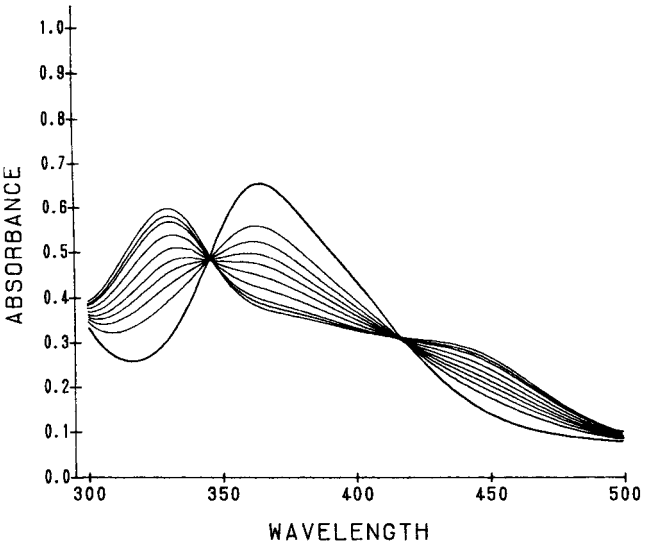

Figure 5. UV−visible spectral changes accompanying formation of the carbon monoxide adduct of $[Fe^{II}(PhMeC_5[16]Cyc)Cl]PF_6$, in a 1.5 M 1-methylimidazole/acetonitrile solution, at 25 °C. Carbon monoxide pressure increases from 0 to 255 Torr.

Table 1. Distal Steric Effect: Effect of the Length of the Polymethylene Bridging Group Over the Active Site, in Acetonitrile/1.5 M 1-Methylimidazole at 25 °C

FePhMeR[1]	k_{on},[a] M^{-1} s^{-1}	k_{off}, s^{-1}	K, M^{-1}
C4	25 (0.06)	0.06	4.2×10^{2} [b]
C5	1.3×10^{2} (0.024)	0.022[e]	5.8×10^{3} [d]
C6	3.72×10^{4} (∼0)	0.0026[c]	1.4×10^{7} [b]
C8	1.55×10^{5} (∼0)	0.0041[c]	3.8×10^{7} [b]

[a] Values quoted in parantheses are for the intercept (s^{-1}) of the plot of k_{obs} versus [CO]. [b] Calculated from kinetic parameters. [c] Determined by replacement reaction of CO adduct by tosylmethyl isocyanide. [d] Determined by spectrophotometric titration. [e] Calculated from $K = k_{on}/k_{off}$.

(bridgehead) nitrogen atoms and, second, by adding substituents (X,Y) to the saturated chelate ring of the macrocycle. The width of the cavity, as measured between the two bridgehead nitrogens, increases rather smoothly from 5.4 Å to 7.8 Å, when the bridging group (R^1) is increased in length by the addition of methylene units, starting with tetramethylene and proceeding to octamethylene. This structural change produces a large variation in the steric hindrance encountered by a small molecule binding at the metal center.[15,19,21−23] The corresponding equilibrium constants and rate constants for carbon monoxide binding are shown in Table 1.

Several conclusions may be drawn from these results. The short tetramethylene bridge (C4) restricts the cavity size so greatly that the CO binding is extremely weak. On extending the length of R^1 to a pentamethylene chain (C5), the affinity and rate of binding increase by about one order of magnitude. Further increasing the length of R^1 to hexamethyl (C6) and octamethyl (C8) provides additional substantial increases in the carbon monoxide affinity. For both complexes, C6 and C8, the binding rate constants increased by two and three orders of magnitude, and the affinities by four orders of magnitude, with C8 having both a higher carbon monoxide affinity and rate of binding than for the C6 complex. These conclusions parallel what has been reported for the dioxygen affinities of cobalt(II) cyclidene complexes.[15,19,21,23]

