Exercises in molecular gymnastics—bending, stretching and twisting porphyrins

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The functional versatility of tetrapyrroles as natural cofactors is related to their conformational flexibility where manipulation of the macrocycle conformation allows a fine-tuning of their physicochemical properties. This feature article gives a personal account of the synthesis and solid state structural characterization of highly substituted, non-planar porphyrins. Their conformational analysis identifies sterically strained tetrapyrroles as a versatile class of biomimetic compounds with tailor-made properties.

Introduction

The last decades have seen quite a renaissance in porphyrin chemistry. Major breakthroughs have been achieved preparing novel classes of porphyrin homologues, *i.e.*, contracted, expanded or heteroatom substituted porphyrins, and continuous advances have been made in the total synthesis of tetrapyrroles and in the development of novel transformation and functionalization reactions.[1] Likewise, a major boost was given to the field by the realization that porphyrins can exhibit a considerable degree of conformational flexibility and that different macrocycle conformations result in significantly altered physicochemical properties and novel chemical reactions. This allowed the development of conformationally designed biomimetic systems and established conformational control as one important principle of how tetrapyrrole dependent biological reactions are facilitated and regulated in nature.

Many groups have been involved in this research during the past decade and it is impossible to give justice to all significant contributions here.[2] In the following I give a personal account of how this area of research has developed using examples of specifically designed porphyrins to highlight important aspects of porphyrin chemistry and biochemistry.

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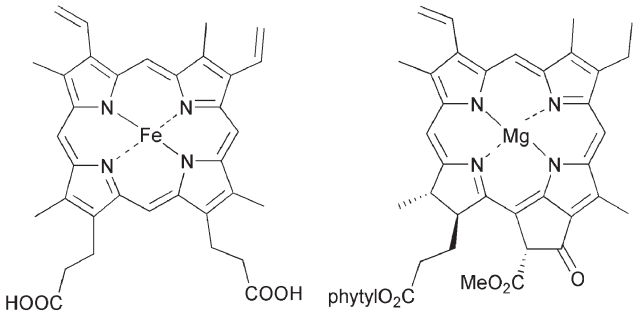
Mathias O. Senge, born in Silbach, Germany (1961), studied chemistry in Freiburg, Amherst, Marburg, and Lincoln and graduated from the Philipps Universität Marburg in 1986. After a PhD thesis in plant biochemistry with Prof. Horst Senger in Marburg (1989) and a postdoctoral fellowship with Prof. Kevin M. Smith at UC Davis, he moved to the Freie Universität Berlin and received his habilitation in Organic Chemistry in 1996. From 1996 on he was a Heisenberg fellow at the Freie Universität Berlin and UC Davis and held visiting professorships at Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes and the Deutsche Forschungsgemeinschaft; recently he was named a Science Foundation Ireland Research Professor. His main interests are the chemistry and biochemistry of tetrapyrroles, photobiology, crystallography, and medicinal and bioorganic chemistry.

Biological background

Tetrapyrrole-containing proteins are one of the most fundamental classes of enzymes found in nature. For many years scientists have tried to give a chemical rationale for the multitude of biological reactions that can be catalyzed by tetrapyrrole-containing pigment–protein complexes.[3] Although over 150 different natural tetrapyrroles have been identified, there are many fundamental processes where the same porphyrin cofactor is involved in chemically quite distinct reactions. For example, heme **1** is the active cofactor for oxygen transport and storage (hemoglobin, myoglobin) and for the incorporation of molecular oxygen into organic substrates (cytochrome P450). It is involved in terminal oxidation (cytochrome c oxidase), the metabolism of H_2O_2 (catalases and peroxidases) and catalyzes various electron transfer reactions in cytochromes. Likewise, in photosynthesis the same cofactor may function as a reaction center pigment (charge separation) or as an antenna pigment (exciton transfer) in light harvesting complexes (*e.g.*, chlorophyll a, **2**).

