the identity of the turnover-limiting step will depend upon the relative olefin and hydrogen concentrations. Neither of these rate constants is particularly large in comparison to other f-element catalysts. Thus, hydrogenolysis is turnover-limiting in the analogous mechanism for $(\mathrm{Cp'}_2\mathrm{LuH})_2$-catalyzed hydrogenation of 1-hexene, and $k_2 \approx 7.7 \times 10^3$ M^{-1} s^{-1} ($k_1 \gtrsim 10^2$–10^3 M^{-1} s^{-1}).[10d] Olefin addition is turnover-limiting for the corresponding hydrogenation of cyclohexene and $k_1 \approx 2.3 \times 10^{-2}$ M^{-1} s^{-1}.[10d] The present results show that k_1 is sterically very sensitive, and the simple transposition of $\mathrm{OCH}(t\text{-Bu})_2 \rightarrow \mathrm{O}\text{-}t\text{-Bu}$ affects a ca. 10^3 increase in k_1. Our earlier results[12] show that k_2 is sensitive to the electrophilicity at the metal center (which is depressed by OR introduction) and the Th–C bond enthalpy. As judged by variation in OR, k_2 is (not surprisingly) sterically rather insensitive. The greater hydrogenolytic reactivity of U–C bonds vis-à-vis Th–C bonds apparently reflects electronic factors that do not dominate An–H olefin insertion chemistry.

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The Nature of π–π Interactions

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Abstract: A simple model of the charge distribution in a π-system is used to explain the strong geometrical requirements for interactions between aromatic molecules. The key feature of the model is that it considers the σ-framework and the π-electrons separately and demonstrates that net favorable π–π interactions are actually the result of π–σ attractions that overcome π–π repulsions. The calculations correlate with observations made on porphyrin π–π interactions both in solution and in the crystalline state. By using an idealized π-atom, some general rules for predicting the geometry of favorable π–π interactions are derived. In particular a favorable offset or slipped geometry is predicted. These rules successfully predict the geometry of intermolecular interactions in the crystal structures of aromatic molecules and rationalize a range of host–guest phenomena. The theory demonstrates that the electron donor–acceptor (EDA) concept can be misleading: it is the properties of the atoms at the points of intermolecular contact rather than the overall molecular properties which are important.

Strong attractive interactions between π-systems have been known for over half a century. They control such diverse phenomena as the vertical base–base interactions which stabilize the double helical structure of DNA,[1] the intercalation of drugs into DNA,[1,2] the packing of aromatic molecules in crystals,[3] the tertiary structures of proteins,[4] the conformational preferences and binding properties of polyaromatic macrocycles,[5] complexation in many host–guest systems,[6] and porphyrin aggregation.[7] To date, no readily accessible or intuitive model has been suggested to explain the experimental observations. Full ab initio calculations have been carried out for a limited number of small systems[8] and these do reproduce the experimental results well, but they do not explain the basic mechanisms of π–π interactions in a way that is helpful or predictive for the practical chemist. We believe that the pictorial model presented here and the rules we derive from it have a general applicability. In essence, the model indicates that the geometries of π–π interactions are controlled by electrostatic interactions but that the major energetic contribution comes from other factors.

This work was stimulated by our experimental results on porphyrin–porphyrin interactions.[5a,b] The model not only reproduces these results remarkably well, it also throws light on the whole question of π–π interactions in general. We show that π–π interactions are not due to an attractive electronic interaction between the two π-systems but occur when the attractive interactions between π-electrons and the σ-framework outweigh unfavorable contributions such as π-electron repulsion. We explain the continuum of attractive geometries that extends from the edge-on relationship that is well-known in the crystal structures of simple aromatics[3] to a coplanar, offset geometry similar to that found in porphyrins.[5c] The model implies that the donor–acceptor concept can be misleading when used to describe π–π interactions: it is the properties of the atoms in the regions of intermolecular contact that control the strength and geometry of interactions, rather than the overall molecular oxidation or reduction potentials.

Experimental Observations on Porphyrin Aggregation

Strong attractive interactions between two porphyrins lead to aggregation in solution.[7] Both in solution and crystals the two porphyrins adopt a cofacial arrangement with their centers offset.[5c,9] This geometry may be summarized as follows: (1) The π-systems of two neighboring porphyrins are parallel, with an interplanar separation of 3.4–3.6 Å. (2) The π-stacked porphyrins

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(1) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984; pp 132–140.

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(3) Desiraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621–623, and references cited therein.

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(7) (a) Alexander, A. E. *J. Chem. Soc.* **1937**, 1813–1816. (b) Hughes, A. *Proc. R. Soc. London, Ser. A* **1936**, *155*, 710–711. (c) Abraham, R. J.; Eivazi, F.; Pearson, H.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1976**, 698–699. (d) Abraham, R. J.; Eivazi, F.; Pearson, H.; Smith, K. M. *J. Chem. Soc., Chem. Commun.* **1976**, 699–701.

(8) (a) Langlet, J.; Claverie, P.; Caron, F.; Boeuve, J. C. *Int. J. Quantum Chem.* **1981**, *19*, 299–338. (b) Price, S. L.; Stone, A. J. *J. Chem. Phys.* **1987**, *86*, 2859–2868, and references cited therein.

(9) Scheidt, W. R.; Lee, Y. J. *Structure Bonding 64*; Springer-Verlag: Berlin, Heidelberg, 1987.

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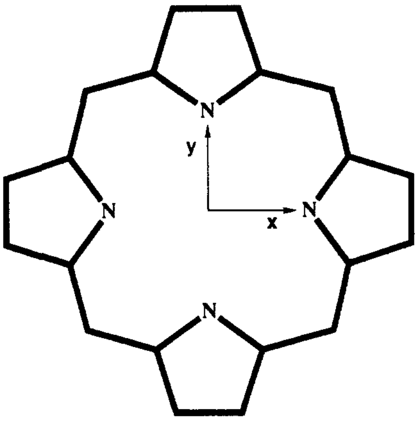

Figure 1. The coordinate system used for porphyrins.

are not rotated relative to one another, i.e., their nitrogen–nitrogen axes (x or y axes in Figure 1) are parallel. (3) One porphyrin is offset relative to the other by 3–4 Å along the nitrogen–nitrogen axis.

The magnitude of the π–π interaction is enhanced by porphyrin metalation, but its geometry is unaltered.[5c,7c,10] The greater the intramolecular polarization between the porphyrin and the metal, the stronger is the π–π interaction between two porphyrins,[7d] while coordination of the metal by a ligand reduces the magnitude of the π–π interaction in metalloporphyrins and generally leads to disaggregation.[5d,11]

π–π attractions of porphyrins are not restricted to self-aggregation, π-stacking being observed between porphyrins and a wide variety of covalently attached π-systems in organic solvents.[12] Metalation with zinc generally enhances the interaction,[13] while use of toluene as solvent can disrupt the interaction and open up folded or stacked conformations.[12c] Examples of π–π interactions have also been found in porphyrin crystal structures: metalloporphyrins can cocrystallize with aromatic solvent molecules,[9,14] the solvent molecules lying parallel to the porphyrin planes. The porphyrin metal atom is the site of the shortest intermolecular contact, and the solvent atom closest to the metal is always electron rich.[9]

Previous Models for π–π Interactions

The Solvophobic Model. π-Stacking has been attributed to solvophobic effects which are essentially entropic in origin.[15] However, the observations discussed above were made in organic solvents where entropic solvophobic effects are not important.[6a] Even in water, enthalpic effects can be the important driving force favoring π–π interactions.[16] In addition, solvophobic effects favor the geometry of maximum π-overlap, a situation which is rarely observed.

The Electron Donor–Acceptor (EDA) Model. It has been suggested that the strong attraction is due to an electronic interaction between an electron donor and an electron acceptor.[6] π–π* or charge-transfer complexes formed between good electron donors and good electron acceptors are of course well-known.[17] They are characterized either by charge-transfer transitions in the UV–visible absorption spectrum or by a broadened UV–visible spectrum.[17] However, in the systems which we discuss here, no such effects are observed;[6,18] even in cases where strong charge-transfer interactions between two molecules are observed spectroscopically, the charge-transfer interaction is only important in the excited state and contributes relatively little to the overall energetic stability of the complex.[17,19]

The Atomic Charge Model. It has also been suggested that the attraction arises from the uneven charge distribution across the π-systems.[20] For a particular orientation of two π-systems, positively charged atoms on one molecule may be aligned with negatively charged atoms on the other, so that there is an attractive electrostatic interaction. We have applied this atomic charge model to the interaction between two zinc porphyrins, by using the charge distribution derived from IEH calculations for zinc porphine.[21] Our calculations did predict an attractive interaction with a porphyrin–porphyrin geometry that was very close to that observed experimentally.[5c,9] However, there was no strong preference for one geometry over any other, and the magnitude of the interaction in the optimum geometry was less than 1 kJ mol^{-1}; our experimental estimate is 48 ± 10 kJ mol^{-1},[5a] so this model was rejected.

