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Intermolecular Forces in Porphyrin Crystals

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Data on the intermolecular forces in crystals of 2,4-substituted porphyrin dimethyl esters (DME's) are reported. Calorimetric measurements show an anomalous behavior at the melting point for two compounds, and vibrational spectroscopy reveals differences in the N−H bonds. Distinctively high T_m values were found for DME's with formyl at position 2. The experimental data are combined with theoretical evaluations of intermolecular forces in the crystal lattice. These forces are related to the physical and physiological properties of free and protein-bound porphyrins and hemins.

1. Introduction

Previous work has shown strong correlations among various physical, chemical, and biological properties of free 2,4-substituted porphyrins and hemins and heme proteins reconstituted with akin artificial prosthetic groups.[1] The effect of 2,4-substitution on CO ligation was independent and thus additive to the influence of the protein,[2] and strong effects of these substituents were also observed on the methine bridges.[3] These correlations apply to all proteins but not to all properties since bulky or polar substituents may alter the coordination of the prosthetic group in the crevice. The latter situation was obvious for the separation of heme from the apoprotein.[4] The kinetics of this reaction was dominated by solvation effects measured as the ratio between protein/heme and water/heme interfacial areas, and large 2,4-substituents resulted in a more loosely bound prosthetic group.

The aim of the present work was to learn more about the intermolecular forces in crystalline porphyrin DME's and eventually to gain further insight into how external forces influence the properties of the prosthetic group in heme proteins. A previous measurement of the melting temperatures of 2,4-substituted porphyrin DME's showed strong correlations with the ferric/ferro reduction potential, the C=O vibrational frequency of the CO compound, and other properties of 2,4-substituted compounds but also anomalous phase-transition values for a few crystalline DME's.[5] It appeared that polar groups at position 2 further stabilized the crystals. Earlier attempts to explain the above predictable trends, as well as the anomalous exceptions, answered some but not all questions.[5] The present work extends previous estimates of the magnitude of van der Waals forces and intermolecular hydrogen bonds to include dipole−dipole interactions.[6,7]

2. Materials and Methods

2.1. Experimental Details. 2.1.1 IR Measurements. A 0.8 mg amount of each solid of 2,4-diformyl-, 2,4-divinyl-, 2-vinyl-4-formyl-, and 2-formyl-4-vinylporphyrin DME was thoroughly ground with 100 mg of dry, powdered KBr and pressed into disks (Figure 1). Care was taken to avoid light exposure. Infrared absorption spectra were measured at 0.5 cm^{-1} resolution with a Mattson Cygnus FTIR. Pure KBr was used as a reference.

2.1.2. Calorimetric Melting Point Measurements. The melting points of the above 2,4-substituted DME's were measured by differential scanning calorimetry (DSC) as described by Mark *et al.*[8] The scans were repeated on fresh samples in both dinitrogen and argon with identical results. The sample mass was 5−10 mg.

2.2. Computational Details. The summation of intermolecular electrostatic forces in a molecular crystal requires knowledge not only of charge distributions within each molecule but also of the effect of screening. The screened potential is often replaced by an effective unscreened potential between point charges located at each atom or, as in our study, by the interaction between dipoles positioned at the center of each molecule. As in our previous estimates of intermolecular forces, we look for trends and magnitudes rather than for absolute numbers.

By the modeling of the porphyrin molecule as a point dipole, the dipole−dipole interaction between porphyrin molecules can be calculated in the form

$$E = (^1/_2)\Sigma_l\Sigma_m\Sigma_n[\mathbf{m}_1\cdot\mathbf{m}_2/|\mathbf{r}_{lmn}|^3 - 3(\mathbf{m}_1\cdot\mathbf{r}_{lmn})(\mathbf{m}_2\cdot\mathbf{r}_{lmn})/|\mathbf{r}_{lmn}|^5]$$

where $\mathbf{m}_1$ and $\mathbf{m}_2$ are the electric dipole moments or porphyrin molecules and $\mathbf{r}_{lmn}$ is the vector joining the two dipoles.