Differences in the apoprotein sequences alone could not explain the often drastic differences in physicochemical properties encountered for the same cofactor in diverse protein complexes. A critical factor for all biological functions must be the close interplay between bound cofactors and the respective apoprotein. Isolated pigments show physicochemical properties quite distinct from those in intact pigment–protein complexes (*e.g.*, absorption maxima, redox potentials). In



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addition, it has been recognized that most naturally occurring porphyrin cofactors exhibit a considerable degree of conformational flexibility. Thus, it became clear that the protein scaffold exerts conformational control on the porphyrin macrocycle and that modulation of the macrocycle conformation is an effective means to fine-tune the cofactor properties *in vivo* and to utilize the same cofactor for different chemical reactions.[3]

Analysis of the various porphyrin–protein structures revealed distinct tetrapyrrole conformations for the chlorophylls in photosynthetic antenna and reaction center complexes, results that often correlate with physicochemical studies; *e.g.*, the unidirectionality of the electron transfer in the reaction center.[3b] The heme proteins of respiration show considerable motion and flexibility of the macrocycles depending on environment, spin state, and axial ligands, and planar and non-planar porphyrins have been identified *in vivo*. Similar results were found for cytochromes involved in electron transfer reactions. For several functional classes of heme proteins a conservation of the porphyrin conformation, *i.e.* a distinct type of distortion, was observed.[4] Examples with a high degree of conformational flexibility were found for vitamin B_{12} derivatives and other corrins and very specific conformational changes have been identified for the sirohemes present in nitrite and sulfite reductase. Evidence now firmly points towards a conformational control of the biological function in these cases.[2–4]

Highly substituted porphyrins

Since the first structural analyses of porphyrins an expanding body of structural data for tetrapyrroles as isolated molecules and in proteins has illustrated the considerable flexibility of the molecules and the significant distortions that can be imposed on tetrapyrrole macrocycles by crystal packing, metalation, steric effects, or protein constraints.[5,6] In fact, a closer look at the many available crystal structures of tetrapyrroles reveals that a planar porphyrin macrocycle is more the exception than the rule.

In order to correlate any physicochemical changes associated with macrocycle distortion it became necessary to look at appropriate biomimetic model compounds and to specifically design conformationally distorted tetrapyrroles. Fig. 1 outlines the many chemical means by which the macrocycle conformation may be altered.

In the early nineties I was working with Kevin Smith at UC Davis and initially concentrated on the investigation of the

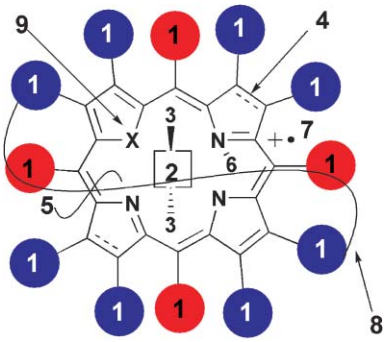
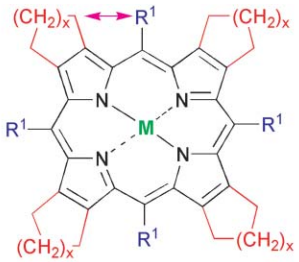


Fig. 1 Possibilities for chemically altering the macrocycle and core conformation of porphyrins. Variations can be achieved by different means: 1) introduction of sterically demanding substituents; 2) metalation; 3) axial ligands; 4) degree of reduction; 5) alteration of the conjugated system; 6) N-substitution; 7) cation radical formation; 8) "strapping" of the macrocycle *via* covalent linkage of the *meso* or β pyrrole positions; 9) heteroatom substitution.

conformational flexibility of photosynthetic pigments.[7] At that time the Davis group together with those of Jack Fajer (Brookhaven) and John Shelnutt (Sandia) was working on the synthesis and characterization of symmetrically dodecasubstituted porphyrins, the archetypical class of so-called highly substituted porphyrins.[8] Such compounds are easily accessible by standard porphyrin condensation reactions using β-substituted pyrroles (red residues in Fig. 1) and aldehydes carrying the *meso*-substituent (blue residues in Fig. 1). I became intrigued by the structural chemistry of these compounds and used the potential of the Davis crystallographic facility for high-throughput structural analyses of such chromophores. A combination of synthesis (Smith's group), NMR spectroscopy (Medforth/Smith), resonance Raman spectroscopy and molecular mechanics calculations (Shelnutt's group) and many crystal structure determinations (Senge/Smith, UCD and Barkigia/Fajer, BNL) aided by frequent Fedex mailings quickly established the basic structural and chemical characteristics of these highly substituted porphyrins.[8f]