A Model for π–π Interactions

We now present a simple electrostatic model which accounts for many of the experimental observations above. In general, the energy of interaction between two molecules can be represented as[22]

$$E_{\text{total}} = E_{\text{electrostatic}} + E_{\text{induction}} + E_{\text{dispersion}} + E_{\text{repulsion}} \qquad (1)$$

Ab initio and semiempirical calculation of the magnitudes of these terms is a well-established procedure.[8,22] Such calculations have proven to be successful in accounting for experimental observations,[8,22] but for large molecules such as porphyrins they are nontrivial and provide little intuitive insight into the mechanism of attraction. Our approach ignores many factors such as short-range effects and induction, but it has a sound theoretical basis and, we believe, provides a powerful insight into the origins

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(10) Magnesium(II) porphyrins differ from other metalloporphyrins: the enhanced interaction and specific geometry generally result from intermolecular coordination of an oxygen atom in the side chains of one porphyrin with the metal center of the other.[7c] However, for most other metalloporphyrins there is no metal–side-chain interaction and some other effect must be responsible for the enhanced aggregation.[7c,d]

(11) Disaggregation of metalloporphyrins by ligand coordination is influenced both by steric and electronic effects.[5d] We interpret the electronic effect observed in ref 5d as an enthalpic reduction in the π–π interaction energy, while the steric effect is due to the entropy associated with disaggregation.

(12) (a) Bentley, M. D.; Dewar, M. J. S. *Tetrahedron Lett.* **1967**, 5043–5047. (b) Sanders, G. M.; van Dijk, M.; van Veldhuizen, A.; van der Plas, H. C. *J. Chem. Soc., Chem. Commun.* **1986**, 1311–1313. (c) Sanders, G. M.; van Dijk, M.; van Veldhuizen, A.; van der Plas, H. C.; Hofstra, U.; Schaafsma, T. J. *J. Org. Chem.* **1988**, *53*, 5272–5281. (d) Gust, D.; Moore, T. A.; Liddell, P. A.; Nemeth, G. A.; Makings, L. R.; Moore, A. L.; Barrett, D.; Pessiki, P. J.; Benasson, R. V.; Rougee, M.; Chachaty, C.; De Schryver, F. C.; Van der Auweraer, M.; Holzwarth, A. R.; Connolly, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 846–856. (e) Harrison, R. J.; Pearce, B.; Beddard, G. S.; Cowan, J. A.; Sanders, J. K. M. *Chem. Phys.* **1987**, *116*, 429–448, and references therein. In contrast, we have found that helicene, benzyl, and benzoate groups covalently attached to porphyrins by flexible chains do not π-stack but prefer open conformations (C.A.H. and J.K.M.S., unpublished) as do some quinone porphyrin adducts.[12d]

(13) The interactions with quinones, anthraquinones, and pyromellitimides are enhanced due to coordination of the metal by a carbonyl oxygen.[12]

(14) (a) Scheidt, W. R.; Kastner, M. E.; Hatano, K. *Inorg. Chem.* **1978**, *17*, 706–710. (b) Scheidt, W. R.; Reed, C. A. *Ibid.* **1978**, *17*, 710–714. (c) Kirner, J. F.; Reed, C. A.; Scheidt, W. R. *J. Am. Chem. Soc.* **1977**, *99*, 1093–1101. (d) Reed, C. A.; Mashiko, T.; Bentley, S. P.; Kastner, M. E.; Scheidt, W. R.; Spartalian, K.; Lang, G. *J. Am. Chem. Soc.* **1979**, *101*, 2948–4958. (e) Shelly, K.; Bartzcak, T.; Scheidt, W. R.; Reed, C. A. *Inorg. Chem.* **1985**, *24*, 4325–4330.

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(16) Smithrud, D. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 339–343.

(17) (a) Strong, R. L. *Intermolecular Forces*; Pullman, B., Ed.; D. Reidel: Dordrecht, 1981; pp 217–232. (b) Morokuma, K. *Acc. Chem. Res.* **1977**, *10*, 294–300.

(18) The UV–visible absorption spectra of cofacial porphyrin dimers in which there are strong π–π interactions can be explained in terms of the absorption properties of the corresponding monomeric porphyrins and the exciton interactions between the two porphyrin moieties (Hunter, C. A.; Sanders, J. K. M.; Stone, A. J. *Chem. Phys.* **1989**, *133*, 395–404). In an aromatic-bridged porphyrin dimer where the folded conformation is controlled by π–π interactions, the UV–visible absorption spectrum is simply the sum of the spectra of the different aromatic components.[5b]

(19) Claverie, P. *Intermolecular Interactions: From Diatomics to Biopolymers*; Pullman, B., Ed.; Wiley: Chichester, 1978; pp 69–306.

(20) Muehldorf, A. V.; Van Engen, D.; Warner, J. C.; Hamilton, A. D. *J. Am. Chem. Soc.* **1988**, *110*, 6561–6562.

(21) Zerner, M.; Gouterman, M. *Theor. Chim. Acta* **1966**, *4*, 44–63.

(22) (a) Rigby, M.; Smith, E. B.; Wakeham, W. A.; Maitland, G. C. *The Forces between Molecules*; Clarendon: Oxford, 1986. (b) Buckingham, A. D. *Intermolecular Interactions: From Diatomics to Biopolymers*; Pullman, B., Ed.; Wiley: Chichester, 1978; pp 1–68.

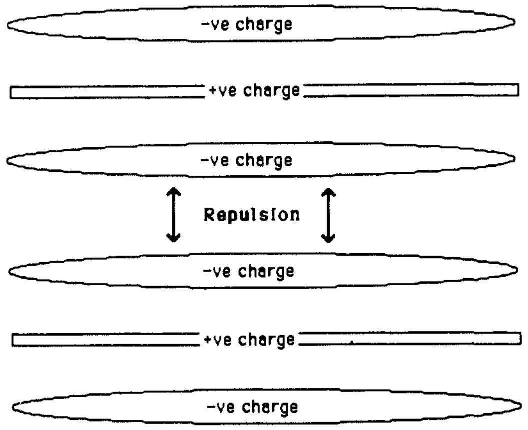

Figure 2. The interaction between two face-to-face π-systems.

of aromatic–aromatic interactions in terms accessible to the practical chemist.

The major contributions to the interaction energy come from the electrostatic and van der Waals components, induction generally being a second-order term.[8,22-24] The apparent energy of interaction between two molecules in solution includes association of the two molecules and displacement of solvent. In nonpolar organic solvents, the electrostatic interactions with the solvent will be negligible, and so the dominant electrostatic interaction will come from the association energy. However, both the association and desolvation energies are likely to be associated with significant van der Waals interactions.

The Contribution of van der Waals Interactions. For interplanar separations of interest (greater than 3.4 Å), this term is always attractive.[22,23] The van der Waals interaction between two molecules can be calculated by using the equation

$$E_{\text{van der Waals}} = \sum_{ij}\left\{A_{ij}\exp(-\alpha_{ij}r_{ij}) - \frac{C_{ij}}{r_{ij}^{6}}\right\} \qquad (2)$$

where r_{ij} is the distance between atom i in one molecule and atom j in the other, and the coefficients C_{ij}, A_{ij}, and α_{ij} are standard parameters.[22,23] This expression, which should be reasonably accurate for the crystal, shows that the van der Waals interaction between molecules of the type we are considering is roughly proportional to the area of π-overlap. In solution, we can say qualitatively that solvent lowers the contribution of the van der Waals interactions to the total π-stacking energy. More sophisticated approaches to estimating the magnitude of the van der Waals energy for desolvation are available[19,22] but not appropriate for our approach.

van der Waals interactions can make an appreciable contribution to the magnitude of the π–π interaction, but since they are proportional to the area of π-overlap, they cannot be the force which controls the experimentally observed geometry of interaction. If they were, then π-overlap would be maximized, and a cofacial arrangement with no offset would be observed. Therefore there must be a large electrostatic barrier to π-overlap which dominates the geometry of interaction. By estimating the electrostatic energy for the porphyrin–porphyrin interaction we should be able to predict the geometry of the π–π interaction; we would also have to estimate the van der Waals energies to obtain a quantitative value for the magnitude of the interaction.

