of the corresponding pentaphenyl derivative, and it is square pyramidal. This suggests that the structure in both cases may be a result of electronic rather than environmental effects. Unfortunately, both ^{13}C nmr and ^{1}H resonance measurements utilizing a 100-MHz instrument (30°)[22] indicate that this molecule is a stereochemically nonrigid system on a magnetic resonance time scale,[23] and they provide no other information concerning the molecular structure. This is not unexpected since, as Muetterties points out, "All ML_5 molecules investigated by nmr have shown apparent magnetic equivalence of ligand nuclei."[23] The relatively clear-cut assignment of the vibrational spectrum of this molecule utilizing C_{4v} point group selection rules presumably indicates that the ground-state lifetime is long with respect to the vibrational time scale.[24]

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(22) Private communication from Professor George Gray of the Oregon Graduate Center. The natural-abundance ^{13}C spectrum taken at 40 Hz/sec on a 1000-Hz sweep showed but two bands with an intensity ratio 55:27 (~2:1), presumably reflecting the ratio of methylene to methyne carbons in the cyclopropyl rings. Although it is possible that this ratio arises because the shifts associated with carbon atoms in structurally nonequivalent cyclopropyl rings of either a C_{4v} or a D_{3h} polyhedron are accidentally degenerate, it seems more likely that the magnetic equivalence arises from structural nonrigidity (see Discussion). Two complex multiplets separated by *ca.* 70 Hz, each of total width 50 Hz, appear in the proton resonance spectrum, and the multiplet intensity ratio is 3:2. Since the ^{13}C spectrum, which should be more sensitive to the molecular symmetry features than the ^{1}H spectrum, indicates that the five ligating carbon nuclei are magnetically equivalent, the proton multiplet ratio is assumed to be the ratio of protons on the opposite side of the cyclopropyl ring from the Sb atom to those on the same side. We appreciate Professor Gray's interest in this problem and his courtesy in informing us of his experimental results.

(23) E. L. Muetterties, *Inorg. Chem.*, **4**, 769 (1965); *Accounts Chem. Res.*, **3**, 266 (1970).

(24) If the traverses of polytopal forms were rapid on a vibrational time scale, then the Raman and infrared selection rules would be determined using a treatment similar to those involving the permutational symmetry groups discussed by Longuet-Higgins.[25] To our knowledge, a treatment of this sort applicable to the nonrigid behavior in question is not available in the literature.

(25) H. C. Longuet-Higgins, *Mol. Phys.*, **6**, 445 (1963).

Ligand Binding by Metalloporphyrins. II. The Effect of Solvent on the Thermodynamic Functions

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Abstract: The study of free energy, enthalpy, and entropy changes accompanying the addition of substituted pyridines to iron(II) porphyrins has been extended to follow the effect of solvent change on these thermodynamic functions. Free energy changes are an unreliable index of strength of binding, but very large solvent effects are observed for enthalpy and entropy changes. Enthalpy effects were most favorable and entropy effects least favorable in carbon tetrachloride with decreasing magnitudes in chloroform and benzene. Statistical treatment of the results (62 data pairs) suggests that the contributions to these thermodynamic functions from different solvents, ligands, and metalloporphyrins operate independently and are additive. A linear model is proposed which simulates these effects. The thermodynamic data may be rationalized in terms of a relaxation in the binding of solvent molecules by heme when ligands are attached. The types of heme–solvent interaction occurring in the three solvents are different and solvation energies appear to decrease in the order benzene > chloroform > carbon tetrachloride. The associated large entropy changes follow the same order.

Because the binding of ligands by metalloporphyrins is of interest to both chemists and biochemists, numerous stability constant measurements and studies of the free energy of reaction have been carried out.[2]

In our previous study[3] the thermodynamic functions for the addition of pyridine ligands to iron(II) porphyrins were determined as ligand and porphyrin were varied. The free energies of reaction varied over a wide range (−1.8 to −9.0 kcal mol^{-1}) and the changes in enthalpy and entropy of reaction were unexpectedly large. It is apparent that the iron(II) porphyrin–pyridine system is very sensitive to substitutions in the porphyrin and the ligand and that the study of enthalpy and entropy changes as well as free energy changes is essential to any understanding of these substituent effects.