From earlier work, hexamethylene (C6) and octamethylene (C8) bridges are known to be able to adopt at least two different low-energy conformations.[24] When no ligand is present, the polymethylene chain is folded inward, resulting in a reduction in the volume of the cavity. In order to bind the ligand, the bridge unfolds and allows relatively open access to the active site. $[Fe^{II}(PhMeC6[16]Cyc)]$ has also been shown to exist in both 5- and 6-coordinate forms in aqueous acetone solution, with the later being favored at lower temperatures.[15] The evidence for the 6-coordinate species comes from visible spectra (the appearance of an absorbance peak at 510 nm) and from magnetic studies over a range of temperatures. In the work described here, a similar equilibrium was found to occur in acetonitrile solutions containing 1.5 M 1-methylimidazole. Changes in the UV−visible spectra indicate that a solvated, 6-coordinate species forms below about 10 °C, and ^1H NMR spectra show the presence only of the diamagnetic, 6-coordinate species below −40 °C. On the basis of the visible spectrum of the corresponding C8 derivative, it was concluded that, in acetonitrile, the C8 complex exists mostly as the 6-coordinate species even at room temperature. Therefore, the binding of carbon monoxide to this complex at 25 °C involves reaction of the carbon monoxide with a coordinately saturated complex, instead of a 5-coordinate iron(II) species. Presumably, the mechanism involves a preequilibrium between the predominant 6-coordinate species and the very rare 5-coordinate species, followed by reaction of the carbon monoxide with the five-coordinate complex. The apparent rate constant determined for carbon monoxide binding then involves contributions from the preequilibrium, and under pseudo-first-order conditions the observed rate constant is given by eq 7,

$$k_{obs} = \frac{k_{on}K^{-S}}{K^{-S} + 1}[CO] + k_{off} \qquad (7)$$

where K^{-S} is the equlibrium constant for solvent dissociation from 6-coordinate complex and k_{on} and k_{off} are kinetic parameters for CO binding to the 5-coordinate species.

Despite this difference in mechanism from those of the predominantly 5-coordinate complexes, the experimentally determined rate is clearly also first order in carbon monoxide concentration. This indicates that carbon monoxide binding remains the rate controlling step, and that the equilibrium between 5- and 6-coordinate iron complexes must be fast when compared to the time scale for carbon monoxide binding.

With the smoothly increasing cavity size for the described series of cyclidene complexes, a corresponding rise in the association rate constant and affinity for ligand binding is expected, as has been observed for dioxygen affinities among cobalt(II) cyclidene complexes.[23] The width of the cavity of the C4 to C8 series of cyclidene complexes, given by the distance between the two noncoordinated nitrogen atoms, regulates the access of the ligand to the active site by steric interaction. This is demonstrated in the increase of the affinity

and, kinetically, mainly in the increase of the binding constant. Over five orders of magnitude change in carbon monoxide affinity along the series of cyclidene complexes can therefore be entirely ascribed to the steric interaction of the superstructure with the carbon monoxide ligand, since it was found that the superstructure does not influence the redox properties of the complexes. The cyclic voltammetry measurements revealed that the $E_{1/2} = -0.28$ V vs ferrocene is constant within experimental error for all four of these complexes.

As described earlier, the spin state of the iron(II) changes upon coordination of the sixth ligand. From structural studies on the 5-coordinate, high-spin iron(II) cyclidene complexes[13] it is known that the iron atom is displaced by some 0.5 to 0.6 Å from the N4 plane, while maintaining the usual ligand shape. In forming the 6-coordinate low-spin iron(II) complexes, the metal moves toward the plane of the equatorial nitrogens and the out-of-plane displacement decreases to about 0.05 Å.

For a variety of other transition metal cyclidenes, only small random deviations from the N4 plane of around 0.1 Å are observed, with the only exceptions occurring for 5-coordinate, high-spin iron(II) complexes. The larger of the more common deviations from the plane are correlated with the ligand structure. Upon decreasing the length of the polymethylene bridging group R^1 from C5 to C3, the metal was displaced by as much as an additional 0.1 Å. At the other extreme, as the cavities in the polymethylene-bridged complexes increase in width from 4.9 Å to 7.8 Å (increasing bridge length from C3 to C8), the cavity appears to more readily accommodate a variety of larger ligands.

The differences in the CO dissociation rate constants across the series of iron(II) cyclidene compounds are much smaller than the changes in the association rate constants. However, the data clearly show that the values of the dissociation rate constants decrease as the cavity sizes increase. The tetramethylene and pentamethylene derivatives have relatively small and distinctly inflexible cavities in contrast to those complexes having longer polymethylene bridges. X-ray studies of these short-bridged complexes also showed that their occupied and unoccupied cavities have almost identical dimensions and their bridges have closely similar conformations.[24] The inflexibility of these shorter chains, combined with the accompanying smaller cavity dimensions, predicts destabilization of the carbon monoxide adducts and therefore higher dissociation rate constants were anticipated.

Steric interaction between the coordinated CO molecule and the polymethylene bridge was demonstrated by an X-ray crystal structure[16] that revealed both the bending of the FeCO linkage from linear by almost 10° and the displacement of Fe−C bond from the expected N4-plane orthogonality.