The Electrostatic Interaction. π–π interactions rarely cause a distortion of the UV–visible spectra of the two chromophores, so the two interacting π-systems do not distort each others molecular orbitals.[6,18] Thus it should be possible to explain this phenomenon on the basis of the ground-state wave functions of the two π-systems, determined in the absence of any intermolecular interaction. A simple model of a π-system is illustrated in Figure 2; it consists of a positively charged σ-framework sandwiched between the two negatively charged π-electron clouds. Now consider the interaction between two such π-systems: an attractive interaction is clearly counterintuitive because the dominant interaction will be the repulsion of the two closest approaching π-clouds. When the separation of the two π-systems is comparable to their thickness, the π-electrons must be considered separately from the σ-framework. We use a set of point charges to represent the electrostatic charge distribution of the molecule (Figure 3) and calculate the electrostatic interaction as the sum of the charge–charge interactions between two such π-systems.[24] This approach is the basis of the DMA method (distributed multipole approach) for calculating intermolecular electrostatic potentials.[8,22]

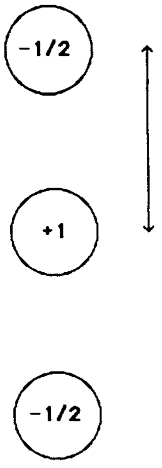

Figure 3. Model for an atom which contributes one electron to the molecular π-system; projection parallel to the plane of the π-system.

In the simplest case, for each carbon atom in the π-system, we use a charge of +1 at the nucleus of the atom and two charges of $-^1/_2$ at a distance, δ, above and below the plane of the π-system (Figure 3). The parameter, δ, was determined by using the experimental value of the quadrupole moment of benzene.[8b] Allowing for C–H bond polarization,[8b] this method gives an optimum value for δ of 0.47 Å; we believe that we are justified in using this value as an approximation for δ in other π-systems.[25] The choice of δ affects the magnitude of the calculated π–π interaction energies but does not alter the relative values for different systems nor does it change any of the geometrical results.

We superimpose on this charge distribution for each atom the polarization of both the σ-framework and the π-system. For example, if an atom which contributes one π-electron to the π-system has a σ-charge of −0.08 and is associated with 1.10 π-electrons, then we use a net σ-charge of +0.92 and two net π-charges of −0.55. Similarly, if an atom which contributes two electrons to the π-system (e.g., a phenolic oxygen) has a σ-charge of +0.20 and is associated with 1.88 π-electrons, we would use a net σ-charge of +1.20 and two net π-charges of −0.94. Estimates of these polarizations for porphyrins are available from IEH and SCF-MO calculations.[21,26] Approximations of the π-polarizations in other systems were obtained from Hückel calculations.[27] For molecules for which no crystal structure data were available, the spatial coordinates were estimated by using Macromodel molecular mechanics calculations. All energy calculations were carried out by using a Macintosh SE microcomputer and our own programs: the flow chart in Figure 4 summarizes the procedure. The parameters C_{ij}, A_{ij}, and α_{ij} were from ref 23.

This model is crude by the standards of modern theoretical chemistry,[8,22] but it has a simple physical and pictorial basis so

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(23) Caillet, J.; Claverie, P. *Acta Crystallogr., Sect. A* **1975**, *31*, 448–461.

(24) This should be true for the atoms of interest, carbon, oxygen, and nitrogen, since they are all second row elements. Clearly, the larger third row atoms, such as sulfur, will be associated with a larger value of δ.

(25) We have used a dielectric constant of one, but the choice of effective dielectric constant, ε, inside molecules and at points of intermolecular contact is not important: a different value of ε would be compensated for by a change in value of the parameter, δ.

(26) Maggiora, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 6555–6559.

(27) Hückel calculations do not yield a very accurate charge distribution, but we have only used this method in qualitative examples.

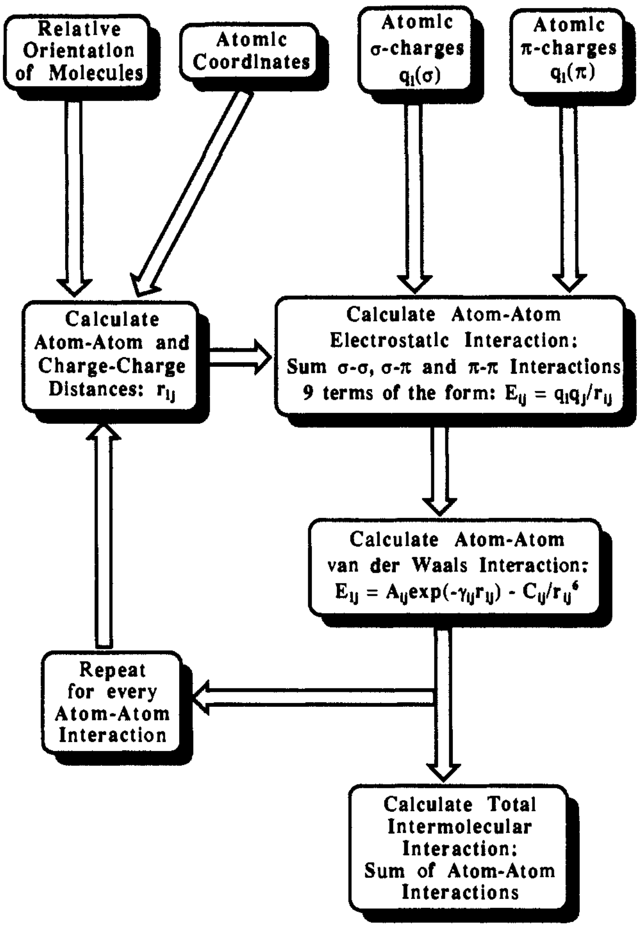

Figure 4. Algorithm used for calculation of π–π interaction energies.

that the results derived can be generalized to explain the presence or absence of attractive π–π interactions in many different systems.

Results

Porphyrin–Porphyrin Interactions in Solution. To model a porphyrin, we first considered only the 24 atoms of the π-system, the carbon atoms were given a charge of +1 and had one π-electron associated with them, and the nitrogens were given a charge of +1.5 and had 1.5 π-electrons associated with them, i.e., each atom is neutral overall, and we neglect the effects of polarization at this stage. The intermolecular electrostatic interaction was calculated by using this charge distribution and plotted as a function of the offset of one porphyrin relative to the other in the *xy* plane for an interplanar separation, *z*, of 3.4 Å (Figure 5). The optimum interaction is predicted for a geometry which places the pyrrole ring of one porphyrin directly above the π-cavity at the center of the other (Figure 6); such an arrangement minimizes π–π repulsion and, at the same time, maximizes attraction between the σ-framework around the inner edge of the π-cavity of one porphyrin with the π-electrons of the pyrrole ring immediately above. There is no rotation of one porphyrin relative to the other; rotation always leads to a less favorable interaction energy, in accord with experimental observations. When the polarization of the σ-framework and π-system of a zinc porphyrin was included,[21] treating the metal ion as a single point charge at the origin, the intermolecular potential was qualitatively unaltered (Figure 7): it is the topography of the π-system rather than the polarization which determines the geometry of interaction in this system.

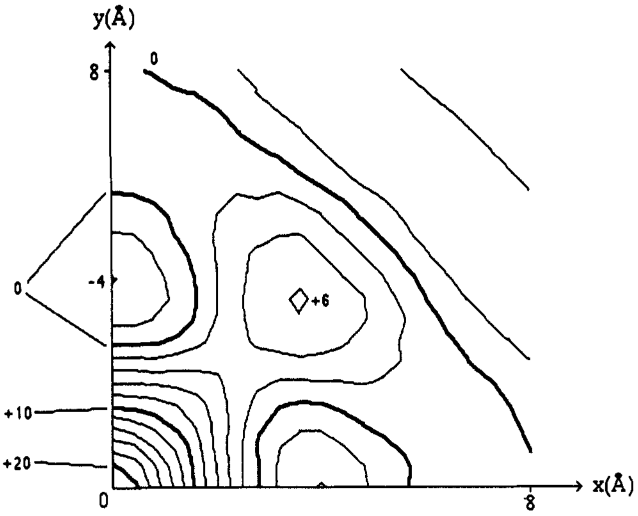

Figure 5. A contour plot showing the electrostatic interaction (in kJ mol^{-1}) between two 24-atom porphyrin π-systems (no polarization included) as a function of their center-to-center offset in the *xy* plane; *z* = 3.4 Å. The porphyrins are not rotated relative to one another.

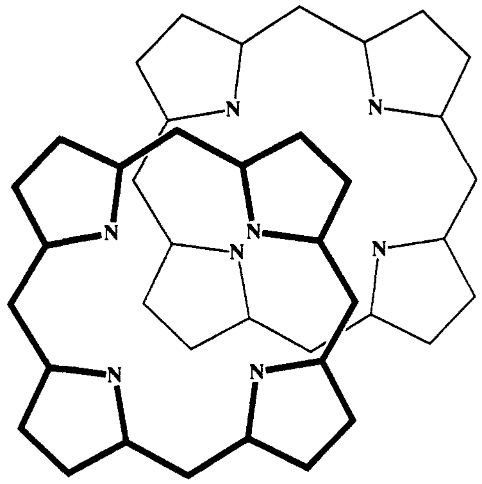

Figure 6. The optimum geometry for the zinc porphyrin–zinc porphyrin interaction predicted by using our model for π–π interactions.

