The Effects of Solvent on Dioxygen Binding to Cobalt(II) Picket Fence Porphyrins

HIROYASU IMAI and EISHIN KYUNO*

Department of Pharmaceutical Science, School of Pharmacy, Hokuriku University, 3, Ho Kanagawa-Machi, Kanazawa 920-11, Japan

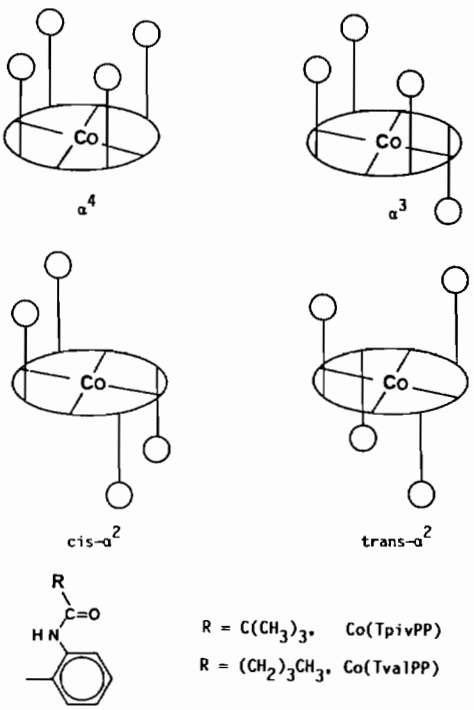
(Received April 7, 1988)

Abstract

The O_2 affinities on base adducts of four atropisomers of picket fence porphyrin Co(TpivPP), and the corresponding α^4 complex containing valeramido pickets instead of pivalamido Co(α^4-TvalPP) were measured in several solvents at 0 or −15 °C. The O_2 affinities of the α^4 complexes are the lowest in DMF which is the most polar of the solvents used, while those of the other isomers are the highest in DMF. This observation was explained in terms of direct and indirect interactions between the solvent and the bound O_2. The *trans*-α^2 complex shows higher O_2 affinity in dichloromethane than those in aromatic solvents because of the preferential solvation of the deoxy complex in the solvents. The variation of the O_2 affinities of this system to solvents is considerably smaller than those of 'flat porphyrin' complexes. This result suggested that the pocket polarity introduced by the amide groups weakens the solvent–solute interaction on the O_2 affinities of this system and also that the solvation of the oxy state rather than the deoxy state predominantly affects the O_2 affinities. It was concluded that the enhanced O_2 uptake by the picket fence may be due to the stabilization of the oxy state by intramolecular interactions rather than to destabilization of the deoxy state by inhibiting solvation for the active site.

Introduction

In order to understand the effective and reversible oxygenation to myoglogin and hemoglobin, many model compounds have been synthesized and studied [1]. Extensive data on oxygenation equilibrium have demonstrated that many factors affect O_2 affinities and, particularly, that an intramolecular cavity to protect the bound O_2 is indispensable for behavior as an oxygen carrier at room temperature. One of the most successful models is 'picket fence' porphyrin Fe(II) and Co(II) complexes developed by Collman *et al.* [2, 3]. Cavities such as the picket fence considerably enhance O_2 uptake compared with unprotected flat porphyrin complexes. The special stabilization of O_2 binding by the picket fence can originate from the attractive intramolecular ligand–ligand forces and/or from the inhibition of undesirable solvation on the active site. The attractive forces which are concerned with the oxy complex may include hydrogen bonding [4–6], pocket polarity [7, 8], and van der Waals forces between the pickets and the bound O_2 [9, 10]. The solvation factor represents the difference of solvation free energy changes between oxy and deoxy complexes when the unit of O_2 affinity is noted as (O_2 pressure)$^{-1}$ [3, 11], and some works have been reported for both protected and flat porphyrin systems [3, 12–15]. Unfortunately, it is still impossible to estimate separately the two factors because of the lack of suitably designed model complexes.



*Author to whom correspondence should be addressed.