The dipole−dipole interaction was calculated from point dipoles, positioned and oriented according to their crystallographic data[9,10] and embedded in a unit cell in the triclinic space, this unit cell being infinitely duplicated throughout space. Both the mutual interaction between the two dipoles in the central unit cell and their interactions with dipoles in repeated unit cells were considered, but the interactions of the dipoles with their self-replicas were excluded from the calculation.[11]

The electric dipole moments needed for the above summation were calculated for free molecules in the self-consisting complete neglect of differential overlap (CNDO) approximation.[12] The CNDO molecular orbital (MO) method is known to give satisfactory descriptions of charge distributions for large molecules such as 2,4-substituted porphyrins.[13]

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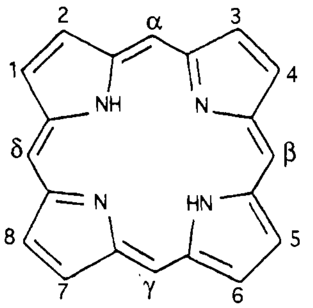

Figure 1. Structure of 2,4-substituted free-base porphyrins. α, β, γ, and δ are hydrogen atoms. Positions 6 and 7 are substituted with CH_2-CH_2COOCH_3. Positions 1, 3, 5, and 8 are substituted with CH_3. Positions 2 and 4 are substituted with $CHCH_2$ (vinyl) or COH (formyl).

Positions 1, 3, and 5–8 remain unchanged for the present set of data and are approximated by H atoms. 2,4-Substituents induce charge asymmetries that constitute the dominant part of the permanent dipole moment of porphyrins with more complex substituents at positions 1, 3, and 5–8.

3. Results and Discussion

3.1. Melting Point Data. The melting temperatures obtained from DSC measurements (Figure 2) agree with those previously obtained from optical inspections.[5] We again note the trend between the electron-withdrawing capacity of the 2,4-substituents and the melting point and again find anomalously high T_m values for porphyrins with a formyl group at position 2.[5] The latter is obvious when we compare T_m for 2-vinyl-4-formyl porphyrin with T_m for the 2-formyl-4-vinyl isomer.

The DSC measurements also show an anomalous release of energy at melting for two compounds (Figure 2). Normal melting requires that heat is added, the amount related to the increased entropy by T_m,[14] but in the above cases heat is released. We believe that this is related to decomposition at melting, and previous studies indicated an irreversible loss of mass corresponding to one methanol molecule per porphyrin unit.[15]

3.2. Intermolecular H Bond. The porphyrin chelate is regarded as an ampholyte with two pyrrolic nitrogen atoms capable of accepting protons and two NH groups capable of losing protons.[16] An intermolecular H-bond should break this similarity between the four nitrogen atoms and also stabilize the crystal lattice. Crystallographic data show remarkably similar structures for the different 2,4-substituted free-base porphyrins and also suggest the possibility of a hydrogen bond with the pyrrolic nitrogen as proton donor and a polar group at position 2 as acceptor.[5,6,17] This bond between adjacent molecules could easily explain the anomalously high melting points for 2,4-diformyl and 2-formyl-4-vinylporphyrin DME's. The vibrational frequency of the N–H bond should be a sensitive monitor of this H-bond, and Figure 3 presents IR spectra in the range 3250–3350 cm^{-1}. The N–H peak positions are given in Figure 3.

The red-shifted frequency for the diformyl N–H vibration could indicate an intermolecular perturbation, but this shift is matched by the wrong monoformyl isomer to be identified with position 2. Hence, we have no spectroscopic indications of a unique intermolecular hydrogen bond for any specific class of porphyrins.