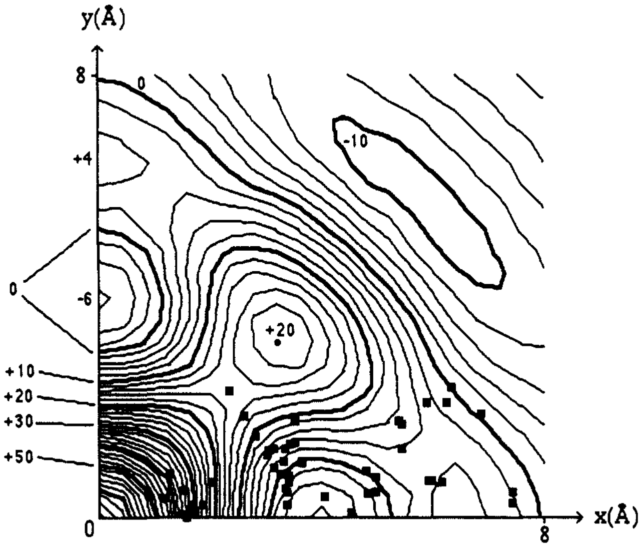

Figure 7. Contour plot showing the electrostatic interaction (in kJ mol^{-1}) between two zinc porphyrins as a function of their center-to-center offset in the *xy* plane; *z* = 3.4 Å. The porphyrins are not rotated relative to one another. The geometries of porphyrin–porphyrin stacking interactions in crystals are indicated.

The geometry illustrated in Figure 6 is in excellent agreement with the experimentally determined low-temperature geometry for the zinc porphyrin–zinc porphyrin interaction in CH_2Cl_2 solution.[5c] In this geometry, the electrostatic contribution to the total π–π interaction is predicted to be 7 kJ mol^{-1}. This is smaller than our experimental estimate of 48 ± 10 kJ mol^{-1},[5a] but there is clearly a strong energetic preference for this geometry over any other: Figure 7 indicates that the face-to-face geometry is unfavorable. If we include the van der Waals term in the calcula-

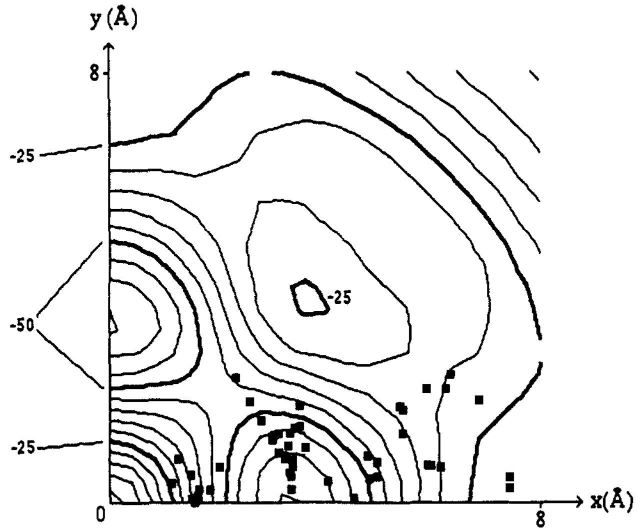

Figure 8. Contour plot showing the total π–π interaction (sum of the electrostatic and van der Waals contributions in kJ mol^{-1}) between two zinc porphyrins in the solid state as a function of their center-to-center offset in the xy plane; $z = 3.4$ Å. The porphyrins are not rotated relative to one another. The geometries of porphyrin–porphyrin stacking interactions in crystals are indicated.

tion,[23] the shape of the contour plot is unaltered, but the magnitude of the interaction energy changes (Figure 8): the geometry is controlled by the electrostatic interaction but van der Waals contribution dominates the net interaction energy.[28] The experimental interaction is somewhat less than the energy at the potential minimum in Figure 8 (65 kJ mol^{-1}) as expected from desolvation considerations.

Similar energy level plots were obtained for the interactions between two free base porphyrins and between two magnesium(II) porphyrins:[26,29] metalation has no effect on the geometry of the π–π interaction but does affect its magnitude. Relative to the zinc porphyrin–zinc porphyrin interaction, the π–π interaction is reduced for two free base porphyrins and increased for two magnesium porphyrins. The role of the metal in enhancing porphyrin aggregation is now clear; metalation places a large positive charge (+0.4 in the case of zinc[21]) in the central cavity of the porphyrin π-system which leads to a favorable interaction with the π-electrons of the pyrrole of the other porphyrin. The greater the net positive charge on the metal, the greater the strength of the π–π interaction, as observed experimentally.[7d] This metal–π-interaction is not a metal–π-bond but a weak electrostatic interaction between two proximate, opposite charges, and it is not a prerequisite for the attractive π–π interaction.

By using this model we can also explain the reduction in the π–π interaction between metalloporphyrins caused by coordination of the central metal by a ligand. When pyridine is bound to a zinc porphyrin, the metal is pulled ca. 0.3 Å out of the plane of the porphyrin. By using this new position for the zinc atom in our calculation, we again find that the geometry of the π–π interaction is unaltered, but the magnitude is reduced. The π–π interaction for a zinc porphyrin dimer is predicted to fall by 3 kJ mol^{-1} when one of the zinc atoms is coordinated, i.e., pulled out of the porphyrin plane by 0.3 Å, and it falls by another 3 kJ mol^{-1} when the second metal is coordinated. This agrees qualitatively with our findings for ligand binding to cofacial porphyrin dimers, where the π–π interaction between the two zinc porphyrins was reduced by 10 kJ mol^{-1} per pyridine binding.[5d] Ligand binding will also have an electronic effect, in that it will lower the net positive charge on the zinc atom: this has not been considered in our calculations and hence the reduction in the π–π interaction which we predict is less than that observed.[30]

Porphyrin–Porphyrin Interactions in the Solid State. To model interactions in the crystalline state, we approximate the total intermolecular interaction energy to the sum of the electrostatic and van der Waals contributions. There are no solvent effects, but the interaction geometry may be distorted by crystal packing forces.

We used the zinc porphyrin calculations (Figures 7 and 8) as an approximation for all porphyrin systems and considered only crystal structures which contain the full porphyrin skeleton, i.e., only fully unsaturated tetrapyrrollic systems. In addition, we have excluded several types of porphyrins for the following reasons: (1) 5,10,15,20-tetraaryl porphyrins, since steric and possibly electrostatic interactions with the aryl rings could affect the interaction; (2) systems in which the porphyrin–porphyrin orientation is constrained by covalent linkages; and (3) six-coordinate metalloporphyrins since steric interactions between the ligands and the neighboring porphyrins will affect the crystal structure.

Taking all other porphyrin crystal structures in ref 9, we plotted the offset (in the xy plane) of the center of one porphyrin relative to its nearest neighbor. The energy plots have high symmetry, and so the experimental observations were transformed to lie in one octant of the xy plane, $x, y > 0$ and $x > y$ (see Figures 7 and 8). In these crystal structures the porphyrins were always parallel, and there was no rotation of one porphyrin relative to another, as predicted by theory. Superimposed on the contour plots in Figures 7 and 8 is the distribution of the center–center offsets. Even though we have restricted the sample of porphyrin crystal structures considered, it is still a diverse set of molecules; the π-systems have all manner of side chains and polarizing substituents. We have only considered the π–π interactions for two porphyrins in isolation, but, in the crystal, interactions with all of the other neighboring porphyrins impose a variety of crystal packing forces which differ for each system. Thus the plot of the relative orientations of two stacked porphyrins shows a large scatter. However, it is striking that this scatter maps out the low-energy regions of the potential surfaces predicted by our theory. There is a cluster of points around the energy minimum at an offset of 3.6–4.0 Å along the x axis, and, apart from a few outliers, the remaining points which deviate from this minimum lie along the low-energy valleys of the electrostatic energy plot (Figure 7). These valleys are smoothed out in Figure 8 which includes the van der Waals energy. This suggests that it is the electrostatic interaction which is important in determining the geometry of porphyrin–porphyrin stacking in the crystal. The cluster of points around $x = 1$ Å, $y = 0$ Å are mainly free base porphyrins. In these systems, the electrostatic interaction is weaker than in metalloporphyrins and so van der Waals interactions are more significant and pull these points closer to the origin (the face-to-face geometry). Our calculations may not predict the relative magnitudes of the contributions of the electrostatic, dispersion and repulsion interactions accurately, but, qualitatively, they account well for the π–π interactions observed between porphyrins in the crystalline state.