0020-1693/88/$3.50

The picket fence porphyrin complex has four atropisomers by restricted rotation of the phenyl rings [2], and the O_2 affinity of the Co(II) complex is remarkably variable for each isomer [9]. The variation in the O_2 affinities might be partly due to the difference of solvation among the isomers. The main purpose of this work is to explore the solvation effects on the O_2 binding of this system and to elucidate the functions on the cavity which enhance the O_2 uptake. It is necessary to investigate the solvent effects on the O_2 affinity of each isomer since solvent molecules may interact differently with the oxy and deoxy complexes of each isomer. A resonance Raman (RR) study on the oxy complexes of this system [6] would be helpful. The bound O_2 in the 'semi-protected' cavity (α^3 and α^2) can interact directly with solvent molecules, while that in the 'protected' cavity (α^4) cannot. Further evidence is given by our previous work on the deoxy complexes [16]. In the deoxy state the cavities of the α^4 and α^3 complexes would be vacant, while that of the *trans*-α^2 complex is occupied by a solvent molecule and better solvated than flat porphyrin complexes in aromatic solvents. Thus, the active site of the α^4 complex could not be solvated in both the oxy and deoxy states, while that of the α^3 complex could be solvated in the oxy state but not in the deoxy state. Those of the α^2 complexes might be solvated in both states.

Experimental

Materials

Each of four atropisomers of *meso*-tetrakis-(*o*-pivalamidophenyl)porphyrinatocobalt(II) Co(TpivPP) and $\alpha,\alpha,\alpha,\alpha$-*meso*-tetrakis-(*o*-valeramidophenyl)porphyrinatocobalt(II) Co(α^4-TvalPP) were prepared by the method reported previously [9]. Pyridine (py) and 1-methylimidazole (1-MeIm) were purified by vacuum distillation from KOH. Solvents were purified as described elsewhere [16].

Measurements

Proton NMR spectra were measured on a Jeol FX-100 spectrometer. Visible absorption spectra were recorded on a Hitachi 340 spectrophotometer. Thermodynamic values for pyridine association and half saturation O_2 pressures $P_{1/2}$ were determined by the methods reported previously [15, 16].

Results and Discussion

Before discussing O_2 affinities of this system, it is worthwhile exploring the situation on the deoxy state of each isomer. In the α^4 and α^3 complexes, the base molecule is forced to bind to the off-cavity side imposed by the steric barrier from the pickets, and the cavities are vacant in the deoxy state [6, 16]. In contrast to these isomers, the binding pocket of the *trans*-α^2 complex is occupied by a solvent molecule in aromatic solvents and is more strongly solvated than that of the corresponding flat porphyrin complex [16]. To examine the situation on the deoxy state of the *cis*-α^2 complex, the thermodynamic values for pyridine binding to the four-coordinate complex were determined in a few solvents and are listed in Table I. Although the difference among the isomers can be mainly attributed to factors other than solvation [16], the variation of the thermodynamic values of the *cis*-α^2 complex is intermediate between those of the α^4 and *trans*-α^2 complexes.

A proton NMR study showed that the methyl signals of the metal-free α^2 isomers shift upfield but pyrrole NH signals shift downfield in toluene compared with those in $CDCl_3$ while those of the α^4 isomer change little (Table II). These shifts of the α^2 isomers can be assigned to the π-current shielding effect induced by the aromatic solvent [16]. Thus, in aromatic solvents, the solvent molecules may nearly stand perpendicular to the porphyrin plane of the *cis*-α^2 isomer similar to that of the *trans*-α^2 isomer.