One of the most versatile and typical compounds turned out to be 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetraphenylporphyrin $H_2\mathbf{L}^3$ (H_2OETPP). This compound can be considered a composite of the well-known standard porphyrins tetraphenylporphyrin (H_2TPP, $H_2\mathbf{L}^1$) and octaethylporphyrin (H_2OEP, $H_2\mathbf{L}^2$) where the close proximity of β- and *meso*-substituents should give rise to significant *peri* interactions.[8]

Indeed, all initial crystal structures of dodecasubstituted porphyrins related to $\mathbf{L}^3$ exhibited quite non-planar macrocycles. While the observation of distorted macrocycles was nothing new[2,5,6] we were astonished to see to what an extent the porphyrin macrocycle could be distorted while still retaining the basic chemical properties of a heteroaromatic system. Fig. 2 shows the molecular structure of the copper complex $Cu^{II}\mathbf{L}^3$, and illustrates the degree of out-of-plane distortion found in such systems.[8d,9] Compounds of this type typically show displacements of the β pyrrole positions of >1 Å and are characterized by an alternating displacement of the pyrrole units above and below the mean plane. In a first approximation this so-called *sad* distortion[6b] is typical for



ML^{1} R^1 = Ph, R^2 = H
ML^{2} R^1 = H, R^2 = Et
ML^{3} R^1 = Ph, R^2 = Et
ML^{4} R^1 = R^2 = Ph
ML^{5} R^1 = Ph, R^2 = Br
ML^{6} R^1 = NO_2, R^2 = Et
ML^{7} R^1 = Bu^t, R^2 = H
ML^{8} R^1 = Bu, R^2 = H
ML^{9} R^1 = Bu, R^2 = Et

ML^{10} R^1 = pentyl, x = 1
ML^{11} R^1 = 3,4,5-triMeO-Ph, x = 1
ML^{12} R^1 = 3,4,5-triMeO-Ph, x = 2
ML^{13} R^1 = 3,4,5-triMeO-Ph, x = 3

dodecasubstituted porphyrins with *meso* sp^2-hybridized substituents. The most significant structural differences compared to planar porphyrins are a smaller core size, an increase in the C_m–C_a–C_b angle and smaller N–C_a–C_m and M–N–C_a angles.

Investigation of various OETPP derivatives showed that the degree of distortion can be influenced by different metals (larger metals leading to less distortion),[9b] oxidation to π cation radicals (increase in non-planarity and changes in distortion modes),[9c] changes in spin state,[9d] and that similar conformations are found in solution and in the solid state.[9e]

The non-planar distortions are clearly a result of the *meso*–β *peri*-type interactions. Structural investigations of the porphyrins $Cu^{II}L^{11}$–$Cu^{II}L^{13}$ with differently sized –CH_2– straps at the β positions showed non-planar distortions for x = 2,3 and a planar conformation for $Cu^{II}L^{11}$ which has the smallest C_b–C_b–CH_2 angles and thus the least degree of steric hindrance (Fig. 3).[8e,10]

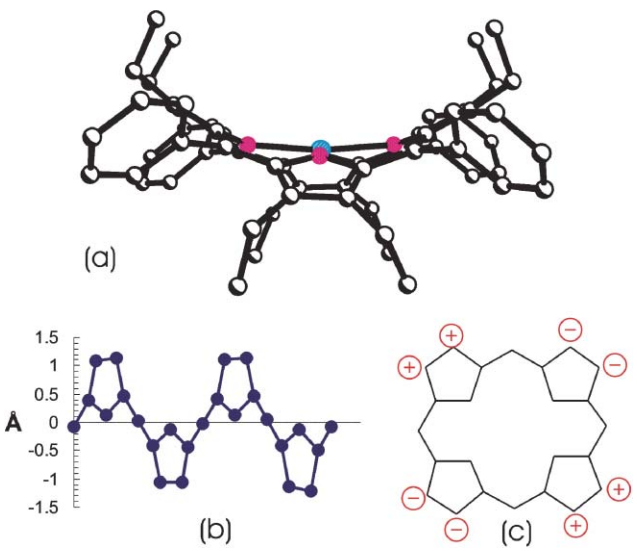


Fig. 2 Illustrations of the molecular structure and conformation of $Cu^{II}L^{3}$. (a) Side view of the porphyrin in the crystal. (b) Linear display of the skeletal deviations of the macrocycle atoms. (c) Illustration of the *sad* (saddle) distortion mode.[9b]

