Spectroscopic Evidence for the Coordination of Oxygen Donor Ligands to Tetraphenylporphinatozinc

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Received July 11, 1985

Abstract

Direct evidence for the coordination oxygen donor ligands to tetraphenylporphinatozinc [Zn(TPP)] is presented. Dissociation constants have been determined for twenty-five zinc porphyrin–ligand complexes. A 1:1 binding stoichiometry is found in all cases. Increasing affinity for complex formation as a function of increasing basicity is observed among a limited set of structurally similar ligands. Steric constraints also strongly influence ligand binding affinity.

Introduction

The interaction of axial ligands with metalloporphyrins has been an active area of research for many years [1]. A wide variety of spectroscopic techniques have been used to study these interactions in both heme proteins and model systems [2]. In a preliminary report, we examined the axial ligation of tetraphenylporphinatozinc(II) [Zn(TPP)][†] with oxygen and nitrogen donor ligands using magnetic circular dichroism spectroscopy [3]. To perform this study, it was necessary to reproducibly form homogeneous Zn(TPP) complexes with oxygen donor ligands. This was accomplished through a titration procedure which allowed the saturation (Y) of the zinc-ligand complex to be determined from the dissociation constant (K_d). Using this method, we have now measured dissociation constants for Zn(TPP) complexes with a wide variety of oxygen donor ligands.

This is the first extensive survey of oxygen donor ligand complexes of Zn(TPP) in which dissociation constants and binding stoichiometries have been determined. Such data provide direct evidence for the coordination of oxygen donor ligands to the zinc atom and rule out solvation effects as the explanation of the spectroscopic changes observed in forming these complexes. In addition, we have found that the K_d values are influenced by both steric and electronic effects induced by the ligand and that in structurally similar molecules, a relationship exists between increasing basicity of the ligand (increasing pK_a) and increasing ligand affinity (decreasing K_d) for the zinc porphyrin.

Experimental

Reagents and Synthesis

Reagent grade benzene was washed with sulfuric acid to remove thiophene impurities and was distilled from sodium benzophenone ketyl under a dinitrogen atmosphere. All oxygen ligands were of reagent grade (Aldrich) and were purified by distillation or recrystallization following published procedures [4]. Perfluoro-1,1-dihydroethanol (K and K-ICN Labs) was found to be of high purity by gas chromatography and was used as received. Precautions were taken to minimize exposure to atmospheric water. Zn(TPP) was obtained as described previously [5]. *Anal.* Calc. for $C_{44}H_{28}N_4Zn$: C, 77.94; H, 4.16; N, 8.26; Zn, 9.64. Found: C, 77.78; H, 4.13; N, 8.20; Zn, 9.23%.

Procedure

The procedures used for K_d determination are similar to those described earlier [3]. Microliter amounts of the neat liquid or the solid material in concentrated solution were added to a Zn(TPP) solution of known concentration in benzene. Absorbance changes were monitored by observing the decrease in intensity of the beta band of the uncomplexed metalloporphyrin at 549 nm. The temperature of the solution was maintained at 24 °C by the use of a thermostatted circulator bath.

Calculations

Equations for the calculations of K_d values and binding stoichiometries have been described prev-

*This work will be presented in partial fulfillment of the requirements for the Ph.D. degree at the University of South Carolina.

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[†]Abbreviations: Zn(TPP), tetraphenylporphyrinatozinc(II); Y, saturation; K_d, dissociation constant; pK_a, acid dissociation constant; MCD, magnetic circular dichroism spectroscopy; DMF, dimethylformamide.

0020-1693/86/$3.50

iously [3] and are briefly summarized below. The dissociation of a ligand, L, from a Zn(TPP) ligand complex, Zn(TPP)L, is defined in eqn. (1) as:

$$Zn(TPP)L \overset{K_d}{\rightleftharpoons} Zn(TPP) + L \quad (1)$$

where

$$K_d = \frac{[Zn(TPP)]\,[L]}{[Zn(TPP)L]}$$

From this equation, it is possible [3] to define a double reciprocal relationship:

$$\frac{1}{\Delta A} = \frac{K_d}{\Delta A_\infty}\frac{1}{[L]} + \frac{1}{\Delta A_\infty} \quad (2)$$

For a typical titration, the reciprocal of the change in absorbance observed after the addition of the ligand to a Zn(TPP) solution, $1/\Delta A$, is plotted *vs.* the reciprocal of the added ligand concentration, $1/[L]$. Nonweighted linear least-squares analysis [6] is used to evaluate the slope and y-intercept of the plotted data, and the K_d for the complex is calculated using eqn. (2). The reciprocal of the y-intercept obtained in eqn. (2) yields the absorbance change observed at infinite (*i.e.* very high) ligand concentrations, ΔA_∞. Substitution of this value into eqn. (3) (see below) allows the saturation, Y, to be calculated after each stepwise addition of ligand [3].

$$Y = \frac{\Delta A}{\Delta A_\infty} \quad (3)$$

Further algebraic manipulation produces the well known Hill equation.

$$\log \frac{Y}{1-Y} = \log[L] - \log K_d \quad (4)$$

The binding stoichiometry is determined from eqn. (4) by plotting $\log[Y/(1-Y)]$ *vs.* $\log[L]$ and evaluating the slope. Based on the description of the metalloporphyrin–ligand equilibrium presented in eqn. (1), a slope of unity indicates the formation of a 1:1 complex.