Another somewhat different bridging group that produces a relatively small and inflexible cavity at the binding site was also used in our studies. This is the aromatic *m*-xylylene (Xy) bridging group. The complexes with this aromatic bridge are remarkable for their resistance to autoxidation and have been the subject of studies on the binding of dioxygen to iron(II) in this novel non-porphyrin environment.[14,15,17,31] The aromatic bridge provides both more extensive sheltering of the cavity contents and a more hydrophobic environment at the active site, either or both of which may be responsible for the unusual stabilities of these derivatives toward autoxidation. The equilibrium constants and rate constants for CO binding to these iron cyclidenes are approximately of the same order of magnitude as those for the pentamethylene-bridged complexes, as is obvious from comparison of Table 1 with Table 2. For

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Table 2. Electronic Effect of Substituents at R^2 and R^3 Positions, in Acetonitrile/1.5 M 1-Methylimidazole at 25 °C

FeR^3R^2Xy	$E_{1/2}$, V vs ferrocene	k_{on},[a] M^{-1} s^{-1}	k_{off},[b] s^{-1}	K,[c] M^{-1}
MeMe	−0.45	3.4×10^2 (0.05)	0.06	5.5×10^3
MeBz	−0.34	3.9×10^2 (0.02)	0.05	7.4×10^3
PhMe	−0.29	6.3×10^2 (0.1)	0.085	6.8×10^3
PhBz	−0.21	2.3×10^3 (0.38)	0.085	2.7×10^4

[a] Values quoted in parantheses are for the intercept (s^{-1}) of the plot of k_{obs} versus [CO]. [b] Calculated from $K = k_{on}/k_{off}$. [c] Determined by spectrophotometric titration.

Table 3. Distal Steric Effect: Effect of the Geminal Dimethyl Group on the Saturated Ring of the Macrocycle, in Acetonitrile/1.5 M 1-Methylimidazole at 25 °C

XFeYPhBzXy	k_{on},[a] M^{-1} s^{-1}	k_{off}, s^{-1}	K, M^{-1}
Fe	2.3×10^3 (0.3)	0.085[b]	2.7×10^4 [c]
Fe(DM)	1.7×10^3 (0.3)	0.07[b]	2.5×10^4 [c]
(DM)Fe	30 (0.02)	0.007[b]	4.2×10^3 [c]
(DM)Fe(DM)	30 (0.003)	0.003	nonisosbestic

[a] Values quoted in parantheses are for the intercept (s^{-1}) of the plot of k_{obs} versus [CO]. [b] Calculated from $K = k_{on}/k_{off}$. [c] Determined by spectrophotometric titration.

two analogous complexes, [Fe^{II}(PhMeC5[16]Cyc)] and [Fe^{II}-(PhMeXy[16]Cyc)], differing only in the R^1 bridging group, the corresponding carbon monoxide affinity values are $K^{CO} = 5.8 \times 10^3$ M^{-1} and $K^{CO} = 6.8 \times 10^3$ M^{-1}, respectively.

A second source of distal steric hindrance was created by attaching geminal dimethyl groups to the saturated chelate rings of the macrocycle in the X and Y positions (Figure 1). Three different derivatives of the parent complex [Fe^{II}(PhBzXy[16]-Cyc)Cl](PF_6) have previously been synthesized and characterized.[19] The geminal dimethyl groups have been placed at two locations. The first complex has them located on the saturated ring where they provide steric hindrance to the entrance of the cavity (X). The second location has the *gem*-dimethyl groups located at the (relatively) closed side of the cavity (Y), where they do not hinder entry of the incoming ligand. The third complex has both sets of *gem*-dimethyl groups. The complexes are labeled as (DM)Fe, Fe(DM), and (DM)Fe(DM), respectively. The kinetic data and equilibrium data for all four compounds, including the parent macrocycle with no *gem*-dimethyl group, are presented in Table 3. From the reported values, placing the *gem*-dimethyl group at the closed side of the cavity, Fe-(DM), has no significant effect on the affinity or kinetic parameters. When the *gem*-dimethyl group is located at the entry (open face) of the cavity, the rate constant for CO binding decreases by a factor of 75. This difference suggests that there is strong steric interaction of this group with the incoming carbon monoxide molecule. This behavior is consistent with that observed when the cavity is made less accessible by shortening the bridging group.