Porphyrin–Aromatic Solvent π–π Interactions. We predict a favorable porphyrin–solvent π–π interaction when the aromatic solvent molecule is parallel to the porphyrin and lies over the central hole in the porphyrin π-system. The electrostatic interaction is strongest for metalloporphyrins, and the attraction between the positive metal site and the negatively charged π-cloud of the solvent is optimized if the most electron-rich solvent atom is the atom closest to the metal center, as is observed experimentally.[9,14] In toluene solution, π–π interactions with porphyrins are significantly reduced because solvent competes for the optimum π-stacking position at the center of the porphyrin.[12c]

Other Porphyrin–Aromatic Interactions. The magnitude of the porphyrin–pyromellitimide interaction is 28–56 kJ mol^{-1} in CH_2Cl_2

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[28] The zinc atom in this molecule has a net charge of +0.4 which may be large enough to cause a sizeable induction energy. Such a metal π-electron interaction would, however, serve to further stabilize the geometry favored by the electrostatic interaction.

[29] For the free base, the two central hydrogen atoms were represented by four half-atoms: point charges of +0.074 placed at (0, ±1.02) and (±1.02, 0).

[30] Ligand coordination would also reduce induction interactions in this system.

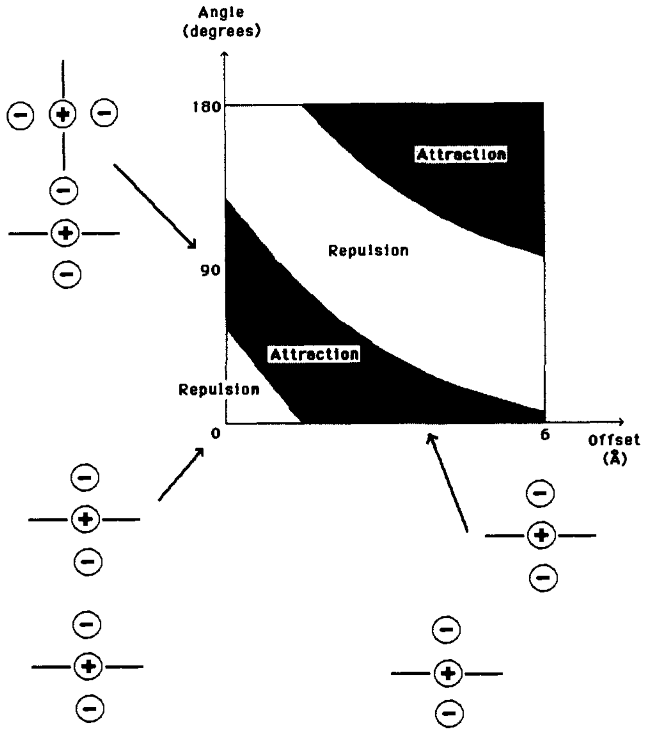

Figure 9. Interaction between two idealized π-atoms as a function of orientation: two attractive geometries and the repulsive face-to-face geometry are illustrated.

solution.[5b] NMR ring current shifts indicate that the pyromellitimide is parallel to the porphyrin π-system with its center offset relative to the center of the porphyrin by 3.9–5.6 Å (C.A.H. and J.K.M.S., unpublished). Photophysical measurements on electron-transfer rates in these systems not only support this conclusion but also indicate that a range of different geometries rather than a single well-defined conformation is adopted.[12e] With this limited structural information let us now turn to the predictions of our π–π interaction model. The model predicts a shallow potential well (not illustrated) including a range of low-energy conformations when the pyromellitimide center is offset from the center of the porphyrin by 3–4 Å and a total π–π interaction energy of approximately 65 kJ mol^{-1} (of which electrostatics contribute 23 kJ mol^{-1}). This is consistent with the experimental value, allowing for desolvation.

The porphyrin–quinone π–π interaction is much weaker than the porphyrin–pyromellitimide interaction in solution; in contrast to monolinked porphyrin–pyromellitimide systems, monolinked porphyrin–quinones adopt open or unfolded conformations in solution.[12d] Our model predicts that, in the optimum geometry for the porphyrin–quinone interaction, the total π-stacking energy is ca. 35 kJ mol^{-1} (the electrostatic contribution 12 kJ mol^{-1}). This is much less than the pyromellitimide–porphyrin interaction in accord with experiment.

A Set of Rules

Having established the validity of our model, we now consider the broader implications.

Geometrical Requirements. To draw some general conclusions about the preferred geometries of π–π interactions, we use the set of three charges shown in Figure 3 to represent an idealized π-system or π-atom and consider the interaction between two such π-atoms (for a fixed vertical separation of 3.4 Å). Figure 9 shows how the electrostatic π–π interaction varies as a function of their relative orientation in the absence of any polarization effects. The y-axis is the angle of anti-clockwise rotation about the central positive charge of the upper π-atom, and the x-axis is the offset toward the right-hand side of the diagram. The face-to-face geometry (angle = 0, offset = 0) is in the repulsive zone, as expected. However, there is an attractive band where one π-atom is rotated by up to 90° relative to the other and where one π-atom is offset laterally relative to the other. Figure 9 shows two limiting geometries which lead to a favorable electrostatic interaction: here σ–π attraction is the dominant interaction, while in a face-to-face geometry, π–π electronic repulsion dominates. A rotation of between 0° and 90° generally leads to attraction at small offsets: it is essentially an edge-on arrangement. A rotation of 90° to 180° leads to repulsion at small offsets: it is a face-to-face arrangement. The effect of C–H bond polarization, as in benzene, is to make the attractive regions more attractive and the repulsive regions more repulsive. We summarize these results for nonpolarized π-systems with three rules: rule 1, π–π repulsion dominates in a face-to-face π-stacked geometry; rule 2, π–σ attraction dominates in an edge-on or T-shaped geometry; and rule 3, π–σ attraction dominates in an offset π-stacked geometry.

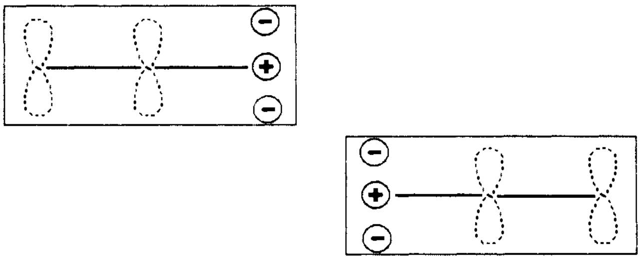

Figure 10. Offset π-stacked geometry.

Rule 2 is well-known, while rule 1 should not be surprising. The explicit recognition of rule 3 is, we believe, new. It predicts a favorable stacking interaction which involves a major offset, rather than merely a slight slip, between the two π-systems (Figure 10). Ab initio calculations on the electrostatic interactions between simple aromatic molecules are consistent with our rules.[8b]

Experimental evidence for the validity of these rules comes from the crystal structures of simple aromatic compounds. Two types of geometry are generally observed: edge-on relationships which give rise to the characteristic herring bone pattern and offset stacked relationships.[3] The crystal structures of kekulene and [18]annulene illustrate this point: in one dimension the π-systems are parallel, stacked, and offset so that the π-system of one molecule lies over the π-cavity at the center of its nearest neighbor (Figure 11); in the other dimensions the molecules are aligned to give perpendicular, edge-on interactions with their neighbors.[31] As detailed above, porphyrins also π-stack in an offset geometry.[5c,7,9]

To predict geometries for whole molecules using the model, we sum the electrostatic interactions over all the atoms. Figure 12 shows the energy we predict for the kekulene stacking interaction as a function of offset, including electrostatic and van der Waals contributions; the experimentally observed geometry is indicated.[31b] The model predicts the geometry of such stacking interactions with a high degree of accuracy: it is the π–π interaction which dominates the geometry of the intermolecular interaction, so crystal packing forces must be relatively weak. This implies that the study of crystal structures may be a very fruitful source of information on intermolecular π–π interactions between more complicated polarized aromatic molecules.

Effects of Polarization. We now consider interactions between π-systems polarized by heteroatoms. The face-to-face stacked geometry is always favored by van der Waals interactions and solvophobic effects but is generally disfavored by π–π repulsion. However, the presence of strongly-polarizing atoms has a major influence on the electrostatic interaction.[8] Figure 13 shows the effect of varying the π-polarization independently in two face-to-face idealized π-atoms. The total electrostatic interaction is plotted for a range of π-electron densities on atom 1 (Figure 14) interacting with an atom 2 which is neutral (non-polarized), electron-rich or electron-deficient. When both atoms are highly charged, the obvious result is obtained: like polarizations repel

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(31) (a) Hirshfeld, F. L.; Rabinovich, D. *Acta Crystallogr.* **1965**, *19*, 235–238. (b) Staab, H. A.; Diederich, F.; Krieger, C.; Schweitzer, D. *Chem. Ber.* **1983**, *116*, 3504–3512.