Results and Discussion

Zinc porphyrins provide a very simple and yet useful system with which to examine the effects of axial ligation upon metalloporphyrin electronic structure. As pointed out by Nappa and Valentine [7], zinc does not undergo spin state or oxidation state changes and, when complexed to a porphyrin, appears to only bind one axial ligand. Thus, zinc porphyrins serve as a natural bridge between metal-free porphyrins and those metal-bound porphyrins which do suffer from the above complications (iron, cobalt, etc.). However, in order to systematically study the effect of different ligands on the spectroscopic properties of zinc porphyrin–ligand adducts, it is particularly important to know that homogeneous, fully saturated (eqn. (3), $Y \geqslant 0.98$) complexes have been formed. This requires that the dissociation constant, K_d, be determined. In the process of our on-going study of the magnetic circular dichroism spectra of zinc porphyrins [3, 8], we have examined Zn(TPP) complexes with over twenty-five different oxygen-donor ligands and report herein the trends observed in the dissociation constants as a function of steric and electronic factors.

Dissociation Constants and Binding Stoichiometries

The dissociation constants for a wide variety of Zn(TPP) complexes with nitrogen donor ligands, particularly substituted pyridine and imidazole derivatives, have been previously determined [9]. Prior to our investigations, such studies with oxygen donor ligands have been limited to the examination of tetramethyl urea [10], methyl oxirane [11], and dimethylsulfoxide [12]. In this study, we have examined an extensive collection of oxygen donor ligands containing alcohol, ether, sulfoxide and carbonyl type oxygen atoms. Upon the addition of an oxygen donor ligand to Zn(TPP), a red shift (*i.e.* to higher wavelengths) is seen for all bands in the electronic absorption spectrum, accompanied by a decrease in intensity of the beta (~550 nm) band and an increase in intensity of the alpha (~600 nm) band. A typical example of this is found in Fig. 1 where the spectral changes following the stepwise addition of tetramethylene sulfoxide to a solution of

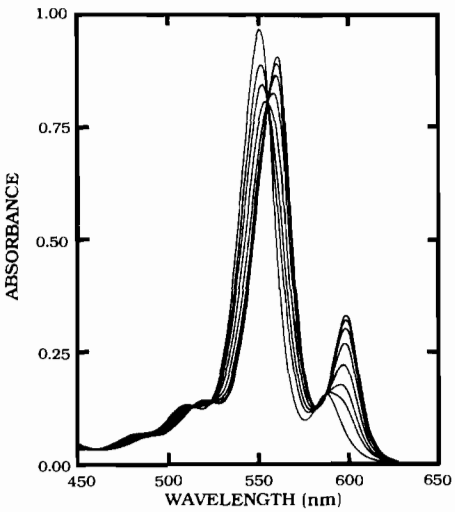

Fig. 1. Spectral changes occurring upon titration of a Zn(TPP) solution with tetramethylenesulfoxide. Porphyrin concentration: 4.0×10^{-5} M. Spectrum recorded at 25 °C with benzene as the solvent. Each step in the titration represents the following ligand concentrations where the saturation (Y) for each addition was calculated using the estimate of ΔA_∞ from equation 3; 3.51×10^{-4} M ($Y = 0.20$), 7.06×10^{-4} M ($Y = 0.34$), 1.40×10^{-3} M ($Y = 0.51$), 2.8×10^{-4} M ($Y = 0.67$), 4.90×10^{-3} M ($Y = 0.78$), 7.64×10^{-3} M ($Y = 0.85$), 1.11×10^{-2} M ($Y = 0.89$) and 1.80×10^{-2} M ($Y = 0.93$).

Zn(TPP) in benzene are displayed. These observations are identical to those reported by Nappa and Valentine [7] who examined a limited number of oxygen donor ligands but did not determine dissociation constants. Drago *et al.* have shown that benzene is a noncoordinating solvent for Zn(TPP) [13] and this property has been confirmed in the present study by the lack of isosbestic points for the relatively small spectral changes resulting from addition of benzene to solutions of Zn(TPP) in cyclohexane. Sharp isosbestic points have been observed during formation of all ligand complexes reported in this study.