It is well known that the ligand-addition reactions of the protein-bound iron porphyrins are greatly influenced by the heme environment. Only in this way can the great changes in reactivity of the different protohemin–protein complexes, *e.g.*, catalase, cyto-

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(2) (a) J. R. Miller and G. D. Dorough, *J. Amer. Chem. Soc.*, **74**, 3977 (1952); (b) J. E. Falk in "Porphyrins and Metalloporphyrins," Elsevier, New York, N. Y., 1964, p 45.

(3) S. J. Cole, G. C. Curthoys, and E. A. Magnusson, *J. Amer. Chem. Soc.*, **92**, 2991 (1970).

chromes, peroxidase, hemoglobin, and myoglobin, be explained.

X-Ray diffraction studies of some of these molecules[4] have shown that the environment of the heme is, in many respects, not too different from that experienced by heme in nonpolar solvents. It has been suggested that differences in the biological activity of heme–protein complexes are largely dependent on the interaction of the heme with the aliphatic groups and aromatic and heterocyclic rings in which it is bathed. The X-ray diffraction studies have shown that some of these amino acid side chains hinder the free approach of ligands to the binding sites, but solvent effects other than steric hindrance are also likely.

Previous studies[2] have shown that the thermodynamic functions for the complex formation reaction show some variation as the solvent is changed. It is of real interest to determine the magnitude of these effects in a system as sensitive to change as the iron(II) porphyrin–pyridine combination has proved to be.

Furthermore, significant solvent effects on the calorimetric results for the addition of pyridines to metal β-diketonate complexes have recently been noted.[5]

In view of this the previous studies on the iron(II) porphyrin–pyridine series[3] have been repeated using carbon tetrachloride and chloroform as solvent in addition to the benzene used previously. Obviously, these three solvents—chosen for the practical reason that the iron(II) porphyrin esters are soluble in them and not too many others—provide very poor simulation of the environment of the biologically important hemoproteins, but they do at least enable us to investigate the sensitivity of the system to solvent change and the magnitude of effects which are possible. As this paper will show, the variety and the magnitude of the solvent effects found make the study of change of environment of the molecules participating in the ligand-binding reaction most important in both the chemical and biochemical applications of this type of reaction.[6]

Experimental Section

The preparation and purification of the iron (III) porphyrin ester chlorides and the ligands have been described previously.[3]

Iron(III) *meso*-tetraphenylporphine was prepared by insertion of iron into *meso*-tetraphenylporphine by the method of Lemberg and Morell.[7]

Chloroform was purified immediately before use by washing with water three times, drying over $CaCl_2$, and collecting the fraction boiling between 62.5 and 63.5°.[8]

The moisture content of solvents was determined by Karl Fischer titration using the dead-stop end point.

The techniques of determination of equilibrium quotients over a range of temperatures and the methods used to reduce Fe(III) have been described previously.[3]

Calorimetric measurements were made in a calorimeter of approximately 500 ml capacity similar to that described by Skinner.[9] Samples were brought to the temperature of the calorimeter by being held in a vessel immersed in the solvent until thermal equilibrium had been reached. When mixing was required solvent and material were brought into contact by removal of a glass stopper. The calorimeter was stirred at a constant rate with a heat-insulated stirrer, and temperature measurements were made with a Beckmann thermometer. The calorimeter was capable of detecting a heat change of 0.2 cal; at the concentrations used here this corresponds to approximately 0.04 kcal mol^{-1}.

Results

The effectiveness of the drying procedures recommended by Weissberger[10] for carbon tetrachloride and benzene was evaluated by measurement of residual moisture content. For benzene and carbon tetrachloride the most effective of the methods of water removal was drying of successive portions by Linde Molecular Sieve 4A. In this way the moisture content of both benzene and carbon tetrachloride was reduced to 0.001%. Analysis of analytical reagent grade benzene and carbon tetrachloride showed moisture contents of 0.0012 and 0.0014%, respectively. In view of this, AR grade solvent was used without further purification in both cases.