A more bizzare behavior is found in the case of the dissociation rate constant, which decreased by a factor 10 compared to the parent complex. The obvious source of such a decrease in dissociation rate would be release of strain, possibly caused by the interaction of a methyl group with the bridging group. Such a repulsion might conceivably have pushed the bridge up and away from the volume occupied by the CO. The results of X-ray studies[19] on the corresponding nickel complex indicate that the height and width of the cavity are not altered significantly when the *gem*-dimethyl group is introduced. However, the crystal structure of the 6-coordinate species is not available. Molecular modeling studies[19] on dioxygen adducts of cobalt cyclidenes show the presence of steric interaction between the bound dioxygen and methyl group

Table 4. Kinetic and Equilibrium Constants for CO Binding to Several Heme and Model Compounds

	T, °C	solvent	k_{on}, M^{-1} s^{-1}	k_{off}, s^{-1}	*K*, M^{-1}	ref
myoglobin	20	H_2O	5×10^5	0.017	2.9×10^7	7
hemoglobin	20	H_2O	6.5×10^6	0.001	6.5×10^9	7
7,7-anthracene-cyclophane heme (DcIm)	20	benzene	6×10^6	0.05	1.1×10^8	8a
6,6-anthracene-cyclophane heme (DcIm)	20	benzene	3×10^4	0.05	6×10^5	8a
FePocPiv (1-MeIm)	25	toluene	5.8×10^5	0.0086	6.7×10^7	9
FeMedPoc (1-MeIm)	25	toluene	1.5×10^6	0.0094	1.6×10^8	9
$FePiv_2(C_{12})$ (1MeIm)	20	toluene	6.3×10^7	0.0027	2.4×10^{10}	10b
$FePiv_2(C_{10})$ (1MeIm)	20	toluene	1.8×10^6	0.0002	9.0×10^8	10b
$FePiv_2(C_9)$ (1MeIm)	20	toluene	1.0×10^6	0.0026	3.8×10^8	10b
$FePiv_2(C_8)$ (1MeIm)	20	toluene	8.0×10^4	0.0082	9.8×10^6	10b
Fe-C12 (1-MeIm)	20	toluene	2.4×10^2	0.08	3.0×10^3	10c
Fe-C14 (1-MeIm)	20	toluene	7.8×10^4	0.11	7.4×10^5	10c
FeSP-13 (1-MeIm)	20	toluene	6×10^2	0.07	8.57×10^3	11
FeSP-14 (1-MeIm)	20	benzene	8×10^3	0.04	2.0×10^5	11
FeSP-15 (1-MeIm)	20	benzene	9.1×10^4	0.04	2.3×10^6	11
FeDurene-4,4 (DcIm)	20	toluene	3.0×10^6	0.7	4.3×10^6	12
FeDurene-5,5 (DcIm)	20	toluene	1.1×10^7	0.13	8.5×10^7	12
FeDurene-7,7 (DcIm)	20	toluene	9.5×10^5	0.014	6.7×10^7	12

in the axial X position. This steric interaction pushes the dioxygen up and into the cavity, causing the displacement of the bridge upward and also displacement of the *gem*-dimethyl group downward and away from bound dioxygen, and in this way releasing the steric constraints on the bound diatomic molecules.

A possible alternative explanation for this change is that the *gem*-dimethyl group may be entrapping the dissociated carbon monoxide molecule in the cavity by imposing steric hindrance along its exit path, which might result in geminate recombination.[32]

For the third complex with the *gem*-dimethyl groups at both positions, (DM)Fe(DM), the kinetic parameters correspond very closely to those found for the (DM)Fe complex. Unfortunately, it was not possible to determine the equilibrium constant by spectrophotometric titration because of nonisosbestic behavior of the corresponding spectral changes. This nonisosbestic behavior is in agreement with previous findings for dioxygen binding, and it was suggested[19] on the basis of electrochemical and magnetochemical studies that the complex exists in acetonitrile solution as a mixture of 4- and 5-coordinate iron(II) species.

The results obtained for the iron(II) cyclidene complexes provide increased understanding of the fundamental processes associated with CO binding when compared to data available on other iron(II) dioxygen carriers **(**Table 4**)**. Dioxygen carrier model compounds incorporate in their designs functional groups that attempt to mimic the protein enviroment of the natural heme compounds. In addition to the shielding against irreversible oxidation, these superstructural features are built-in in order to sterically discriminate between different ligands, such as dioxygen, bound in a bent fashion, and carbon monoxide, bound in a linear mode. Many encumbered porphyrin derivatives have been prepared and studied in order to clarify and distinguish between various steric and polar factors affecting dioxygen, carbon monoxide, or other ligand affinities. The effort to isolate and investigate a purely steric effect on the distal side of the porphyrin led to development of models with different degrees of congestion at the metal center. Some of these models are listed in Table 4. The superstructure in these models is formed by anchoring the aromatic group above the binding site to the porphyrin ring via two or more strings of variable length, such as anthracene heme cyclophanes[8a] and pocket (PocPiv) porphyrins.[9] Alternatively, the adjustable strap may be placed across the face of the porphyrin ring, such as in hybrid[10b] or strapped porphyrins.[10c,11] From the affinity parameters of these model compounds it is obvious that the more sterically constrained models have lower carbon monoxide affinities. Kinetic investigation revealed that for the majority of these complexes, the decrease in affinity is displayed primarily by decreased association rate constants. The rates of dissociation remain constant or are only negligibly changed.