Table I contains K_d values from eqn. (2) for twenty-five Zn(TPP)-ligand complexes. The K_d values range from 1.4 mM (moderate affinity) to 5300 mM (very low affinity); in three cases, no evidence for coordination was obtained. In representative cases, K_d values were found to be reproducible to within 1% for three separate titrations.

Binding stoichiometries determined using eqn. (4) are also listed in Table I. The range of values (0.96 to 1.04) demonstrates that 1:1 complex formation occurs in all cases. This is consistent with our preliminary study of a selected number of oxygen and nitrogen donor ligand complexes [3] and with previous data reported for nitrogen donor ligands [10]. However, these data directly contradict reports of bis-ethanol and bis-DMSO Zn(TPP) complexes generated in benzene [14]. X-ray crystal structures of the unliganded Zn(TPP) and of the mono-aquo Zn(TPP) complexes have been reported by Scheidt and Hoard, respectively [15, 16]. Kadish and Shiue have discussed the reasons why Zn(TPP) should only bind one axial ligand [17].

In summary, direct evidence for the coordination of oxygen donor ligands to Zn(TPP) has been obtained through the determination of dissociation constants and binding stoichiometries for a large number of such ligands. These data, together with the conclusions of Nappa and Valentine [7] regarding the relationship between ligand coordination and the red shifts observed in the UV–Vis absorption spectrum upon ligand addition clearly shows that Zn(TPP) is able to form ligand complexes with an extensive variety of oxygen donor ligands.

Factors Influencing Ligand Binding Affinities

A correlation between the pK_a of a ligand and its affinity for a metalloporphyrin has been observed in a number of metalloporphyrin–ligand binding studies. Studies by Kadish and Shiue [18] on the coordination of substituted pyridines and imidazoles to tetraphenylporphinatomagnesium (Mg(TPP)) have demonstrated a linear relationship between the stability constants of the complexes and the pK_a of the ligand, namely that increasing basicity (increasing pK_a) leads to increased affinity (decreasing K_d).

TABLE I. Dissociation Constants for Zn(TPP) Complexes with Oxygen Donor Ligands[a]

Ligand	K_d (mM)[b]	pK_a	Slope[c]
Alcohols			
methanol	104	15.5[d]	0.98
ethanol	101[e]	15.9[d]	1.00
n-butanol	87	16.1[f]	1.01
n-pentanol	87	16.2[f]	1.01
perfluoro-1,1-dihydroethanol	5300	12.4[d]	0.99
sec-butanol	94	16.1[f]	1.03
tert-butanol	251	18[c,d]	1.00
iso-butanol	114	16.2[f]	0.99
cyclohexanol	107	16[g]	1.01
benzyl alcohol	61	14.8[h]	1.01
benzhydrol	412	13.8[h]	1.03
triphenylcarbinol	i	12.0[j]	–
phenol	1200	9.95[k,l]	1.04
o-cresol	i	10.28[l]	–
m-cresol	2500	10.08[l]	0.96
p-cresol	2600	10.19[l]	0.97
Ethers			
diethyl ether	695	–	0.99
anisole	i	–	–
tetrahydrofuran	22[e]	–	0.99
Esters			
ethyl acetate	915	–	1.00
n-butyl acetate	892	–	0.99
4-butyrolactone	499	–	1.03
Sulfoxides			
dimethylsulfoxide	1.4[e]	–	1.01
tetramethylenesulfoxide	1.8	–	0.96
Ketones			
methyl ethyl ketone	1100	–	0.98
cyclohexanone	419	–	1.04
benzaldehyde	1000	–	1.04
Amide			
dimethylformamide	17[e]	–	0.99

[a]All titrations were carried out in benzene solution at 24 °C. Zn(TPP) concentration: 3.0×10^{-5}. [b]K_d values were determined from double reciprocal plots using eqn. (3). [c]Slope calculated from eqn. (4) using Hill plots. This value represents the binding stoichiometry. [d]Taken from ref. 21. [e]K_d value previously determined [4]. [f]pK_a values were estimated using Hammett and Taft equations as described by ref. 22. [g]Estimated based on the value of sec-butanol, which is also a secondary aliphatic alcohol. [h]Taken from ref. 23. [i]Complex formation not observed. [j]Taken from ref. 24. [k]Taken from ref. 25. [l]Taken from ref. 26.

Similar studies with Zn(TPP) involving the same group of nitrogen donor ligands led to the same conclusion [19]. It should be noted that in both cases this correlation was only valid for structurally similar ligands.