Interference with the normal addition of ligands to iron(II) porphyrins is possible from the formation of oxo-bridged iron(III) porphyrin dimers due to autoxidation of the iron(II) species. The presence of excess reducing agent (see ref 2) during the experiments precludes this. Mauzerall[11] has found spectral differences due to small changes in solvation of iron porphyrins. We have studied the possibility that traces of water might interfere by recording the spectra of the iron(II) porphyrins in the presence of added water up to the saturation points of the solvents. Differential spectroscopy was used to increase the sensitivity of the technique. No significant changes in the spectra were recorded with any solvent.

Free Energies, Enthalpies, and Entropies of Ligand Addition. Equilibrium quotients determined for reactions of the form

$$\text{Fe(II) porphyrin ester(solv)} + 2\text{ligand(solv)} = \text{Fe(II) porphyrin ester(ligand)}_2\text{(solv)}$$

between protoporphyriniron(II) and deuteroporphyriniron(II) with 4-methylpyridine, pyridine, and 4-cyanopyridine in carbon tetrachloride, chloroform, and benzene appear in Table I as free energies of reaction calculated from the relation $\Delta G = -RT \ln Q$. The dependence of these ΔG values on temperature was used to compute the ΔH and ΔS values shown in the same table. The precision of the values quoted is not high; the uncertainties (standard errors) quoted in Table I were calculated during the variance analysis of the data.

As in the previous paper[3] a deliberate choice was made to survey a wide variety of iron(II) porphyrin–ligand–solvent systems rather than to attempt to obtain highly accurate results on a very few combinations. The unexpectedly large differences in enthalpies and

(4) H. Muirhead, J. M. Cox, L. Mazzarella, and M. F. Perutz, *J. Mol. Biol.*, **28**, 117 (1967).
(5) W. Partenheimer, and R. S. Drago, *Inorg. Chem.*, **9**, 47 (1970).
(6) Nonideal behavior with the same solvents and consequent solvent effects on enthalpies of reaction have been reported for other reactions also; see W. Partenheimer, T. D. Epley, and R. S. Drago, *J. Amer. Chem. Soc.*, **90**, 3886 (1968).
(7) R. Lemberg, B. Bloomfield, S. Caizer, and W. Lockwood, *Aust. J. Exp. Biol.*, **33**, 435 (1955); D. B. Morell, J. Barrett, and P. S. Clezy, *Biochem. J.*, **78**, 793 (1961); D. B. Morell and M. Stewart, *Aust. J. Exp. Biol.*, **34**, 211 (1956).
(8) J. E. Falk in ref 2b, p 120.
(9) H. A. Skinner, *Exp. Thermochem.*, 2, 188 (1962).
(10) A. Weissberger, *Tech. Org. Chem.*, 7, 317, 413 (1955).
(11) D. Mauzerall, *Biochemistry*, 4, 1801 (1965).

Table I. The Effect of Solvent Change on Thermodynamic Functions for the Addition of Pyridine Ligands to Iron(II) Porphyrins

Heme	Ligand	Solvent	$\Delta G(298)$, kcal mol^{-1}	$\Delta H(298)$, kcal mol^{-1}	$\Delta S(298)$, cal deg^{-1} mol^{-1}
Iron(II) protoporphyrin dimethyl ester	4-Methylpyridine	CCl_4	-3.8 ± 0.8	-24.6 ± 2.6	-70 ± 11
		$CHCl_3$	-1.5 ± 0.8	-12.2 ± 1.0	-36 ± 6
		Benzene	-9.0 ± 0.6	-14.0 ± 1.0	-16 ± 5
	Pyridine	CCl_4	-0.6 ± 0.8	-16.0 ± 1.0	-50 ± 6
		$CHCl_3$	-0.3 ± 0.8	-10.8 ± 1.5	-35 ± 7
		Benzene	-1.8 ± 0.6	-3.3 ± 0.6	-5 ± 4
	4-Cyanopyridine	CCl_4	-4.7 ± 0.8	-25.6 ± 3.0	-70 ± 13
		$CHCl_3$	-3.7 ± 0.8	-19.3 ± 3.6	-52 ± 13
		Benzene	-4.1 ± 0.6	-9.0 ± 1.0	-16 ± 5
Iron(II) deuteroporphyrin dimethyl ester	4-Methylpyridine	CCl_4	-3.8 ± 0.8	-7.5 ± 1.9	-12 ± 8
		Benzene	-3.3 ± 0.6	$+0.8 \pm 0.6$	$+13 \pm 4$
	Pyridine	CCl_4	-3.6 ± 0.8	-14.2 ± 1.8	-35 ± 7
		Benzene	-2.4 ± 0.6	-3.5 ± 0.6	-4 ± 3
	4-Cyanopyridine	CCl_4	-4.2 ± 0.8	-17.4 ± 2.3	-44 ± 9
		$CHCl_3$	-2.1 ± 0.8	-12.0 ± 0.4	-33 ± 4
		Benzene	-4.8 ± 0.6	-6.9 ± 1.0	-7 ± 5