Our investigations on iron(II) cyclidene complexes confirmed this conclusion. The main effect in the reduction of the affinity of iron(II) cyclidenes is due to the change of the binding rate for carbon monoxide. Small, but sizable, changes in the rates of dissociation for Fe(II) cyclidene complexes arise from the weakening of the bond to the carbonyl group by the inflexible, shorter bridge groups (C4, C5). Longer and flexible groups undergo conformational changes which lower the steric interaction with bound carbon monoxide.

The increase of CO dissociation rates with increased steric hindrance was also observed in the Fe(II)−durene−capped porphyrins.[12] The difference among shorter 4/4 and longer 5/5 and 7/7 membered linking systems was attributed to porphyrin ring deformation and was not attributed to a distal steric effect, in agreement with the observation that distal steric effects often influence association rate constants. For our system, the decrease of the dissociation rate constant by a factor of 10 upon proceeding from the C5 to the C6 derivative is ascribed entirely to the steric interaction that is associated with the length of the polymethylene group at the distal site. The abrupt change between the C5 and C6 derivatives can be assigned to the great diminution in the steric hindrance between the bound CO and its environs because of the onset of flexible bridges at C6, accompanied by the appearance of an accommodating change in conformation, and also by the increased width of the cavity, which may reach a critical dimension at this point. In a manner similar to the conformational change found for C6 through C8 cyclidenes, the displacement of the phenyl roof in the basket handle porphyrins was also observed by Momenteau.[10a]

Electronic Effects. Electronic effects on the rate constants for carbon monoxide binding for iron(II) cyclidene complexes have been investigated by varying the substituents at the R^2 and R^3 positions while keeping the bridging group unchanged; *m*-xylylene was used as the R^1 bridging group. The data for

(32) The observation of the geminate recombination process would require the use of a fast, e.g., picosecond, kinetic method and is presently under investigation.

four different derivatives are listed in Table 2. The iron(III)/(II) redox potentials have been measured to assess the electronic properties of the metal center. From the data in Table 2, it may be seen that the rate of binding of the carbon monoxide molecule increases as the iron(III)/(II) redox potential becomes more positive. However, the increase in the rate of carbon monoxide binding is not proportional to the change in the redox potentials. The changes in the rate constants for the first three derivatives are very small, close to experimental error, but there is a more pronounced increase for the phenylbenzyl derivative. There are marked differences in the redox potentials among the four complexes that are not reflected by changes in the rate of binding. The dissociation rate constants show only marginal changes. On the basis of these results it must be concluded, that even though there may be small electronic effects on the binding constant, other factors are important in determining the affinity and kinetics of small molecule binding to these complexes. The fact that the PhBz derivative has a measurably more rapid rate of CO binding and significantly greater CO affinity joins a previously known extreme property of that complex. It is much slower to undergo autoxidation than are the closely related derivatives listed in Table 2.

The electronic effects of substituents vary among the various porphyrin systems, making it difficult to draw clear and simple conclusions. Whereas Traylor et al.[33] found no change in the affinity or kinetics for CO binding to chelated porphyrins with ethyl, vinyl, and acetyl groups on the 2- and 4-positions of the porphyrin ring, Sono et al.[34] reported decreasing binding constants with increasing electron withdrawing power of the porphyrin substituents. These authors[35] also reported the opposite effect for reconstituted myoglobins, specifically an increase in the binding constants as the electron density at the heme iron decreases. Hashimoto et al.[36] reported that placing the electron withdrawing NO_2 group on a capped porphyrin ring enhances the CO binding by a factor of 1.3 to 2.6 depending on the proximal base. Collman et al.[9b] found that several para-substituted iron(II) tetraphenylporphyrins substituents (−OMe and −Cl) had only marginal electronic effects on the CO affinities. Clearly the influence of electronic properties on the kinetics and affinity of carbon monoxide binding to iron porphyrins is a complex issue and many facets of this subject remain to be clarified.

Solvent Effects. Five different solvents have been used to investigate the influence of the medium on the kinetics of binding and affinity for CO of [Fe^{II}(PhBzXy[16]Cyc)Cl](PF_6). The solvents used, together with their dielectric constants and the kinetic and equilibrium parameters for carbon monoxide binding to this iron(II) complex, are presented in Table 5. The results show that the rate constant for carbon monoxide binding increases with increasing dielectric constant of the medium. Changing the solvent from acetone to water, increases the carbon monoxide binding rate constant by more than two orders of magnitude. Since the rate of the dissociation doesn't change significantly, the same increase is found in the equilibrium constant data.