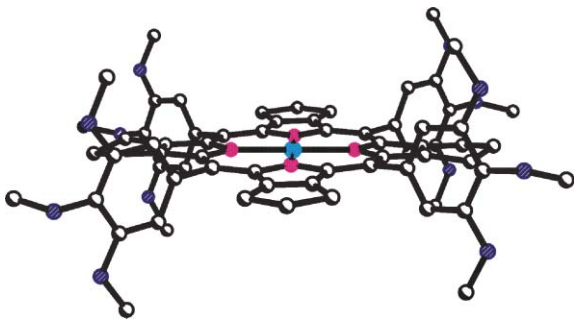


Fig. 3 Side view of the molecular structure of $Cu^{II}L^{11}$.[10b]

An important feature of the non-planar structures is the formation of cavities above and below the porphyrin core. Together with the upward tilting of the N–H vectors this makes such compounds versatile ligands for supramolecular chemistry (formation of clathrates and nanochannels filled with solvate molecules) and the binding of small molecules. Almost all compounds of this type crystallize with solvate molecules and a typical example is given by a structure of dodecaphenylporphyrin (H_2L^4)[11] where ethanol molecules are hydrogen bonded to the pyrrole nitrogen atoms (Fig. 4).[11b] Studies of this ligand also indicated the considerable conformational flexibility inherent in such systems. Indeed, Fajer and co-workers showed that a wide variety of different conformational surfaces [*sad*, *wav* (wave), *etc.*] were found within a single family of compounds with the same peripheral substituents.[11c]

Many other dodecasubstituted macrocycles have been used in these studies.[5] For example, β-halogenated *meso*-arylporphyrins (*e.g.*, ML^5)[12] have elicited widespread interest due to their potential as oxidation catalysts and we found 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetranitroporphyrin (H_2OETNP, H_2L^6) to be a versatile compound for studying metal and axial ligation effects.[13] For example, a comparison of the conformation of the severely distorted free base H_2L^6 with the respective $Tl^{III}L^6$(Cl) complex [Fig. 5(a)] illustrates the severity of metal effects. Here, the large sitting-atop metal manages to almost planarize the macrocycle, resulting in a more domed conformation albeit with widened C_a–C_m–C_a

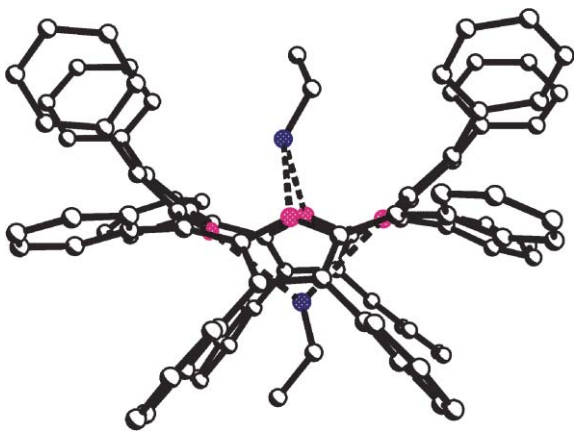


Fig. 4 Side view of the molecular structure of the ethanol solvate of H_2L^4.[11b]