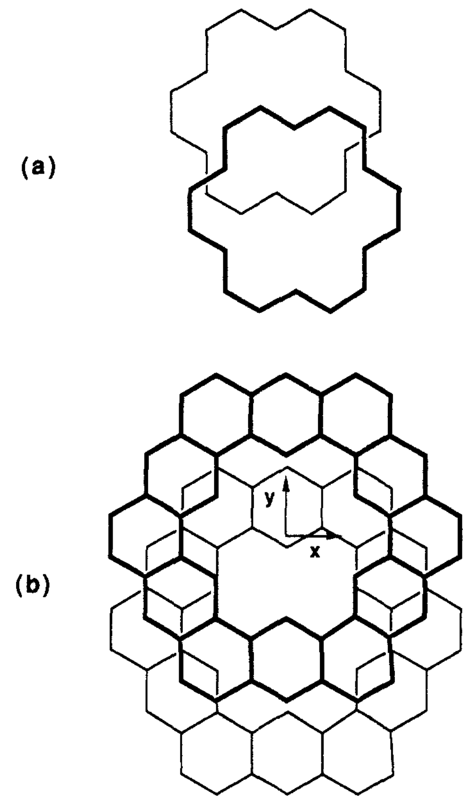

Figure 11. The geometry of π-stacking interactions in the crystal structures of (a) [18]annulene and (b) kekulene (the axes used in Figure 12 are shown).

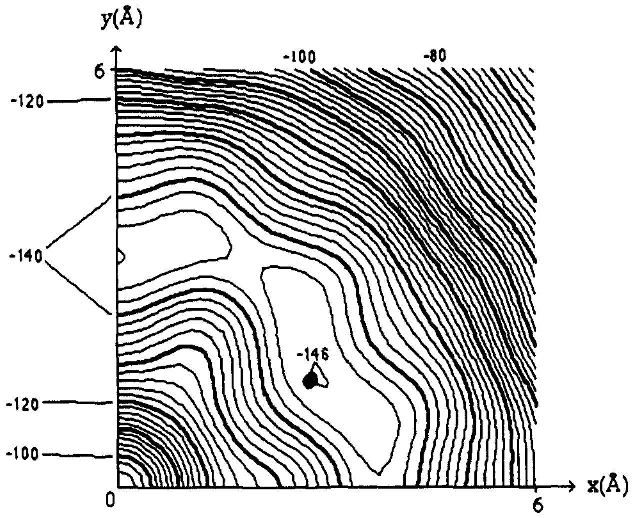

Figure 12. Contour plot showing the kekulene–kekulene interaction (in kJ mol^{-1}) as a function of offset; z = 3.4 Å. The interaction energy is the sum of the electrostatic and van der Waals contributions. The geometry observed in the crystal structure is marked ●.[35b]

and unlike polarizations attract. For neutral atoms in this geometry, the dominant interaction is π-electron repulsion, so an atom which is π-deficient stabilizes the interaction by decreasing this repulsion. Conversely, a π-rich atom would destabilize the interaction further.

Figure 13 is not symmetric about neutrality (the dashed vertical line): the point at which the three energy plots intersect is shifted to the π-poor side of this neutral line. A consequence of this asymmetry is the prediction that the interaction between two π-deficient atoms can be more favorable than that between a π-deficient and a π-rich atom. The region where this effect operates is shaded in Figure 13. This shaded region covers only a narrow range of polarizations, but we believe that it embraces the majority of aromatic carbons which are not directly bonded to heteroatoms, so the predicted counterintuitive behavior in this zone should be significant in real systems: we predict that electron acceptor–acceptor (or EAA) interactions should be favorable in appropriate orientations and this is supported by the observation that some quinones crystallize in a face-to-face geometry (Figure 15).[32,33]

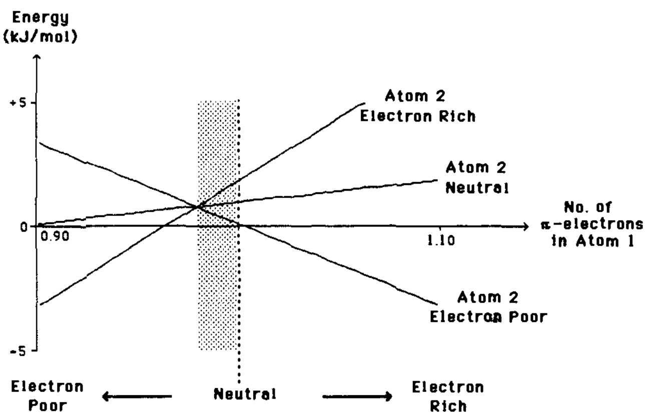

Figure 13. Effect of π-electron polarization on the interaction between two idealized π-atoms in a face-to-face π-stacked geometry. Electron deficient and electron rich refer to net charges of ±0.10.

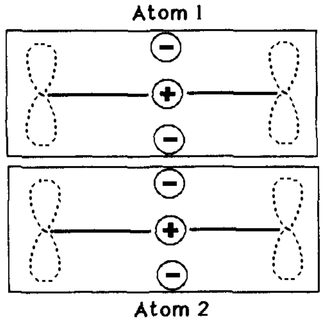

Figure 14. Face-to-face π-stacked geometry.

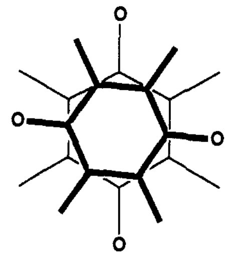

Figure 15. Geometry of the nearest neighbor intermolecular interaction in the crystal structure of tetramethyl *p*-benzoquinone.[32]

If a face-to-face geometry is not significantly stabilized by the effects of polarization, then an offset π-stacked or edge-on geometry (or an intermediate geometry, see Figure 9) will be preferred as predicted by rules 2 and 3. However, interactions in these geometries are also modified by polarization. Figures 16 and 17 show how π-polarization affects π–π interactions in an edge-on orientation (Figure 18). The results are conceptually similar to those obtained above, but the direction of the asymmetry in these plots differs because the dominant interaction is now π–σ attraction. The direction of the asymmetry in the corresponding plot for an offset stacked geometry (Figure 10) varies with the sizes of the vertical and lateral offsets and has not been shown. We summarize these results for polarized π-systems in the following additional rules. Rule 4, for interactions between highly charged atoms, charge–charge interactions dominate. Rule 5, a

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(32) (a) Bernstein, J.; Cohen, M. D.; Leiserowitz, L. *The Chemistry of the Quinoid Compounds, Part I*; Patai, Ed.; Wiley: London, 1974; pp 83–105. (b) Rabinovich, D.; Schmidt, G. M. J. *J. Chem. Soc. B* **1967**, 144–149.

(33) Foster, R.; Foreman, M. I. *The Chemistry of the Quinoid Compounds, Part I*; Patai, S., Ed.; Wiley: London, 1974; pp 257–303.

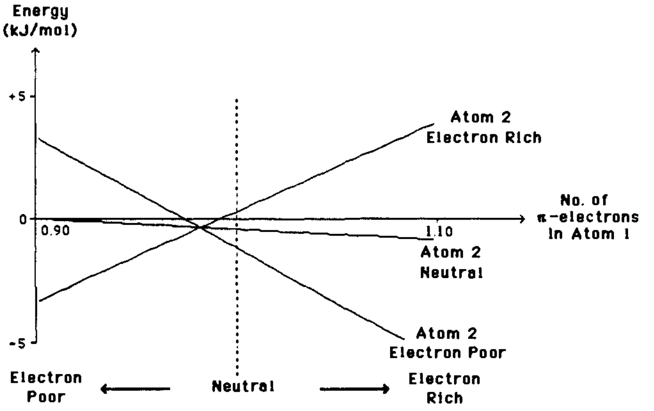

Figure 16. Effect of π-electron population on atom 1 (Figure 18) on the interaction between two idealized π-atoms in an edge-on geometry. Electron deficient and electron rich refer to net charges of ±0.10.

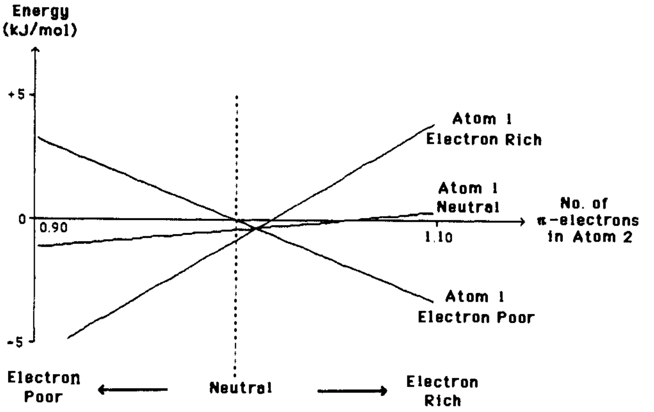

Figure 17. Effect of π-electron population on atom 2 (Figure 18) on the interaction between two idealized π-atoms in an edge-on geometry. Electron deficient and electron rich refer to net charges of ±0.10.