As was previously established,[15] iron(II) complexes remain high-spin and 5-coordinate in a variety of solvents (including acetonitrile, water, and acetone). The formation of solvated 6-coordinate species is usually indicated by absorbance changes in the visible spectra. The UV−vis spectra of the iron(II) complex in all of the solvents used in these studies show no evidence of formation of low-spin 6-coordinate species. The isosbestic behavior observed for the systems during CO titration also fails to reveal any complications in the simple addition mechanism for small molecule binding. The rate data in Table 5 are also inconsistent with the possibility that solvent molecules might enter the cavity and influence the rate of CO binding by competition for the available site. The rate of dissociation of the bound ligand from the iron(II) would then be the source of the solvent effect. This predicts that the rate of CO binding would be most rapid with the weakest ligating solvent, acetone, and slowest with the strongest binding solvent, water—the reverse of that which is observed.

Table 5. Solvent Polarity Effect for [Fe^{II}(PhBzXy[16]Cyc)Cl]PF_6 in the Presence of 1.5 M 1-Methylimidazole at 25 °C

solvent[b]	ϵ	k_{on},[a] M^{-1} s^{-1}	k_{off},[c] s^{-1}	K,[d] M^{-1}
acetone	20.7	1.0×10^2 (0.145)	0.14	6.9×10^2
benzonitrile	25.2	2.7×10^2 (0.11)	0.08	3.6×10^3
methanol	33	1.3×10^3 (∼0)	0.2	6.1×10^3
acetonitrile	37.5	2.3×10^3 (0.3)	0.085	2.7×10^4
water	78.5	1.64×10^4 (∼0)	0.06	2.7×10^5

[a] Values quoted in parantheses are for the intercept (s^{-1}) of the plot of k_{obs} versus [CO]. [b] Solubilities of CO: acetone, 10.46 mM;[28b] benzonitrile, 5.5 mM;[28c] methanol, 7.89 mM;[28b] water 0.955 mM.[28b] [c] Calculated from $K = k_{on}/k_{off}$. [d] Determined by spectrophotometric titration.

In the case of iron porphyrins, diverse results have been found for the influence of solvent. Traylor[37] observed no solvent effect on the rate of carbon monoxide binding for imidazole and pyridine chelated mesoheme. The carbon monoxide rate constants did not significantly change with variation of the solvent from dichloromethane or toluene to dimethylformamide, 2:1 mixture of dimethylformamide and water, or 2% aqueous cetyltrimethylammonium bromide. In contrast, Collman et al.[9b] reported an increase of one order of magnitude for the carbon monoxide affinity for the Picket Fence porphyrins on changing from toluene to a more polar solvent, a 1:1 toluene−methanol mixture. Small changes in carbon monoxide affinities were found also for capped porphyrins,[36] where kinetic parameters and affinity constants were obtained in toluene, tetrahydrofuran, and dimethylformamide. Despite the small differences reported by others for the solvent polarity effect on carbon monoxide binding in general, the effects of solvent polarity on dioxygen affinities are widely recognized, which is in agreement with the assumption of bigger charge separations in dioxygen adducts ($Fe^{\sigma+}-OO^{\sigma-}$) compared to little or no charge separation in Fe−CO complexes.

In contrast to the porphyrins, cyclidenes are neutral ligands, and therefore the iron(II) complexes are (1) accompanied by two counteranions, usually chloride and hexafluorophosphate, and (2) readily soluble in a wide range of polar solvents. Porphyrins are dianionic ligands which satisfy the positive charge on the iron cation, producing neutral complexes. The overall electrostriction of the solutions of the cyclidene complexes is higher due to their existence as salts. This effect can contribute to the extensive solvation effects observed for the iron(II) cyclidene complexes in different solvent media. For example, in solvents of low polarity, the complex may be present as closely associated ion pairs or clusters; whereas in more polar solvent, the anions may be separately solvated and thus increase accessibility of the complex to the carbon monoxide.