These results indicate that the binding site of the *cis*-α^2 complex is solvated intermediately between

TABLE I. Thermodynamic Data for Pyridine Binding to Co(II) Porphyrins[a]

Complex	Solvent	log K_B [b]	ΔH (kcal/mol)	ΔS (eu)
Co(α^4-TpivPP) [c]	toluene	3.51	−9.8 ± 0.1	−16.7 ± 0.2
	chlorobenzene	3.45	−9.1 ± 0.1	−14.8 ± 0.4
	o-dichlorobenzene	3.48	−9.7 ± 0.1	−16.6 ± 0.4
Co(*cis*-α^2-TpivPP)	toluene	3.94[c]	−11.0 ± 0.1[c]	−18.7 ± 0.1[c]
	chlorobenzene	3.63	−9.6 ± 0.1	−15.6 ± 0.4
	o-dichlorobenzene	3.75	−10.2 ± 0.1	−17.2 ± 0.4
Co(*trans*-α^2-TivPP)[c]	toluene	4.50	−12.9 ± 0.1	−22.8 ± 0.3
	chlorobenzene	4.21	−10.7 ± 0.1	−16.8 ± 0.4
	o-dichlorobenzene	4.34	−11.7 ± 0.2	−19.2 ± 0.6

[a]Error limits are standard deviations from van't Hoff plots. [b]At 25 °C. [c]Ref. 16.

TABLE II. Proton NMR Data of Porphyrins

Compound	Solvent	CH_3 δ (ppm)	NH (pyrrole) δ (ppm)
$H_2(\alpha^4$-TpivPP)[a]	$CDCl_3$	0.07	−2.60
	toluene-d_8 + $CDCl_3$ (7:1)	0.05	−2.54
H_2(*cis*-α^2-TpivPP)	$CDCl_3$	0.14	−2.58
	toluene-d_8 + $CDCl_3$ (4:1)	0.02	−2.43
H_2(*trans*-α^2-TpivPP)[a]	$CDCl_3$	0.25	−2.55
	toluene-d_8 + $CDCl_3$ (7:1)	0.05	−2.19

[a]Ref. 16.

TABLE III. Qualitative Explanation on Solvation of Picket Fence Porphyrin Complexes in Aromatic Solvents

	α^4-	α^3-	*cis*-α^2-	*trans*-α^2-
Deoxy	non-solv	non-solv	solv[a]	solv[a]
Oxy	non-solv	solv	solv	solv

[a]The order of solvation is *trans*-α^2- > *cis*-α^2- > flat porphyrin complex.

those of the *trans*-α^2 and of flat porphyrin complexes. This finding is supported by the observation for thermal equilibria among four atropisomers of picket fence porphyrins in aromatic solvents [17, 18], in which the ratios of the isomers may depend on the difference of solvations [16, 18]. Together with the previous results stated in the 'Introduction', the environments of the active sites on this system are summarized in Table III.

The equilibrium among O_2, deoxy and oxy complexes is as follows

$$\text{CoPB} + O_2 \overset{K_{O_2}}{\rightleftharpoons} \text{CoPB}\cdot O_2$$

where CoPB and CoPB·O_2 represent five-coordinate Co(II) and its O_2 adduct, respectively, and half saturation O_2 pressure $P_{1/2}$ is equal to $(K_{O_2})^{-1}$. The $P_{1/2}$ values were determined by spectrophotometric titration of O_2. As shown in Fig. 1, good isosbestic points were observed in all of the cases investigated.

The solvation factor on oxygenation reaction implies the difference of free energy changes between the oxy and deoxy complexes. If such a difference is present, O_2 affinity will vary from solvent to solvent. The $P_{1/2}$ values obtained in several solvents are listed in Table IV. It is generally acceptable that increased solvent polarity increases O_2 affinities due to the stabilization of the expected charge separation in the M(II)–O_2 (M = Co or Fe) bond [8, 12, 13]. Of particular interest is the observation that the O_2 affinities of the α^4 complexes are the lowest in DMF