entropies of reaction between the systems chosen justifies this approach. In any case, determinations of high precision are not feasible for this type of system, a point discussed at length in ref 3. Because of the level of uncertainty in the measurements and because of lack of information about activity coefficients, which in any case are expected to be close to unity at the low concentrations used in nonpolar solvents, results were not extrapolated to infinite dilution. Errors from this source will not be significant in relation to other sources of error as indicated by the uncertainties in the tables. It happens that the differences between different systems are so much greater than the typical errors that this removes the usual hazards of comparing thermodynamic data when no reference can be made to standard states.

It was not possible to obtain data for the binding of 4-methylpyridine or pyridine by iron(II) deuteroporphyrin in chloroform solution since in this solvent all the available reducing agents attacked the porphyrin nucleus too rapidly to allow the spectra of the iron(II) porphyrin complexes to be recorded. The products of the attack were not studied in detail, but the appearance of a strong band at approximately 650 mμ and the overall final green color indicate the possibility of chlorin formation in some cases.[12] With other reducing agents the loss of the sharp absorption bands in the visible and the appearance of a steadily decreasing broad band from the ultraviolet to the visible suggest that attack at one or more bridge positions may have occurred, interrupting the conjugation of the system.[13]

It is immediately apparent that we must go to the enthalpy and entropy data for any significant trends in the solvent effects. Free energy changes are, as before, an unreliable index of what is actually happening. The free energy and the enthalpy often change in different directions when the solvent is changed, and furthermore, the magnitudes of the changes are unrelated.

The plot of ΔH against ΔS values for the various systems studied here displays good linearity and the slope of the curve corresponds to an isoequilibrium temperature of approximately 340°K. A strikingly similar isoequilibrium line was obtained in our previous study with a wider range of hemes and ligands but without solvent variation.

This linear relationship (correlation coefficient $r = 0.96$) between ΔH and ΔS as solvent, heme, and pyridine are changed, and the opposing effects of these contributions, is the reason that free energy changes are so insensitive to changes in combinations of reactants. The isoequilibrium temperature (the temperature at which ΔG would be constant if ΔH and ΔS were perfectly linearly related) is only 30–40°K from the temperature at which these equilibria were studied.

We now turn to the actual enthalpy changes encountered with the different solvents (Table I). They are large in comparison to the free energy changes and adhere to the order $CCl_4 > CHCl_3 >$ benzene. For iron(II) protoporphyrin dimethyl ester the average ΔH values over all ligands for the three solvents are -22.1, -14.1, and -8.8 kcal mol^{-1}, respectively. A significant difference also occurs among the average ΔH's for the three ligands studied. This is not surprising in view of the results previously reported.[3] It is most significant, however, that in all solvents the trend in ΔH as the ligand is varied is the same as that observed previously in benzene for both hemes.

The entropy changes observed were almost always unfavorable (*i.e.*, negative) to the addition of the pyridine ligands. Only two favorable entropy changes—both for iron(II) deuteroporphyrin—were observed. With change in solvent the magnitude of ΔS follows the order $CCl_4 > CHCl_3 >$ benzene; it is in CCl_4 as solvent that the entropy change associated with ligand addition to the iron(II) porphyrin is most unfavorable. For the solvent change from CCl_4 to benzene the average difference in ΔS (over all ligands) is approximately -33 cal deg^{-1} mol^{-1} for iron(II) protoporphyrin dimethyl ester.