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Proximal Base Effect. At least two effects of axial bases, acting at the proximal site, have been proposed to account for the various affinities of dioxygen carriers. The obvious effect arises from the basicity and, therefore, electron donor abilities of the molecules at the proximal position. In general, it is accepted that higher π basicity of the axial base increases the dioxygen affinity, i.e., the so-called trans effect.[1,3,38,39] For carbon monoxide the situation is not so clear, as has been discussed recently by El-Kasmi et al.[39] Most of the studies on porphyrin derivatives were carried out employing nitrogenous bases, methylimidazole derivatives, and pyridine. Those observations comply with the known trans effect—for increased basicity of the proximal base, the affinity of carbon monoxide increases—although the changes occur in much smaller increments compared to the results of studies on dioxygen binding. Extending the scope of this study[39] to a much wider pK_a range using thiolates and alcoholates (pK_a > 10) in addition to nitrogen heterocompounds (p$K_a \leq 7$) shows the opposite trend: a decrease in carbon monoxide affinities as available electron density increases. The dioxygen affinities follow the expected changes: with increased basicity, the affinity constants increase. This variation was explained in terms of different σ and π bonding contributions for the different ligands.

The second effect attributed to the axial base and usually called the proximal base tension was first introduced by Perutz.[40] According to this theory, the movement of the metal center perpendicular to the heme plane, due to the binding of the axial bases, may vary depending on the steric hindrance encountered by the axial base. These differences in the metal ion position alter the affinity for small molecule binding on the opposite (distal) axial position. The steric strain on the proximal side for some model compounds was introduced by Brault and Rougee[41] and studied systematically by Traylor[42] and Collman.[9b] The former authors found that the carbon monoxide binding constants decrease with the introduction of this kind of strain. Collman characterized the system kinetically and found that the decrease in affinities is reflected in decreased association and increased dissociation rates for the carbonyl ligand. These porphyrin model compounds without or with proximal base tension were found to mimic the behavior of R and T state hemoglobin, respectively. Crystal structures of the CO adducts of capped porphyrins in the presence of 1-MeIm and 1,2-DMeIm have been recently determined,[43] and related to the R and T state of hemoglobin, respectively.

The data for carbon monoxide binding to [Fe^{II}(PhBzXy[16]-Cyc)]$(PF_6)_2$ in the presence of several nitrogenous base molecules is summarized in Table 6. Unlike all other complexes in our studies, the chloride counteranion in this compound had been removed by a simple metathesis procedure[44] in order to avoid the complications from other possible equilibria in the solution.[45] The axial bases 1-methylimidazole, pyridine, acetonitrile, and 1,2-dimethylimidazole were used in our studies. The complexes with acetonitrile in the axial position have lower equilibrium constants for CO binding than does the 1-methylimidazole derivative because of relatively high dissociation constants. The higher basicity of 1-methylimidazole is responsible for the formation of the more stable carbon monoxide adduct compared to systems having pyridine as the axial base. In summary, in the absence of proximal base tension, the axial base effect is reflected mainly in the rates of CO dissociation, which is a reflection of the strength of the iron−CO bond.

Table 6. Proximal Base Effect for [Fe^{II}(PhBzXy[16]Cyc)]$(PF_6)_2$ in CH_3CN

axial base (concn, M)	k_{on},[a] M^{-1} s^{-1}	k_{off},[b] s^{-1}	K,[c] M^{-1}
1-MeIm (1.5)	2.3×10^3 (0.44)	0.085	2.7×10^4
Py (1.5)	2.3×10^3 (0.85)	0.6	3.9×10^3
CH_3CN	6.4×10^3 (3.75)	1.2	5.3×10^3
1,2-DMeIm (1.5)	4.5×10^2 (0.8)	0.3	1.7×10^3

[a] Values quoted in parantheses are for the intercept (s^{-1}) of the plot of k_{obs} versus [CO]. [b] Calculated from $K = k_{on}/k_{off}$. [c] Determined by spectrophotometric titration.

1,2-Dimethylimidazole is more basic than 1-methylimidazole; however, both the CO affinity and kinetics of binding are lower due to the increased steric requirements of the base for binding to the iron(II) ion, i.e., proximal base tension. Brief reflection on how this structural factor must operate places it in sharp contrast to the steric effects created by alterations in accessibility of the cavity. The cavity size effects are attributed mostly to alterations in the opening that the randomly moving small molecule must penetrate. On the other hand and insofar as the CO is involved, the main restriction imposed by 1,2-DMeIm is to hinder the motion of the iron atom, from its displaced position, up into the N4 plane, a motion necessary in order to bind to CO on the opposite side of that plane. The equilibrium constant reduction for this proximal base is assigned to the decrease of the binding rate constant (a factor of 5) and a smaller increase of the dissociation rate constant (a factor of 3.5). That accompanying increase in the rate of dissociation is an indication that bond strain is indeed exerted by the steric demands of 1,2-DMeIm. In contrast, comparing the binding parameters for 1-methylimidazole to those for acetonitrile as the axial base, the lower affinity of the acetonitrile arises entirely from an enhancement of the dissociation rate. The smaller increase in association rate observed with acetonitrile over 1-MeIm would have reversed the order of stabilities.