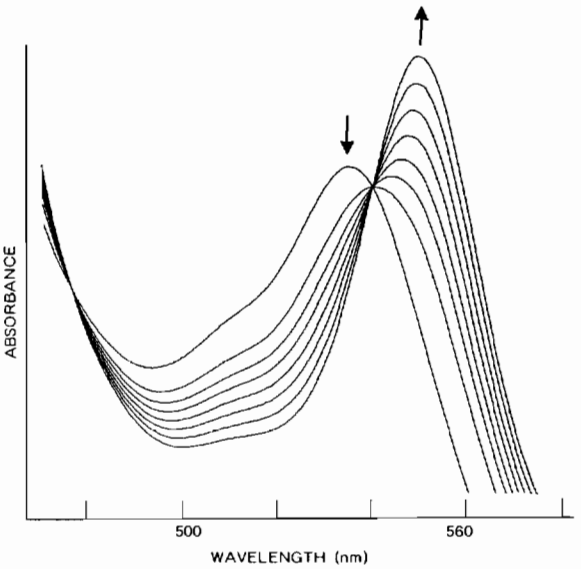


Fig. 1. Spectroscopic determination of $P_{1/2}$ values for Co(α^3-TpivPP)(1-MeIm) in DMF at 0 °C. O_2 partial pressures for spectra are 0, 60.9, 106, 149, 213, 298, 446, 744 Torr, respectively.

but the highest in toluene. It is in good agreement with the previous result reported by Collman *et al.* [3], although no explanation was given by them. The cavities of the α^4 complexes inhibit access of solvent molecules to the active sites, hence it should weaken the solvent effects on the O_2 affinities [3, 15, 20] This suggestion, however, cannot account satisfactorily for the observation on the α^4 complexes. Judging from the fact that the O_2 affinity of iron 'bis-pocket' porphyrin which has a completely protected and non-polar cavity shows similar solvent effects to flat porphyrin complexes [8], it is certain that the amide groups of the pickets cause the reverse trend on the O_2 affinities of the α^4 complexes. A probable and tenable explanation will be as follows. Polar solvent molecules can interact directly with the polar amide groups of the pickets

TABLE IV. Oxygenation Constants of Co(II) Porphyrins[a]

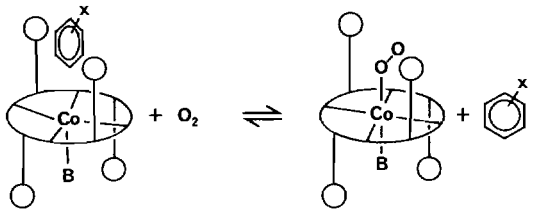
Complex	Temperature (°C)	$P_{1/2}$ (Torr)				
		TOL[b] (2.38)[c]	CB (5.62)	DCM (9.08)	DCB (9.93)	DMF (36.71)
Co(α^4-TpivPP)(1-MeIm)	0	21[d], 23[e]	24	27	24	53
	−15	5.7[e]				
Co(α^4-TpivPP)(py)	0	220	234	279	255	592[f]
Co(α^4-TvalPP)(1-MeIm)	0	79	85	96	123	346
Co(α^3-TpivPP)(1-MeIm)	0	199[e]	215	312	217	154
	−15	53[e]				
Co(*cis*-α^2-TpivPP)(1-MeIm)	−15	366	283	261	219[f]	47
Co(*trans*-α^2-TpivPP)(1-MeIm)	−15	667[f]	416	288	409	91[f]
Co(Tp-OCH_3PP)(1-MeIm)	−15	1,640[g]		77[g]		

[a]Error limits are smaller than 10%, unless otherwise noted. [b]TOL = toluene; CB = chlorobenzene; DCM = dichloromethane; DCB = *o*-dichlorobenzene. [c]Dielectric constants from ref. 19 are in parentheses. [d]Ref. 2. [e]Ref. 9. [f]Error limits are smaller than 25%. [g]Ref. 13.

but cannot interact with the bound O_2 in the α^4 complexes. The direct polar interaction will weaken the alternative polar interaction between the amide groups and the bound O_2 and/or elongate the separation [21]. This proposal should depend on the ability of the hydrogen bond formation between the amide groups and the bound O_2. In fact, the O_2 affinity of Co(α^4-TvalPP)(1-MeIm) is more sensitive to solvent polarity than that of Co(α^4-TpivPP)(1-MeIm), since the O_2 adduct of the former will form a stronger hydrogen bond than that of the latter [6]. Thus, the indirect interaction via the amide groups between polar solvents and the bound O_2 will reduce the O_2 affinities of this system.