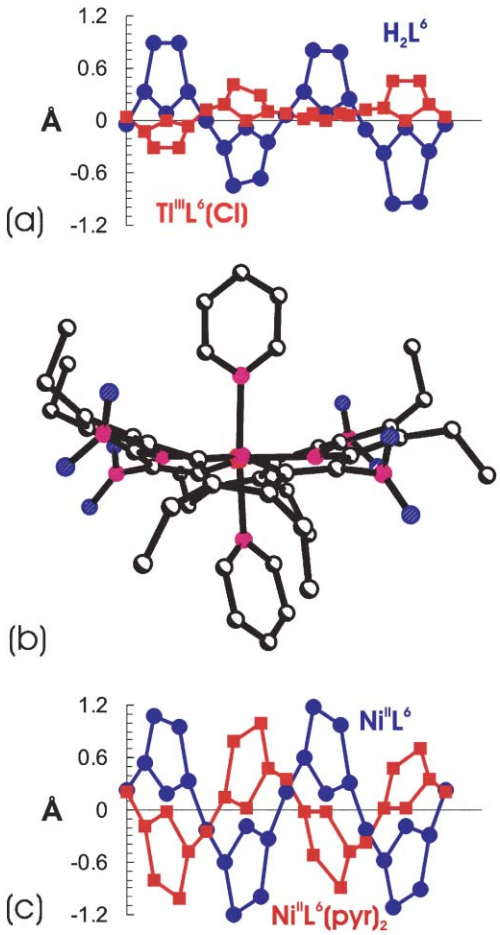


Fig. 5 (a) Skeletal deviation plot of $H_2\mathbf{L^6}$ (●, blue) *vs.* $Tl^{III}\mathbf{L^6}(Cl)$ (■, red). (b) View of the molecular structure of $Ni^{II}\mathbf{L^6}(pyr)_2$. (c) Skeletal deviation plot of $Ni^{II}\mathbf{L^6}$ (●, blue) *vs.* $Ni^{II}\mathbf{L^6}(pyr)_2$ (■, red).[13]

angles (*i.e.*, in-plane distortion compared to unhindered Tl^{III} porphyrins).[13a,f] This clearly shows the multitude of conformational landscapes available for non-planar porphyrins and the amazing flexibility of the porphyrin system to accommodate different conformations.

Likewise, the combination of electron withdrawing substituents and non-planar conformations could be used for the formation of self-assembled supramolecular, 3D polymeric forms of $[Zn^{II}\mathbf{L^6}]_n$ and $[Co^{II}\mathbf{L^6}]_n$.[13b,c] Of more biological relevance was the identification of subtle differences that can be imposed on the macrocycle conformation *via* spin state changes, axial ligand interactions, crystal packing, and hydrogen bonding.[13c–e] Many tetrapyrrole-containing enzymes undergo cofactor spin changes during the catalytic cycle. Fig. 5 shows that conversion of the low spin (4-coordinate $Ni^{II}\mathbf{L^6}$) to the high spin (6-coordinate) form [Fig. 5(b)], which is accompanied by an increase in the Ni–N bond lengths, results in an overall decrease of non-planarity.

A closer inspection of the Ni^{II} complexes in Fig. 5(c) indicates some ''twisting'' of the pyrrole rings in addition to the *sad* distortion. Indeed, such a *ruf* (ruffled) deformation is frequently found in metalloporphyrins, typically as a result of the binding of metal ions that are too small for the core and thus tend to shorten the M–N bonds resulting in a twist about the C_b–C_b axes and large out-of-plane displacements for the *meso* atoms.[6a,b] For example, $Ni^{II}\mathbf{L^{10}}$ exhibited a *ruf* conformation but the presence of the small Ni^{II} made it difficult to distinguish between metal and steric effects.[11a]

The first structure of a porphyrin with *ruf* distortion induced solely by steric effects was obtained in the course of studies on 5,10,15,20-tetraalkylporphyrins with *meso*-substituents of different steric demand (*e.g.*, Bu, *s*-Bu, *i*-Pr, *t*-Bu, *etc.*).[14] As shown in Fig. 6, $Zn^{II}\mathbf{L^7}$(pyr) exhibits a *ruf* distorted macrocycle with displacements of the *meso* carbons of up to 1 Å. A closer look even reveals smaller degrees of out-of-plane displacements for the porphyrin side bearing the pyridine, indicating the structural influence of axial ligands. In very general terms this type of distortion is most often found for sterically hindered porphyrins with bulky sp^3-hybridized *meso*-substituents (or as the result of small metal effects).