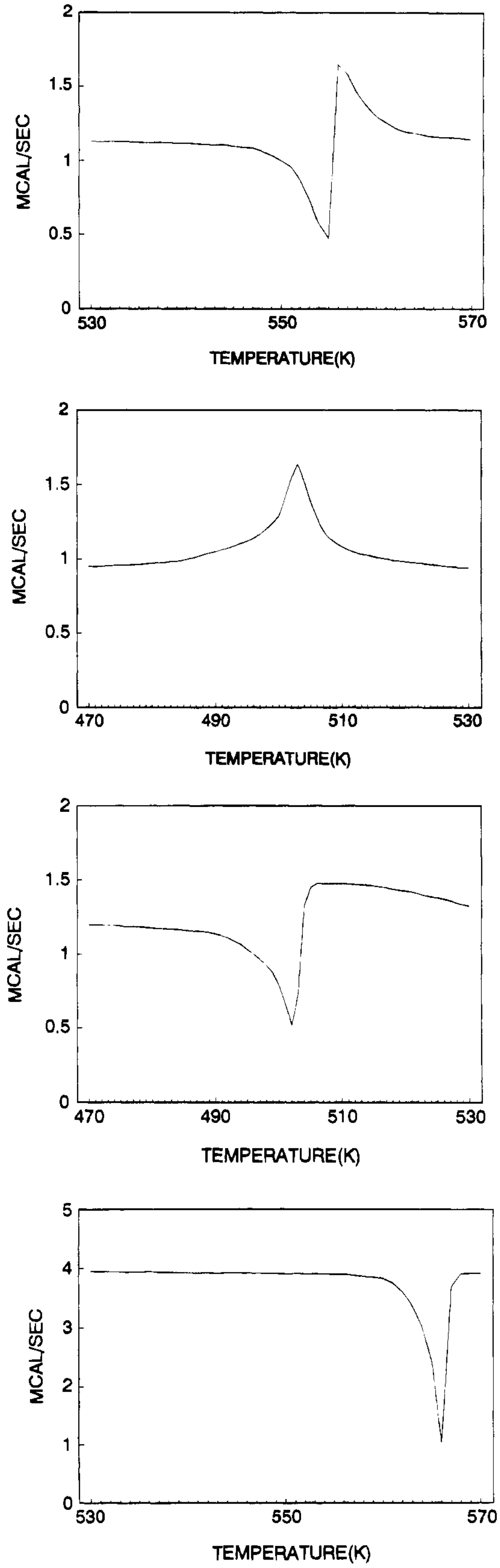

Figure 2. DSC scans of different 2,4-substituted free-base porphyrins: (a) 2-formyl-4-vinylporphyrin, T_m = 281.6 °C; (b) 2,4-divinylporphyrin, T_m = 229.8 °C; (c) 2-vinyl-4-formylporphyrin, T_m = 229.2 °C; (d) 2,4-diformylporphyrin, T_m = 292.8 °C. All measurements were done in nitrogen. A negative peak means an endothermic reaction, and a positive peak, an exothermic reaction.

3.3. Dipole–Dipole Interaction. Table 1 gives the addition dipole moments of porphyrin molecules induced by 2,4-substituents and the interaction energies between dipoles. The

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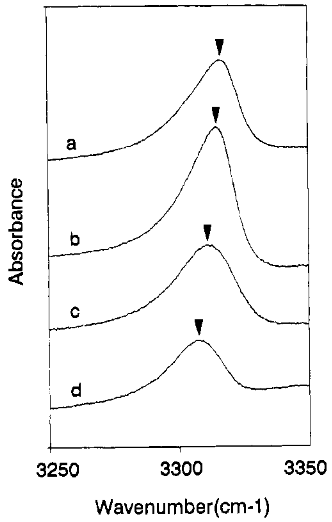

Figure 3. IR spectra of the N−H stretch frequency range of 2,4-substituted free-base porphyrins: (a) 2-formyl-4-vinylporphyin, 3317.1 cm^{-1}; (b) 2,4-divinylporphyrin, 3315.3 cm^{-1}; (c) 2-vinyl-4-formylporphyrin, 3311.6 cm^{-1}; (d) 2,4-diformylporphyrin, 3307.9 cm^{-1}.