In contrast with the case of the α^4 complexes, the O_2 affinities of the other isomers are the highest in DMF. A similar result has been obtained for the 'tailed picket fence' porphyrin complex [11] which has the same cavity as the α^3 complex. Since the cavity of the α^3 complex is vacant in the deoxy state similarly to the α^4 complexes, this result can be attributed to direct interaction between the bound O_2 and the polar solvent (DMF) in the oxy state. Although the amide groups of the pickets are very polar, the separation between the groups and the bound O_2 is limited by the rigid structure of the cavity [6]. The solvent molecule, however, can freely access to the bound O_2 and may nearly attain an optimum position in the semi-protected cavities. This interaction should enhance the O_2 uptake in polar solvents. In DMF solution polar interaction between the bound O_2 and the solvent molecule would become stronger than that between the O_2 and the pickets in the case of the α^3 complex. The solvent effects on the O_2 affinity of the α^3 complex imply both the direct solvent–O_2 interaction and the indirect one introduced via the pickets as noted above. The fact that the affinity of the complex is the lowest in dichloromethane would cause competition between the two kinds of interactions.

In the case of the α^2 complexes, the situation becomes obviously more complicated since both complexes are solvated even in the deoxy state. The O_2 affinity of the *trans*-α^2 complex in dichloromethane is substantially higher than those in the aromatic solvents. The cavity of the complex is occupied by a solvent molecule in aromatic solvents, while in dichloromethane the solvent molecule will be too bulky to be accommodated into the cavity. This means that the binding pocket of the deoxy state of the complex can be less solvated in dichloromethane than in aromatic solvents. As illustrated in the following equilibrium



the release of a solvent molecule should reduce the O_2 affinity of the *trans*-α^2 complex in the aromatic solvents as oxygenation progresses.

If one realizes that the solvent effects on the oxy state of the α^3 and *trans*-α^2 complexes are similar in dichloromethane and *o*-dichlorobenzene and compares the O_2 affinities of these complexes, the difference of solvation free energy changes of the deoxy state between these complexes will be evaluated as −0.4 kcal/mol. This value may be afforded as a stabilizing factor on the deoxy state of the *trans*-α^2 complex in aromatic solvents. It is interesting to note that this is comparable to the value ($\Delta G^\circ = -0.5$

kcal/mol) estimated roughly from thermal equilibria among four atropisomers in aromatic solvents [17, 18].

In accordance with the results listed in Table III, the O_2 affinities of the *cis*-α^2 complex show an intermediate variation between the α^3 and *trans*-α^2 complexes, except for those in DMF. The O_2 affinities of the α^2 complexes are considerably lower in DMF. This result may be correlated to the fact that the cavities of these complexes are more freely admittable than that of the α^3 complex. In the α^2 complexes the indirect interaction via the pickets becomes weaker and will be compensated by the increased direct interaction between the solvent molecule (DMF) and the bound O_2, causing the former influence to be negligible.