(12) J. E. Falk in ref 2b, p 74.

(13) Hydrogenation of metalloporphyrins (up to the hexahydro derivative) alters the pattern but does not remove the absorption bands in the visible region. Reduction at the bridge positions blocks conjugation. However, conjugation may be weakly transmitted by means of the coordinated metal atom—hence the extension of a broad absorption band into the visible spectrum. See G. R. Seely and M. Calvin, *J. Chem. Phys.*, 23, 1068, (1955); J. E. Falk, ref 2b, p 11; K. M. Baker and R. G. Wilson, *J. Chem. Soc. B*, 236 (1970).

Table II. Contribution Excesses to Be Added to the Grand Mean Entropy and Enthalpy Change for Iron(II) Porphyrin Esters, Ligands, and Solvents

Class	Name	Contribution to entropy, cal deg^{-1} mol^{-1}	Contribution to enthalpy, kcal mol^{-1}
Iron(II) porphyrin	Iron(II) mesoporphyrin dimethyl ester	−12	−3.0
	Iron(II) deuteroporphyrin dimethyl ester	+3	+1.0
	Iron(II) protoporphyrin dimethyl ester	−12	−4.5
	Iron(II) 2,4-diacetyldeuteroporphyrin dimethyl ester	+21	+7.5
Ligand	4-Methylpyridine	−1	−0.9
	4-Vinylpyridine	−3	−1.3
	Pyridine	+7	+3.5
	4-Carboxybutylpyridine	+1	−0.3
	4-Cyanopyridine	−4	−0.6
Solvent	Carbon tetrachloride	−25	−8.2
	Chloroform	−3	+3.0
	Benzene	+26	+5.1
Grand mean		−34	−11.0

The entropy change for the three ligands does not follow the same order for the two hemes. For iron(II) protoporphyrin pyridine shows the most favorable entropy change whereas for iron(II) deuteroporphyrin the most favorable entropy change is shown by 4-methylpyridine. Similar behavior, but in the other direction, was noted for the ΔH changes with these ligands.

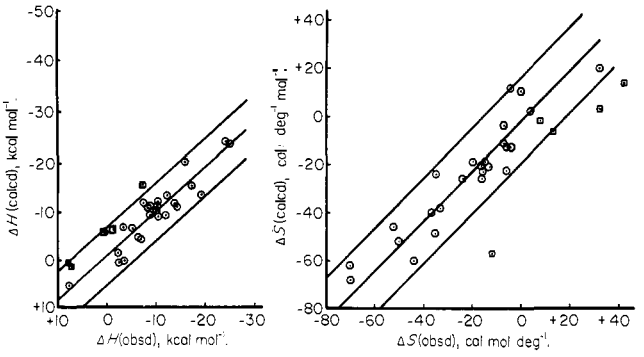

Figure 1. Correlation of thermodynamic data for addition of pyridine ligands to Fe(II) porphyrin esters with data predicted by the linear model proposed in the text: left, enthalpy data; right, entropy data. The central line on each diagram is the line of best fit (least-squares method) and is spanned by lines representing the 95% confidence limits; *i.e.*, all points inside the two outer lines are within two standard deviations of the value predicted by the regression. Points shown by □ are those for which we have previously suggested an abnormal relationship between σ and π components of the binding.[3]

A Linear Model. We have applied statistical tests to see how well these data conform to a linear model in which the enthalpies and entropies of ligand addition are subdivided into independent contributions from the solvents, porphyrins, and ligands used. Apart from the simplification of being able to confine discussion to the few parameters obtained by factorial analysis of the large number of data presented,[14] there is the advantage of greater reliability of the values assigned to each effect. The model chosen was of the form

$$X(i, j, k) = \bar{X} + H_i + L_j + S_k + \epsilon_{ijk}$$

where $X(i, j, k)$ is the thermodynamic function being considered, $\bar{X}$ is a constant for all sets of data, H_i is a contribution from the ith iron(II) porphyrin dimethyl ester, L_j is a contribution from the jth ligand, S_k is a contribution from the kth solvent, and, ϵ_{ijk} is a random error term.