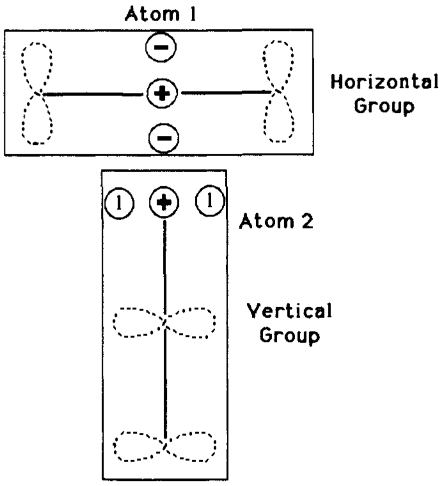

Figure 18. Edge-on or T-shaped geometry.

favorable interaction with a neutral or weakly polarized site requires the following π-polarization: (a) a π-deficient atom in a face-to-face geometry (Figures 13 and 14), (b) a π-deficient atom in the vertical T-group in the edge-on geometry (Figures 16 and 18), and (c) a π-rich atom in the horizontal T-group in the edge-on geometry (Figures 17 and 18). Rule 6, a favorable interaction with a neutral or weakly polarized site requires the following σ-polarization: (a) a positively charged atom in a face-to-face geometry, (b) a positively charged atom in the vertical T-group in the edge-on geometry (Figure 18), and (c) a negatively charged atom in the horizontal T-group in the edge-on geometry (Figure 18).

Reversing the polarizations in rules 5 and 6 leads to repulsion. Implicit in these rules are strong geometrical requirements for face-to-face π-stacking interactions as is observed experimentally.[1,5] Experimental evidence for their validity can be found for example in the crystal structures of quinones as mentioned above (Figure 15).[32] Benzene and other nonpolarized aromatics π-stack in a face-to-face geometry with quinones, as predicted by rule 5a.[33] The porphyrin results described above also obey these rules; a positively charged site, a metal atom at the center of the porphyrin, makes the π–π interaction more attractive since this atom has a face-to-face orientation with respect to the pyrrole π-system of the other porphyrin (rule 6a).[5c,7] Further evidence is presented below.

Table I. Electrostatic Contribution to π-Stacking Interactions between Polarized π-Systems (in kJ mol^{-1})

		Orientation[a]					
-R$_1$[b]	-R$_2$[b]	1	2	3	4	5	6
-H	-H	14.9	14.8	-2.0	-2.0	-1.9	-2.0
-H	-NH$_2$	17.8	17.6	-1.4	-1.1	-1.0	-1.4
-H	=O	-1.5	-1.7	-5.3	9.1	9.1	-5.3
=O	=O	22.7	-13.6	-0.3	-1.4	0.6	-1.4
=O	-NH$_2$	3.3	-1.7	-7.6	-7.5	10.9	11.6
-NH$_2$	-NH$_2$	25.9	22.2	-0.3	-0.4	-0.6	-0.4

[a] See Figure 19 for an illustration of orientations of 1–6. Negative values indicate attractive interactions, while positive values correspond to repulsive interactions. [b] -H corresponds to benzene; -NH$_2$ is p-phenylenediamine; =O is p-benzoquinone.

These results have important implications in the field of molecular recognition. The widespread use of the simple EDA concept can be misleading since within any one molecule there will be both electron-rich or donor regions and electron-poor or acceptor regions,[6] and the net intermolecular interaction depends critically on how such regions are aligned. *It is the properties of the atoms at the points of intermolecular contact rather than the overall redox properties of the molecules which determine how π-systems interact.* So, while EDA interactions undoubtedly exist,[6] they are not reliable or predictable because they are just a special case of the more general π–π interaction. Charge-transfer transitions observed for such complexes are *a consequence not a cause* of the π–π interaction.[19]

Table I demonstrates how polarization effects influence π–π interactions, emphasizing that the geometry of interaction is of critical importance. We consider interactions between three different π-systems: benzene, a nonpolarized π-system; p-phenylenediamine, an electron donor; and p-benzoquinone, an electron acceptor.[29] The electron donor is polarized so that the aromatic ring has a net negative charge and the substituents have a net positive charge, and the electron acceptor is polarized so that the aromatic ring has a net positive charge and the substituents have a net negative charge. Table I shows the predicted magnitudes of the electrostatic components of the π–π interaction energies for all possible combinations of these π-systems in the six orientations illustrated in Figure 19. The magnitudes and conclusions should be considered as qualitative only.[27] The contribution of van der Waals interactions to the total energy will be proportional to the area of π-overlap and will vary with solvent as outlined above.

The values in Table I can be interpreted by using our set of rules. In general, offset stacking (orientations 3–6) is attractive, and face-to-face stacking (orientations 1 and 2) is repulsive. However, rule 4 predicts that π-overlap can be favorable in cases where the atoms at the site of contact are π-deficient, and so attractive face-to-face stacking is predicted for the acceptor–acceptor interaction in orientation 2 (see Figure 19).[32b] Large repulsive interactions are predicted when the atoms at the site of contact are π-rich.

π–π Interactions in Host–Guest Systems. We now use these rules to rationalize the behavior of a range of aromatic host–guest complexes.[6] The most important features of π–π interactions in these systems are the geometrical constraints imposed by the structure of the host: the range of relative orientations available to the host and guest is usually limited, and Table I demonstrates that orientation can significantly affect π–π interactions.

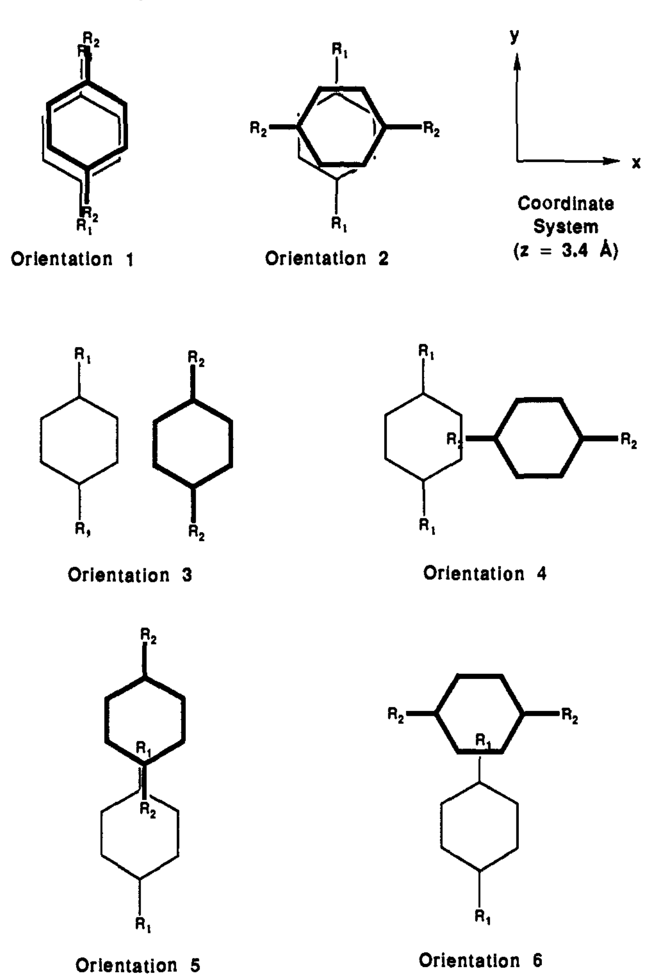

Figure 19. Orientations for the $\pi-\pi$ interactions between polarized π-systems. R_1 and R_2 are the polarizing groups.

An outstanding success in the field of host–guest $\pi-\pi$ interactions is the work of Diederich et al.[6d,e,16] Their cyclophane hosts complex a range of aromatic guests in both water and organic solvents. The reason for this success is clear if we assume that the complexes adopt the geometry observed in crystal structures (Figure 20a) with the host and guest π-systems inclined at 45°.[6e,34] The host–guest $\pi-\pi$ interaction falls in the center of the shaded 0°–90° electrostatic attractive zone in Figure 9. Rotation of the guest away from this geometry would be accompanied by a slight opening of the host and so such a rotational breathing motion of the complex would simply move the $\pi-\pi$ interactions along the attractive shaded zone in Figure 9. Even a rotation of 45° would yield attractive offset π-stacking interactions with two walls of the cavity and edge-on interactions with the other two walls (Figure 20b).