Clearly, simple up and down tilting of the pyrrole units is not the only way to distort a porphyrin. From metal coordination studies it was known that other types of distortion modes can occur, the most prominent ones being *sad*, *ruf*, *dom* (domed), and *wav* distortions.[6a,c] A more detailed analysis based on a normal-coordinate structural decomposition (NSD) was developed by Shelnutt.[4,5e] This method characterizes structures in terms of the normal modes of vibration of the molecule. In a simplified form it reveals six main types of out-of-plane distortion: *sad*dle (B_{2u}), *ruf*fled (B_{1u}), *dom*ed (A_{2u}), *wav*e [*wav*(x) $E_g(x)$ and *wav*(y), $E_g(y)$], and *pro*peller (A_{1u}).[15] Illustrations of the *dom* and *wav* type distortion modes are given in Fig. 7. Typically these six types (or a combination thereof) serve to describe the non-planar conformations of porphyrins and NSD has since become the standard tool to classify and compare porphyrin conformations.

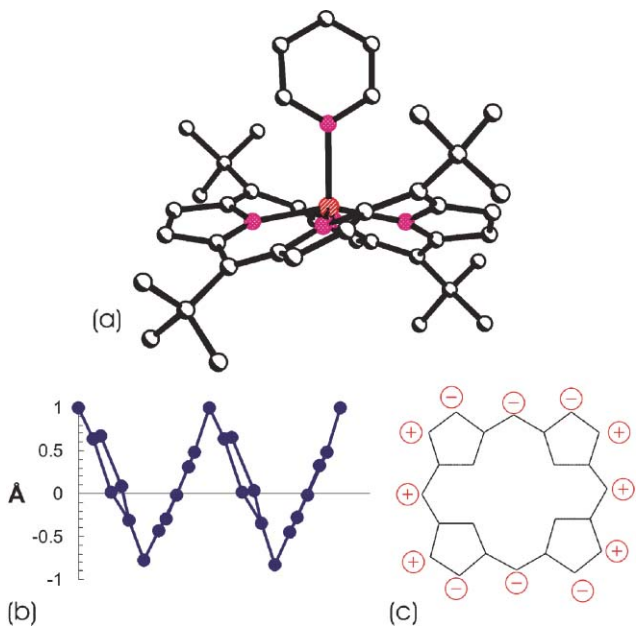


Fig. 6 Illustrations of the molecular structure and conformation of $Zn^{II}\mathbf{L^7}$(pyr). (a) Side view of the porphyrin in the crystal. (b) Linear display of the skeletal deviations of the macrocycle atoms. (c) Illustration of the *ruf* distortion mode.[14b]

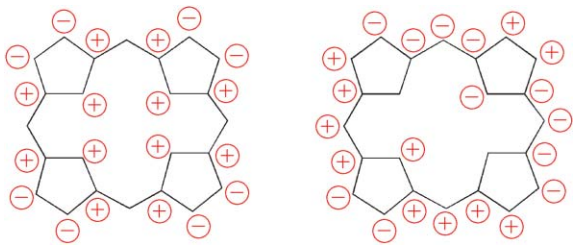
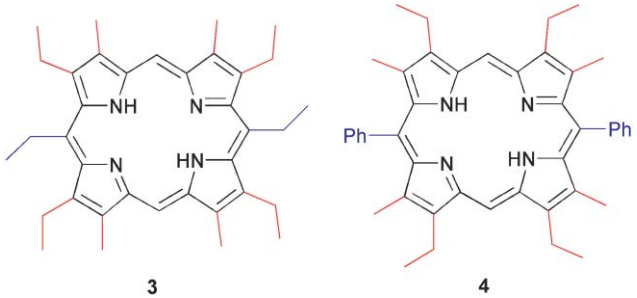


Fig. 7 Illustrations of the *dom* (left) and *wav* (right) distortion modes.

To a lesser degree the structural and conformational consequences of steric strain at the periphery of highly substituted porphyrins are also found in porphyrins with *peri* interactions in only one, two, or three *meso* quadrants (*e.g.*, nona-, deca- or undecasubstituted porphyrins or chlorins).[16] To some extent the conformational effects are localized in individual quadrants. Nevertheless, the structural effects of individual substituents are not simply additive and the conformational landscapes for macrocycles with different substituent patterns can vary considerably.[16f]