In summary, the CO binding rate is controlled by steric interactions involving the cavity in the main ligand and the position of the iron with respect to the N4 plane. The CO dissociation rate is controlled by electronic factors and the metal-centered steric effect. As outlined above, axial bases play two opposing roles. An electronic contribution stabilizes the carbon monoxide complex by strengthening the iron−CO bond and this is manifested in a lowering of the dissociation rate. Axial bases also pull the iron out of the N4 plane, which hinders CO binding to the opposite side. For the iron cyclidenes these effects are all well-defined.

The carbon monoxide affinities for both imidazole and pyridine with a chelated mesoheme were reported by Traylor and his co-workers[37] to be of very similar value, and they concluded that carbon monoxide affinity is insensitive to the nature of the nitrogenous base. In contrast, for Picket Fence

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(45) For 1.5 M 1-methylimidazole in acetonitrile, the presence of chloride has little effect on the kinetics of carbon monoxide binding and dissociation from the iron(II) complex. The kinetic and equilibrium parameters for [Fe^{II}-(PhBzXy[16]Cyc)Cl]PF_6 were found to be the same as those for the chloride free complex [Fe^{II}(PhBzXy[16]Cyc)]$(PF_6)_2$. With use of 1.5 M pyridine in the solution for the chloro derivative $K^{CO} = 690$ M^{-1}, in the presence of 1,2-DMeIm $K^{CO} = 1200$ M^{-1}, and in the absence of the external base molecule $K^{CO} < 660$ M^{-1}. The deviation in these data compared to the data in Table 6 is ascribed to the influence of the chloride anion present in the solution.

porphyrins[38] the decreased basicity from covalently attached imidazole to the analogous pyridine axial base gives a 13-fold reduction in carbon monoxide affinity, due to an increase in the dissociation rate constant. The role of the axial bases is less clear among the porphyrin complexes.

Conclusions

The iron(II) cyclidene complexes reversibly bind both dioxygen and carbon monoxide, and they have been studied as models for the heme-based biological dioxygen carriers. The affinity for both gases is known to depend strongly on ligand substituents and for that reason, the cyclidene platform provides a unique opportunity to study the structure−function relationships of dioxygen carriers. Remarkably, in the present studies of CO binding, four distinctly different steric effects have been observed.

Variations in the R^1 bridge length have a profound effect on the carbon monoxide affinity, which varies over five orders of magnitude as R^1 varies from tetramethylene to octamethylene. *First steric effect*: This change in affinity arises primarily from an increase in the rate of carbon monoxide binding (four orders of magnitude) and less from the rate of carbon monoxide dissociation (one order of magnitude). The dominant effect is therefore believed to be a steric interaction experienced by the incoming carbon monoxide molecule because of the limited access provided by the lacunae. *Second steric effect*: The lesser, but distinctive, effect on dissociation rates is attributed to steric effects on the strength of the iron−CO bond, and is the first unambiguous demonstration of this phenomenon for CO adducts among dioxygen carriers. *Third steric effect:* The carbon monoxide affinity can also be reduced by placing sterically bulky groups on the N4 macrocycle that provide steric hindrance in the path of the incoming carbon monoxide molecule, which results in a lowering of the binding rate constant. These groups also lowered the dissociation rate constant, indicating that geminate recombination processes may be occurring. Whereas one might argue that the reduction in binding rate is a manifestation of the first steric effect we identified above, the steric inhibition of ligand dissociation is quite a different and unusual phenomenon.

Ligand substituents that change the iron(III)/(II) redox potential have only a small effect on the kinetics of carbon monoxide binding. Increasing the solvent polarity, from acetone to acetonitrile to water, increased the carbon monoxide binding rate constant to [Fe^{II}(PhBzXy[16]Cyc)] by over two orders of magnitude and had only a small effect on the dissociation rate. These effects, which are relatively large compared to those observed for porphyrins, are believed to be associated with increased solvation interactions which, in turn, are related to the existence of cyclidene complexes as salts.

Two axial base effects were observed, the first electronic and the second steric. Adding 1-methylimidazole to an acetonitrile solution of [Fe^{II}(PhBzXy[16]Cyc)] increased the overall CO equilibrium constant by ca. 50 times. This is clearly an electronic effect and arises primarily from a decrease in the rate of dissociation. *Fourth steric effect:* 1-Methylimidazole contrasts with 1,2-dimethylimidazole, which has a much lower rate of carbon monoxide association and a higher rate of carbon monoxide dissociation. The difference in behavior is assigned to the increased steric interaction between the 1,2-dimethylimidazole and the cyclidene ligand, reflecting the extent to which the axial base could pull the iron atom out of the N4 plane.

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