Examination of the K_d values in Table I suggests that a similar relationship between K_d and pK_a may exist form some Zn(TPP) complexes with oxygen donor ligands. However, because of the obvious role that steric factors may contribute to the K_d value, only a few comparisons are possible where steric factors are minimized to the point that electronic influences can be accurately revealed. For example, the binding of ethanol and perfluoro-1,1-dihydroethanol to Zn(TPP) provides a useful comparison because C–F bond lengths and the atomic radius of fluorine are sufficiently similar to C–H bond lengths and the atomic radius of hydrogen to rule out steric factors as major influences on the K_d value. As seen in Table I, the normal alcohol is substantially more basic than the fluoroalcohol and, as indicated by the relative K_d values, the normal alcohol is a much better ligand than the fluoroalcohol. A second comparison of this type can be found with phenol and cyclohexanol. Once again, cyclohexanol is substantially more basic and also a much better ligand than is phenol A third, although less dramatic, example of this trend is found with the homologous series of primary alcohols: methanol through n-pentanol As the chain length increases, the basicity of the alcohol and the binding affinity both increase by a moderate amount. In fact, in this case, one might predict that steric factors would diminish the binding affinities as the chain length increases. Thus, in spite of possible steric influences, increased basicity correlates with increased affinity.

For the series of benzyl alcohols, both steric and electronic factors predict the same trend in binding affinity. In going from benzyl alcohol, itself, to benzylhydrol to triphenyl carbinol, the basicity decreases and, as expected, so does the affinity. However, steric considerations also predict the same trend in binding affinities. In fact, triphenyl carbinol does not bind to Zn(TPP) at all Thus for this series of ligands it appears that both electronic and steric factors are working in the same direction.

The binding affinity of oxygen donor ligands for Zn(TPP) can also be influenced by steric factors. For example, despite the fact that tert-butyl alcohol is the most basic of all the alcohols listed in Table I, it has the lowest affinity of any aliphatic alcohol examined. Steric factors also appear to play a role in the binding of the aromatic alcohols. The cresols are all more basic than phenol and as such would be expected to show increased binding affinity. Instead, decreased affinity is observed. The extreme example is o-cresol where no evidence for binding was found, presumably due to steric interference from the *ortho* methyl group.

Steric influences can be seen among other functional groups in Table I. For example, the cyclic ketone, cyclohexanone, has a higher affinity than the acyclic ketone, methyl ethyl ketone. With the ethers, tetrahydrofuran, a cyclic ether, has a greater affinity than the acyclic ether, diethyl ether. Likewise, with esters it is the cyclic lactone that has the highest affinity. In all of these cases, the higher affinity is found with the cyclic molecules possibly as a result of less steric hindrance However, the two sulfoxides examined have very similar K_d values despite the fact that one is cyclic and the other acyclic. The sulfoxides have the highest affinity for Zn(TPP) of any oxygen donors in this study and, as such, may be less subject to steric influences.

Dimethylformamide (DMF) also shows a high affinity for Zn(TPP). Since it contains a carbonyl group one might have expected a low affinity as was observed for the ketones. A possible explanation for the high affinity comes from the fact that a resonance form of DMF exists with a partial negative charge on oxygen The high affinity of the sulfoxides may result from a similar, charge separated, resonance structure with an anionic oxygen. Anionic oxygen ligands have a high affinity for Zn(TPP) as has been recently demonstrated for the superoxide anion [20] Nappa and Valentine [7] have demonstrated that the magnitude of the red shift of the alpha band observed upon the coordination of an axial ligand to Zn(TPP) is greater for anionic ligands than it is for neutral ligands. In fact, the positions of the alpha bands of the DMF and dimethylsulfoxide adducts of Zn(TPP) are red-shifted relative to that of the complex with a neutral oxygen donor such as tetrahydrofuran [7]. Thus the ligand binding properties of DMF and the sulfoxides suggest that their oxygen donor atoms have considerable anionic character.

In summary, we have presented the first extensive equilibrium study of the interaction of oxygen donor ligands with Zn(TPP). We have established that there is direct coordination of oxygen donor ligands to the zinc atom and that the binding stoichiometry is 1.1 for all cases where ligand binding is observed. Among a limited set of structurally similar ligands, there is a relationship between basicity of the ligand and the affinity that it has for Zn(TPP) However, it is sometimes difficult to predict whether steric or electronic factors will exert a greater influence on ligand binding affinity.

Acknowledgements

This research was supported by a grant from the National Institutes of Health (GM-26730) J. H D is

(i) a Camille and Henry Dreyfus Teacher–Scholar (1982–1987), (ii) an Alfred P. Sloan Foundation Research Fellow (1983–(1987), and (iii) a recipient of a National Institutes of Health Research Career Development Award (1983–1988). We thank Dr. Masanori Sono and Elisabeth Kintner for helpful discussions, and Dr. Elka V. Elenkova for her translation of ref. 14.

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