If the data are well described by such a model, the error term should arise solely from the random experimental errors of individual measurements and be normally distributed with about the same average error as the measurements themselves. This expectation seems to be met, as may be seen from Table I and Figure 1, where previously reported data are included with those reported in this paper. In the following discussion, we will refer to the contribution data derived from the model rather than the more extensive experimental data of Table I.

The values to be assigned to the various iron porphyrins, ligands, and solvent are termed contribution excesses. The numerical values of these, and of the constant $\bar{X}$, were estimated by statistical methods.[15] Their values are shown in Table II.

The success of the linear model in representing both entropy and enthalpy data is shown in Figure 1, where predicted values from the model are plotted against the values obtained by experiment.

There are only two discrepant sets of data. These are shown with different symbols in Figure 1; they refer to the same two systems for which anomalous behavior was noted previously,[3] namely the deuteroporphyrin–4-methylpyridine and –4-vinylpyridine combinations and the 2,4-diacetyl deuteroporphyrin–4-cyanopyridine and –4-carboxybutylpyridine combinations.

(14) R. A. Fisher in "The Design of Experiments," 5th ed, Oliver and Boyd, London, 1949, p 99; E. L. Bauer in "A Statistical Manual for Chemists," Academic Press, New York, N. Y., 1960, p 26.

(15) R. A. Fisher in "The Design of Experiments," 5th ed, Oliver and Boyd, London, 1949, p 93; G. V. Yule and M. G. Kendall in "An Introduction to the Theory of Statistics," 14th ed, Charles Griffin, London, 1968, p 510.

Discussion

The conclusions to be drawn here about the effects of porphyrin and ligand substituents on the thermodynamic functions are the same as those of our previous paper.[3] Discussion here is confined to the importance of and possible reasons for the very large solvent effects which have been found.

The main task is to account for the magnitude of the entropy and enthalpy changes. Substitution of chloroform and benzene for carbon tetrachloride as solvent affects ΔS by up to 50 cal deg^{-1} mol^{-1} and ΔH by as much as 17 kcal mol^{-1}. For the same three solvents, the entropy and enthalpy changes accompanying pyridine addition to a copper bisdiketonate vary over only 2.5 cal deg^{-1} mol^{-1} and 1.6 kcal mol^{-1}, respectively.[16]

It is apparent that unusually strong solvent–solute interactions are occurring. For a number of reasons, we attribute the solvent effects to solvation–desolvation of metalloporphyrin rather than ligand.[17]

Enthalpy Changes. There are two reasons for rejecting solvation–desolvation of the pyridine ligand as the major factor in the differences in the enthalpies of complex formation in the three solvents.

(i) The results in Table III and literature values which are available[18] show the ligands to have greater (more negative) solvation enthalpies in chloroform than in benzene; these results would have to be inverted to explain the observed enthalpies of reaction of the heme series.

Table III. Heats of Solution (kcal mol^{-1}) of Substituted Pyridines in Solvents[a]

Solvent	Base		
	4-Cyano-pyridine	Pyridine	4-Methyl-pyridine
Benzene	+4.6 ± 0.3[b]	+0.1 ± 0.3	0.0 ± 0.3
$CHCl_3$	+2.5 ± 0.3	−1.5 ± 0.3	−2.0 ± 0.3
CCl_4	+5.0 ± 0.3	+0.2 ± 0.3	0.0 ± 0.3

[a] Pyridine solution between 10^{-3} and 10^{-2} *M*. See comment on sign convention in Experimental Section. [b] Average standard error of estimate for all measurements.

(ii) The solvation energies are too small. Independent evidence that the strength of binding increases in the order CCl_4, $CHCl_3$, C_6H_6 suggests an explanation of these solvent effects in terms of binding of solvent molecules by the ligand-free heme and their removal following interference by the ligand.

Since magnitudes and not only trends in the experimental data require explanation, we now consider a number of possible solute–solvent interactions that have been proposed in situations of this kind:[19] (a) π complexes, (b) charge-transfer complexes, (c) hydrophobic interactions, (d) dipole orientation forces, (e) dispersion forces, and (f) H bonding.