An important observation was made upon the structural analysis of 2,3,***5***,7,8,12,13,17,18-nona- and 2,3,***5***,7,8,12,13,***15***,17,18-decasubstituted porphyrins (*e.g.*, **3** or **4**). A rudimentary inspection of their crystal structures reveals a flat macrocycle despite the presence of steric hindrance in two quadrants. However, a closer analysis showed that a significant degree of in-plane distortion had taken place.[16d–f] This is illustrated in Fig. 8, which shows that the core of the macrocycle **3** is elongated ("stretching").[16d] The two N vectors are not equivalent anymore and notably a widening of the C_a–C_m–C_a angles in the quadrants without steric interactions has taken place. Thus, both in-plane *and* out-of-plane distortions have to be taken into account when describing porphyrin conformations. In terms of Shelnutt's NSD analysis this requires additional analysis of the lowest frequency in-plane modes [B_{2g}, B_{1g}, $E_u(x)$, $E_u(y)$, A_{1g}, A_{2g}]. This effect is most pronounced in porphyrins with *meso* sp^3 substituents. Related 5(,15)-(di)aryl substituted porphyrins exhibit smaller in-plane distortions. However, in contrast to other porphyrins, they typically show a tilting of the *meso*-aryl residues out of the mean plane resulting in a quasi *anti* orientation of the *meso*-aryl residues [Fig. 8(b)].[16e–g]



3 **4**

So, how much can we distort the porphyrin macrocycle or is there a breaking point? In order to address this question we prepared porphyrins that possess both peripheral and core steric strain. Examples of the latter are N-substituted porphyrins and the porphyrin (di)cations.[17] In fact, simple protonation of a "planar" porphyrin such as H_2TPP or

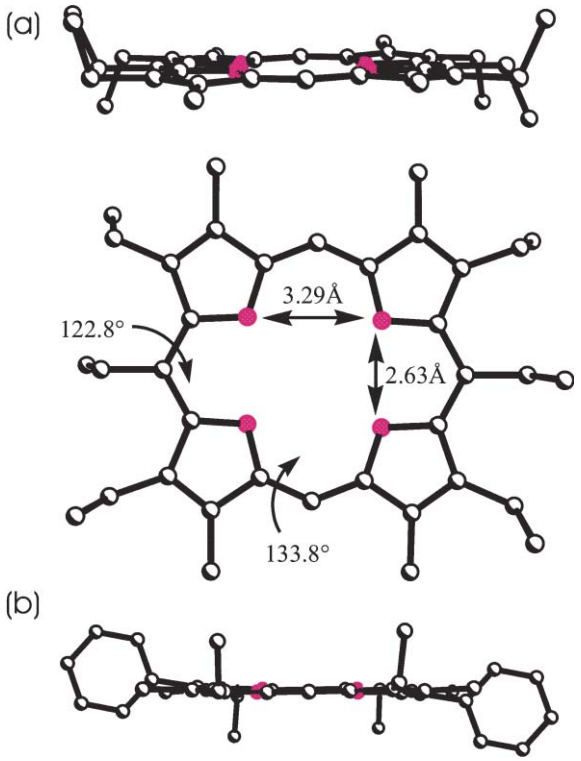


Fig. 8 Decasubstituted porphyrins. (a) Top and side view of the molecular structure of **3**.[16b] (b) Side view of the molecular structure of **4**.[16d]

H_2OEP results in the formation of highly non-planar structures, often of the *sad* type, as the four hydrogen atoms do not have enough space in the 4N core unit.[17b] Fig. 9(a) shows illustrations of the molecular structure of the ditrifluoroacetate salt of $\mathbf{L^5}$, one of the most non-planar porphyrins described so far. A comparison with the related dication of TPP $[H_4\mathbf{L^1}]^{2+}$ [Fig. 9(b)] shows that additional effects of the peripheral substituents are clearly present. A comparison of dodecasubstituted free base porphyrins with the respective dications showed core protonation to result in an increase in non-planarity by 13–25% depending on the type of macrocycle.[18a] This effect is more pronounced in sterically unhindered systems and can reach up to 300% for TPP, indicating that there is a maximum degree of distortion for porphyrins.