The active sites of the α^2 complexes should be better solvated in aromatic solvents than those of flat porphyrins. Nonetheless, the variation of the O_2 affinities of the former is considerably smaller than that of the corresponding flat porphyrin complex (Co(Tp-OCH_3PP)(1-MeIm)). This fact can only be explained as follows. Since all of the picket fence complexes investigated here have amide groups near the active sites and form an intramolecular hydrogen bond or the like between NH and the bound O_2, even in non-polar solvents the O_2 would experience a strongly polar environment. Thus, the pocket polarity itself would weaken the dependence of O_2 affinity on solvent polarity. This interpretation may only concern the oxy state. If the stabilization of the deoxy state of the flat porphyrin complex reduced the O_2 affinity in aromatic solvents, the affinities of the α^2 complexes should be further decreased in the solvents. Further, the solvation of the deoxy flat porphyrin complex in aromatic solvents seems to be mainly a 1:1 π-complex formation, but the stabilization is weak in TPPs (tetraphenylporphyrin derivatives) and the formation occurs on the porphyrin periphery [22]. Therefore, we concluded that the solvation factor which reduces the O_2 affinities of flat porphyrin complexes by stabilizing the deoxy state will be much weaker than that estimated by Collman *et al.* [3, 20]. Although the magnitude of solvation on flat porphyrin complexes cannot be quantitatively compared with this system because of the disparity in temperatures for measurements, the solvation factor on the deoxy state would be smaller than the value $\Delta G^\circ = 0.4$ kcal/mol in aromatic solvents (*vide supra*). This value is much smaller than the difference of the O_2 affinities ($\Delta\Delta G^\circ = 2.9$ kcal/mol at -15 °C in toluene) between Co(α^4-TpivPP)(1-MeIm) and Co(Tp-OCH_3PP)(1-MeIm).

This suggestion is clearly supported by kinetic studies on the iron porphyrin system [7, 23]. Increased polarity of the solvent has little effect on the O_2-on rates but leads to the substantially decreased O_2-off rates resulting in an overall enhanced O_2 affinity. Thus, the solvation of oxy complexes rather than deoxy complexes should predominantly affect O_2 affinity.

Implication of O_2 Affinity

As discussed so far, the stabilization of O_2 binding by picket fence in aromatic solvents can be attributed mainly to intramolecular interactions in the oxy state rather than to the inhibition of the undesirable solvation in the deoxy state. In this system, O_2 affinity decreases remarkably with an opening of the cavity (Table IV), and this tendency is still retained in the solid state [9]. One can, therefore, address the lowering of the O_2 affinity to the destabilization of the oxy state. In accordance with this finding, the $\nu(O_2)$ of the O_2 adducts of the α^4, α^3, and *cis*-α^2 complexes are 1156, 1160, and 1164 cm^{-1}, respectively [6]. However, to compare quantitatively the O_2 affinities of this system is obviously more difficult than that discussed previously [9]. For instance, direct interactions between the pickets and the bound O_2 are decreased in the semi-protected α^2 and α^3 complexes compared with the protected α^4 complex. The interactions include not only hydrogen bond and/or pocket polarity introduced by the amide groups, but also van der Waals forces from alkyl groups of the pickets as seen in the difference between pivalamido and valeramido pickets and for similar systems [9, 10]. Indirectly, steric interactions between the ligated base and the pickets in the *cis*-α^2 complex [16] may reduce the O_2 affinity. Also, restricted orientation of the base imposed by the pickets of the *trans*-α^2 complex should decrease the π-electron flow from the base to the bound O_2, leading to a substantial decrease in O_2 affinity [6, 24]. Thus, the reduction in O_2 affinities of the semi-protected complexes will be attributed to a combination of each of these factors on the oxy state.

Acknowledgement

This work is supported by a Grant-in-Aid for Scientific Research from the Ministry of Education (No. 62740356).

References

1 J. P. Collman, T. R. Halbert and K. S. Suslick, in T. G. Spiro (ed.), 'Metal Ion Activation of Dioxygen', Wiley, New York, 1980, Chap. 1.
2 J. P. Collman, R. R. Gagne, C. A. Reed, T. R. Halbert, G. Lang and W. T. Robinson, *J. Am. Chem. Soc., 97,* 1427 (1975).
3 J. P. Collman, J. I. Brauman, K. M. Doxsee, T. R. Halbert, S. E. Hayes and K. S. Suslick, *J. Am. Chem. Soc., 100,* 2761 (1978).