In one set of Diederich's hosts,[16] the aromatic side-walls of the hosts are polarized by alkoxy groups. The phenolic oxygen atoms are electron donating and so in our nomenclature are π-poor, while the rest of the aromatic ring is correspondingly π-rich. Thus the regions of the host which lie above the plane of the guest π-system (in a pseudo-stacking or face-to-face position) are π-deficient, while the regions which contact the guest hydrogen atoms (i.e., in a pseudo-edge-on position) are π-rich (Figure 20). Rule 5 predicts that these polarization effects should all enhance the binding interactions, and efficient complexation is observed for neutral aromatic guests. The geometry of the cavity is such that polarizing groups on the guest molecules are forced outside the cavity, into the solvent, and so the atoms at the sites of intermolecular contact are only weakly polarized. Rules 5 and 6 therefore apply: a π-deficient guest enhances both the pseudo-edge-on and stacking interactions, while a π-rich guest reduces both binding interactions.

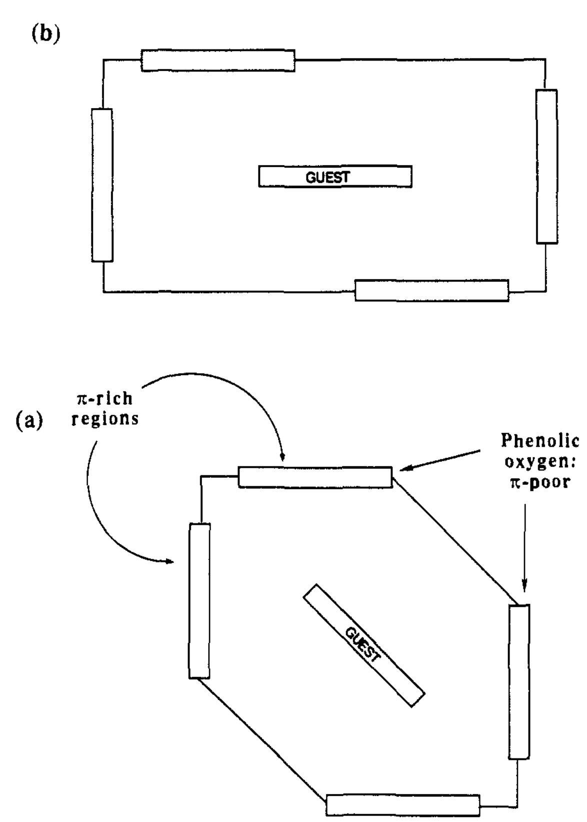

Figure 20. The successful cyclophane hosts of Diederich et al. (a) This geometry, observed in crystal structures, leads to a favorable interaction (see Figure 9). (b) This geometry is also favorable due to attractive edge-on and offset stacking interactions; addition of the illustrated polarization effects enhances binding in some hosts.[6e]

The result is an apparent EDA effect: Diederich et al. observed stronger binding of π-deficient guests (acceptors) and weaker binding of π-rich guests (donors). These measurements were made in aqueous solution where hydrophobic effects are the major driving force for complexation. However, for this series of closely related systems this effect should be reasonably constant allowing us to use the relative binding energies as measures of the effects of polarization on the strength of the $\pi-\pi$ interactions. The trends are clearly in accord with our model.

Schneider et al. attribute the enhanced complexation of aromatic guests inside their hosts to higher order electric effects.[6h] In essence, they have observed rule 6a. These systems are related to Diederich's and can be explained by using Figure 20. When complexation occurs, positively charged sites on the host lie above the plane of the aromatic guest and interact favorably with the guest π-electrons.

Lehn et al. have observed an attractive electron acceptor–acceptor interaction, but the geometry of interaction has not been completely defined. In one orientation, π-overlap is stabilized by specific charge–charge interactions between the negatively charged guest oxygens and the positively charged carbonyl carbons of the host.[6f] The donor–acceptor stacks in Stoddart's systems also clearly show offset and cross-interactions.[6i]

Highly polarized π-deficient molecules such as tetranitrofluorenone form stable π-stacked complexes with a range of π-systems due to the reduced π-electron density at the site of π-overlap (rule 5) and favorable charge–charge interactions (rule 4). This explains why Zimmerman's molecular tweezers work.[6b] The $\pi-\pi$ interactions in these systems are most likely to be associated with an offset geometry: crystal structures show that two tweezers can mutually complex one another but that the stacking interactions are associated with minimal π-overlap.[35]

Hamilton et al. have observed $\pi-\pi$ interactions in complexes of 1-butylthymine and diamidopyridine receptors.[20,36] The two

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(34) Krieger, C.; Diederich, F. *Chem. Ber.* **1985**, *118*, 3620–3631.

(35) Zimmerman, S. C.; Mrkisch, M.; Baloga, M. *J. Am. Chem. Soc.* **1989**, *111*, 8528–8530.

aromatic bases form a hydrogen-bonded complex, and the interactions between this extended π-system and a third aromatic component, a naphthalene derivative, have been investigated. The naphthalene derivative is constrained to lie over the π-systems of the bases. Electron-donating substituents increase the naphthalene π-electron density so that electronic repulsion would dominate in the stacked geometry and so an edge-on interaction is observed. In contrast, electron-withdrawing substituents decrease the naphthalene π-electron density so that electronic repulsion is reduced and the stacked arrangement is favored.[20] Hamilton et al. pointed out that there are also specific charge–charge interactions in these two systems which stabilize the stacked geometry for the π-deficient naphthalene and destabilize it for the π-rich one (the net charges on some atoms in these π-systems are large and so rule 4 holds).

π–π Interactions in Biological Systems. Some of the best characterized examples of π-stacking interactions can be found in nucleic acids.[1] The base–base stacking interactions are usually associated with an offset rather than a face-to-face geometry,[1] and this offset is complementary to the twist of the helix. We estimate that, on average, a twist of ca. 30°–40° of one base pair relative to its π-stacked neighbor about the helix axis will optimize the π–π interactions,[8a,19,37] and this correlates well with experimental observations.[1] π-stacking interactions also characterize the intercalation of drugs into DNA.[2,38] Many intercalating agents are π-systems which have a net positive charge:[2] on the basis of rules 5 and 6, it is clear why such molecules should form stable face-to-face π-stacked complexes with the aromatic DNA bases.

π–π interactions have also been observed in proteins[4] and may be an important force in determining how proteins fold. Strong geometrical preferences have been observed in, for example, phenylalanine–phenylalanine interactions, and the preferred geometries of interaction fall in the attractive zone illustrated in Figure 9. The magnitude of a single π–π interaction for such small π-systems may not be large, but it can significantly influence the tertiary structure of a protein.[39]

Conclusion

We have shown that the simple picture of a π-system as a sandwich of the positively charged σ-framework between two negatively charged π-electron clouds accounts well for the observed interactions between π-systems. It is a π–σ attraction rather than a π–π electronic interaction which leads to favorable interactions. These electrostatic effects determine the geometry of interaction, while van der Waals interactions (and solvophobic effects) make the major contribution to the magnitude of the observed interaction. Our results are not different from those obtained in other theoretical studies,[8,19,22,37] but our simple physical model allows us to highlight the important features of π–π interactions in terms accessible to the practical chemist.

This work has implications in the field of molecular recognition and host–guest chemistry. Many groups have been trying to synthesize host molecules which will bind guests by virtue of a strong favorable π–π interaction between host and guest. Conventional wisdom is that rigidity is a requirement for efficient host–guest binding.[6] However, rigidity can be a problem in host–guest systems if the nature of the binding interaction is not well understood, and the appropriate geometry is not available. Of course, flexibility can lead to cavity collapse as we observe in porphyrin dimers,[5a,b] resulting in an enthalpic barrier to cavity opening; this barrier can be overcome only if the host–guest interaction is strong enough.[5a,b] On the other hand, an attractive feature of our flexible systems is that they can relax into the optimum geometry for attractive π–π interactions, allowing us to characterize the geometric preferences exhibited by these interactions and hence to develop a theoretical model.

Intermolecular interactions usually have strong geometric requirements, so where the nature of the interaction is not well understood, it is impossible to design a rigid system to optimize the interaction; in such cases the best way forward in the first instance is to investigate the behavior of flexible systems.

Another consequence of our results is that molecular mechanics calculations which do not allow for the spatial charge distribution of the π-electron system are unlikely to prove successful in modelling systems with interacting aromatic groups. In particular, modelling or designing host–guest systems of the type discussed above is not possible with conventional algorithms: π-electron repulsion is missing and so energy minimizations are dominated by van der Waals interactions and will always yield the geometry of maximum π-overlap. We have established some general rules for predicting the nature of π–π interactions, and, by using these rules, it will now be possible to design efficient host–guest systems so that the magnitudes of these important interactions can be investigated. With more experimental results, it should then be possible to test and improve, quantitatively more accurate descriptions of intermolecular interactions.

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