Table 1. Dipole Moments of Porphyrin Molecules and Dipole−Dipole Interaction between Porphyrin Molecules

porphyrin	*m* (D)	*E* (kJ/mol)	porphyrin	*m* (D)	*E* (kJ/mol)
2-vinyl-4-formyl	4.1464	4.22	2-formyl-4-vinyl	4.7536	5.74
2,4-divinyl	4.1490	4.34	2,4-diformyl	6.2056	6.90

dipole−dipole interaction is affected by the magnitude of the dipole moments, the angle between the dipoles, and the angles between the dipoles and the vectors joining the dipoles. The dipole moment of a molecule, a vector which is a measure of the magnitude of charge displacement in the molecule, characterizes its electric configuration.

The introduction of substituting groups in the molecule is directly reflected in its dipole moment.[18] The structural arrangement of the substituents in a porphyrin molecule is connected with a redistribution of the electron density by induction and conjugation mechanisms. Our calculation indicates that the formyl group at position 2 results in a very high charge density redistribution for 2-formyl-4-vinyl- and 2,4-diformylporphyrins, contrasting a small redistribution for porphyrins with a vinyl group at position 2.

The difference between the two isomers 2-formyl-4-vinyl and 2-vinyl-4-formyl is linked to protonation. We model neutral porphyrins with two protons located on the four nitrogen atoms. This gives a C_{2v} symmetric electrons structure even for the unsubstituted deuteroporphyrin.[19] Supported by crystallographic data we also make the assumption that opposite nitrogen atoms are protonated.[16] Our calculations show that a formyl group induces a much stronger dipole moment in combination with a protonated nitrogen atom than a vinyl group does.

Table 1 also gives the changes of electrostatic energy caused by 2,4-substitutions. This interaction reflects the dipole strength and is much weaker for porphyrins with a vinyl group at position 2 than for porphyrins with a formyl group at the same position. This explains the anomalously high melting points and the difference between the two isomers. Following the above discussion, we must assume that the high melting points are linked to protonation of the α-pyrrole and also the 2-fold symmetry of the neutral metal-free porphyrin. The same anomalos difference between the two isomers should not be expected for 2,4-substituted hemin, which is more symmetric in the inner ring.[20]

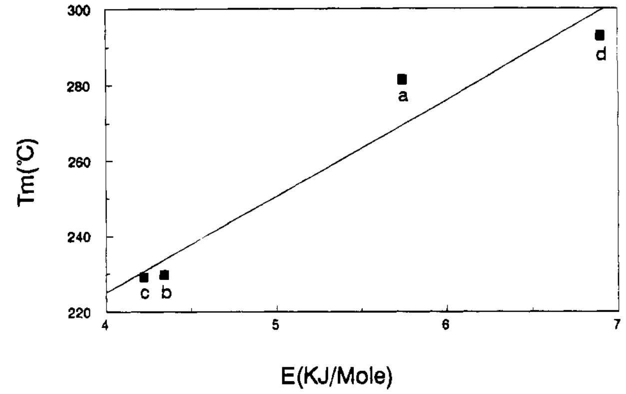

Figure 4. Experimentally observed changes of melting temperature vs changes calculated from dipole−dipole interactions in the crystal: (a) 2-formyl-4-vinylporphyrin; (b) 2,4-divinylporphyrin; (c) 2-vinyl-4-formylporphyin; (d) 2,4-diformylporphyrin.

Figure 4 compiles our results in a comparison between experimentally determined melting points and calculated changes from dipole−dipole interactions.

4. Conclusions

The present work shows that dipole−dipole interactions determine the melting points of 2,4-substituted porphyrin DME's. In particular we note the influence of electronegative groups to induce a larger dipole moment thereby strengthening intermolecular bonds. A difference in charge asymmetry is observed between 2-formyl-4-vinyl- and 2-vinyl-4-formyl porphyrins, and further work may reveal if this difference is present also for heme proteins recombined with artificial prosthetic groups.

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