4 (a) M. Momenteau and D. Lavalette, *J. Chem. Soc., Chem. Commun.*, 341 (1982); (b) J. Mispelter, M. Momenteau, D. Lavalette and J. M. Lhoste, *J. Am. Chem. Soc., 105*, 5165 (1983); (c) M. Momenteau, B. Loock, C. Tetreau, D. Lavalette, A. Croisy, C. Schaeffer, C. Huel and J. M. Lhoste, *J. Chem. Soc., Perkin Trans. 2*, 249 (1987).

5 F. A. Walker and J. Bowen, *J. Am. Chem. Soc., 107*, 7632 (1985).

6 J. Odo, H. Imai, E. Kyuno and K. Nakamoto, *J. Am. Chem. Soc., 110*, 742 (1988).

7 T. G. Traylor, N. Koga and L. A. Deardurff, *J. Am. Chem. Soc., 107*, 6504 (1985).

8 (a) K. S. Suslick and M. M. Fox, *J. Am. Chem. Soc., 105*, 3507 (1983); (b) K. S. Suslick, M. M. Fox and T. J. Reinert, *J. Am. Chem. Soc., 106*, 4522 (1984).

9 H. Imai, K. Nakata, A. Nakatsubo, S. Nakagawa, Y. Uemori and E. Kyuno, *Synth. React. Inorg. Met.-Org. Chem., 13*, 761 (1983).

10 S. Takagi, T. K. Miyamoto and Y. Sasaki, *Bull. Chem. Soc. Jpn., 58*, 447 (1985).

11 J. P. Collman, J. I. Brauman and K. M. Doxsee, *Proc. Natl. Acad. Sci. U.S.A., 76*, 6035 (1979).

12 (a) H. C. Stynes and J. A. Ibers, *J. Am. Chem. Soc., 94*, 5125 (1972); (b) W. S. Brinigar, C. K. Chang, J. Geibel and T. G. Traylor, *J. Am. Chem. Soc., 96*, 5597 (1974).

13 C. M. Wicker, Jr., R. D. Morgan and D. P. Rillema, *Inorg. Chim. Acta, 78*, 181 (1983).

14 T. Hashimoto, R. L. Dyer, M. J. Crossley, J. E. Baldwin and F. Basolo, *J. Am. Chem. Soc., 104*, 2101 (1982).

15 H. Imai, S. Sekizawa and E. Kyuno, *Inorg. Chim. Acta, 125*, 151 (1985).

16 H. Imai and E. Kyuno, *Inorg. Chim. Acta, 153*, 175 (1988).

17 (a) R. A. Freitag, J. A. Mercer-Smith and D. G. Whitten, *J. Am. Chem. Soc., 103*, 1226 (1981); (b) R. A. Freitag and D. G. Whitten, *J. Phys. Chem., 87*, 3918 (1983).

18 M. J. Crossley, L. D. Field, A. J. Forster, M. M. Harding and S. Sternhell, *J. Am. Chem. Soc., 109*, 341 (1987).

19 J. A. Dean (ed.), 'Lange's Handbook of Chemistry', McGraw-Hill, New York, 1979, pp. 10–103.

20 J. P. Collman, J. I. Brauman, B. L. Iverson, J. L. Sessler, R. M. Morris and Q. H. Gibson, *J. Am. Chem. Soc., 105*, 3052 (1983).

21 V. Gutman, 'The Donor–Acceptor Approach to Molecular Interactions', Plenum, New York, 1978, Chap. 1.

22 (a) G. P. Fulton and G. N. La Mar, *J. Am. Chem. Soc., 98*, 2119 (1976); (b) G. P. Fulton and G. N. La Mar, *J. Am. Chem. Soc., 98*, 2124 (1976).

23 C. K. Chang and T. G. Traylor, *Proc. Natl. Acad. Sci. U.S.A., 72*, 1166 (1975).

24 (a) Y. Uemori and E. Kyuno, *Inorg. Chim. Acta, 125*, L45 (1986); (b) Y. Uemori, H. Miyakawa and E. Kyuno, *Inorg. Chem., 27*, 377 (1988).