The solvent system is complex in that the reducing agent was always present in small excess and is capable of interacting with the other species present. In view of this it is not possible to rule out completely any of the above-mentioned types of interaction; types a–d are, however, quantitatively much less important than the others.

Each of these effects will depend on the solvent and for this reason the solvents will be discussed in turn.

1. Chloroform. Of the possibilities listed above, hydrogen bonding would seem to be the most important. H bonding is a strong possibility between nitrogen heterocycles and chloroform. If chloroform is to be attached to iron(II) porphyrins by this method, it is clearly necessary that no ligand be attached to the iron atoms because of its proximity to the H acceptors, the pyrrole nitrogens.

Interaction between the chloroform proton and the porphyrin π system, as distinct from the pyrrole nitrogen atoms, is also a possibility but, on the basis of published values of the energy of such interactions, it cannot be very important.[20]

2. Benzene. The mechanism of attachment of benzene must be different from that for chloroform. It is known that dispersion forces may operate between aromatic planes to produce a significant degree of "vertical stacking" of heterocyclic compounds in nonpolar solvents.[21] Murrell and Gil's value of ΔH = 1.2 ± 0.4 kcal mol^{-1} for the association of pyrimidine and toluene may be a guide to the ΔH expected in the metalloporphyrin–C_6H_6 system. However, it seems that the surface of the metalloporphyrin would need to be fully occupied by attached benzene molecules if the fairly small energies involved in the interaction of pyrimidine and toluene are typical.

The chief means of investigation is use of the solvent-dependent and concentration-dependent shifts in nmr spectra of solutions, and we must await the application of this technique to these compounds before making any definite proposals about the origins of the large changes observed here.

Rather larger energies are implied by recent studies of intermolecular potentials in aromatic crystals.[22] Craig and coworkers find the dispersion-force contribution to the lattice energy of benzene to be about 6 kcal mol^{-1} in the neighborhood of 0°.

Another comment on the solvation by benzene of large molecules containing aromatic rings is provided by the fact that it is not unusual to find benzene molecules of crystallization in the crystal.[23]

3. Carbon Tetrachloride. Carbon tetrachloride solvent interactions are expected to be small. That they

(16) B. L. Libutti, B. B. Wayland, and A. F. Garito, *Inorg. Chem.*, **8**, 1510 (1969).

(17) Aggregation of metalloporphyrins and of ligands is not considered to be important at the concentrations studied. (See ref 3, Discussion.)

(18) T. J. V. Findlay and R. S. Kenyon, *Aust. J. Chem.*, **22**, 865 (1969).

(19) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *J. Amer. Chem. Soc.*, **91**, 3817 (1969).

(20) T. Schaffer and W. G. Schneider, *J. Chem. Phys.*, **32**, 1218 (1960); A. A. Bothner-By and R. E. Glick, *ibid.*, **26**, 1651 (1957); L. W. Reeves and W. G. Schneider, *Can. J. Chem.*, **35**, 251 (1957).

(21) J. N. Murrell and V. M. S. Gil, *Trans. Faraday Soc.*, **61**, 402 (1965).

(22) D. P. Craig, P. A. Dobosh, R. Mason, and D. P. Santry, *Discuss. Faraday Soc.*, **No. 40**, 110 (1965).

(23) N. C. Payne and J. A. Ibers, *Inorg. Chem.*, **8**, 2714 (1969). It is interesting that a recent crystal structure determination shows a metal-phthalocyanine complex to possess pyridine molecules of crystallization: L. H. Vogt, Jr., A. Zalkin, and D. H. Templeton, *ibid.*, **6**, 1725 (1967).

may not be zero, however, is evidenced by Morcom and Travers'[24] measurements of the heats of solution of quinoline and various pyridines in this solvent. The values are small and negative, ranging as low as −0.6 kcal mol^{-1} for 3,5-dimethylpyridine,

Entropy Changes. Entropy changes, ranging from about −70 cal deg^{-1} mol^{-1} to approximately +40 cal deg^{-1} mol^{-1}, must be accounted for in any explanation of the effects of these solvents on ligand binding by the iron porphyrin system.

In the reaction

$$\text{Fe(II) porphyrin ester(solv)} + 2\text{ligand(solv)} \longrightarrow \text{Fe(II) porphyrin(lig)}_2\text{(solv)}$$

the overall entropy change will be made up as follows: (i) a negative entropy contribution due to the loss of translational and rotational entropy by two ligand molecules; (ii) a slight increase in entropy due to the increase in molecular weight of the complex over the ligand-free porphyrin; (iii) an entropy decrease due to restriction of rotation about the metal–nitrogen bond by π bonding; (iv) an increase in entropy as solvent molecules bound to the ligand are released; and (v) a negative (or positive) contribution to the entropy of reaction as the complex is more (or less) solvated than the free iron porphyrin.

Approximate values for the contributions from some of these sources may be obtained from the work of Cobble[25] and from the assumption that the available rotations will each contribute the theoretical amount to the energy of the system at room temperature. Using these figures, the entropy change for the addition of two ligands, to the iron porphyrin, apart from that due to solvation effects on the iron porphyrins and the ligands, would be about −50 cal deg^{-1} mol^{-1} for loss of translational entropy and about −20 cal deg^{-1} mol^{-1} for the loss of rotational freedom. The contributions from (ii) and (iii) above would be small (in the order of 3 or 4 cal deg^{-1} mol^{-1}) and would oppose each other; the contribution from the release of solvent from the ligand would also be fairly small. The large contribution due to release of solvent from the iron porphyrin when the complex is formed would be positive, the magnitude depending on the degree of solvent interaction with the iron porphyrin, and this would tend to offset the unfavorable entropy change due to the binding of ligands. If solvent interactions in carbon tetrachloride solution are very small, as the more negative enthalpy changes in that solvent lead us to postulate, we may expect an unfavorable entropy change of about −70 cal deg^{-1} mol^{-1} to accompany the attachment of the ligands, as observed. The less negative entropy changes found for $CHCl_3$ and C_6H_6 are then to be associated with a greater degree of solvent–porphyrin interaction, as already suggested.

Depending on the strength of solvent binding to metalloporphyrin molecules, some two to four molecules of solvent per iron(II) porphyrin molecule need to be invoked in the solvation–desolvation mechanism to explain our observations.

The smaller variations in entropy changes for the reaction as the substituent on the iron porphyrin is changed may have their origin in a solvation effect. Quite small variations in the net change in solvation as the ligand is attached to the iron porphyrin are sufficient to explain the fairly small differences in Table II between differently substituted iron porphyrins.

Conclusion

The thermodynamic functions have been measured as the iron(II) porphyrin, the ligand, and the solvent have been changed. The data are all consistent with a model in which solvation of the iron(II) porphyrin ester is accompanied by an enthalpy and an entropy change which are dependent mainly on the solvent and to a much lesser degree on the iron(II) porphyrin ester and the ligand. The changes produced by varying the solvent are large, covering, on the average, a range of over 50 cal deg^{-1} mol^{-1} for ΔS and as much as 17 kcal mol^{-1} for ΔH. In all cases the change in the heat of reaction is opposite in sense to that in the entropy of reaction, and since the corresponding isoequilibrium temperature is close to that at which the reactions were studied, it is not possible to obtain any linear free energy relation involving solvent, ligand, or porphyrin properties.

The effects of change in iron(II) porphyrin ester, ligand, and solvent are, in general, additive, and the changes in one are independent of the particular combination of the others used for the measurements. Important exceptions to the additivity occur in those systems previously characterized as having more than usually important metal–ligand π bonds or unusually strong σ bonds.

The effect of changes in the nature of the solvent or the surrounding medium is most important in determining the thermodynamic functions for this system and may prove to be significant in interpreting the information available for the biological heme systems. The reactions studied here may serve as a model for such systems.

The large porphyrin macrocycle seems to be capable of functioning as acceptor for H bonds from several $CHCl_3$ molecules simultaneously and of significant van der Waals interactions with several benzene or pyridine molecules.

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(25) J. W. Cobble, *J. Chem. Phys.*, **21**, 1451 (1953).