An ongoing systematic analysis of porphyrin dications showed that different macrocycle systems can exhibit quite distinct conformational flexibilities.[18] For example, the Δ24 values[18c] for OEP dications range from 0.02–0.33 Å indicating quite different conformations. In contrast TPP dications showed only a moderate degree of flexibility (Δ24 = 0.42–0.52 Å) while $[H_4OETPP]^{2+}$ showed almost none (Δ24 = 0.61–0.63 Å).[18a]

More drastic effects of the peripheral substituents are observed in the dications of 5,10,15,20-tetraalkyl substituted porphyrins.[18b] Protonation of (planar) free base porphyrins with primary or secondary alkyl residues results in *sad* distorted porphyrin dications with Δ24 = 0.37–0.47 Å {*e.g.*, $[H_4\mathbf{L^8}][C_2F_3O_2]_2$ in Fig. 9(c)}. However, protonation of the

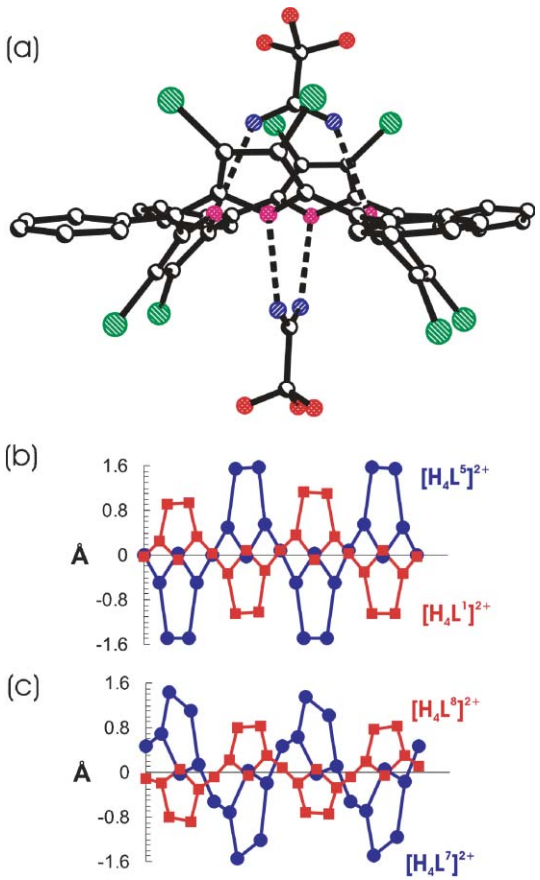


Fig. 9 Porphyrin dications. (a) View of the molecular structure of $[H_4\mathbf{L}^5][C_2F_3O_2]_2$.[18a] (b) Linear display of the skeletal deviations in $[H_4\mathbf{L}^5][C_2F_3O_2]_2$ (●, blue) *vs.* $[H_4\mathbf{L}^1][ClO_4]_2{\cdot}CH_3OH$ (■, red).[18a] (c) Linear display of the skeletal deviations in $[H_4\mathbf{L}^7][C_2F_3O_2]_2{\cdot}2CF_3CO_2H$ (●, blue) *vs.* $[H_4\mathbf{L}^8][C_2F_3O_2]_2{\cdot}2CF_3CO_2H$ (■, red).[18b]

severely *ruf* distorted *tert*-butyl free base ($H_2\mathbf{L}^7$)[19] results in significant changes in the type and composition of the distortion modes. Here protonation leads to an additional *sad* distortion (with C_b displacements of 1.3 Å) while retaining a substantial degree of *ruf* distortion (C_m displacements of 0.5 Å). Thus, both the degree and type of distortion in a given free base macrocycle can be altered by core substitution.

Even more core strain can be imposed on the macrocycle by introducing bulkier substituents in the core.[20] This can be easily achieved by N-alkylation; *e.g.*, with methyl triflate or methyl iodide. Fig. 10(a) shows a comparison of the trimethylated monocations of TPP and OETPP. Again the higher degree of non-planarity in the peripherally dodecasubstituted porphyrin is evident. A comparison of free base OETPP ($\Delta 24 = 0.54$ Å) with its N-methylated derivatives (di-, tri-, tetramethyl: $\Delta 24 = 0.59$–0.61 Å) indicates that the additional distortion that can be imposed on the macrocycle is limited.[20a,b] Another example of the peculiar conformations that may be imposed on β-octasubstituted porphyrins is shown in Fig. 10(b). In $[Me_2H\mathbf{L}^2][F_3CSO_3]$ the two *N*-methyl groups are located at neighboring nitrogen atoms (N21, N22) resulting in severe distortion in only one half of the macrocycle.[20a]

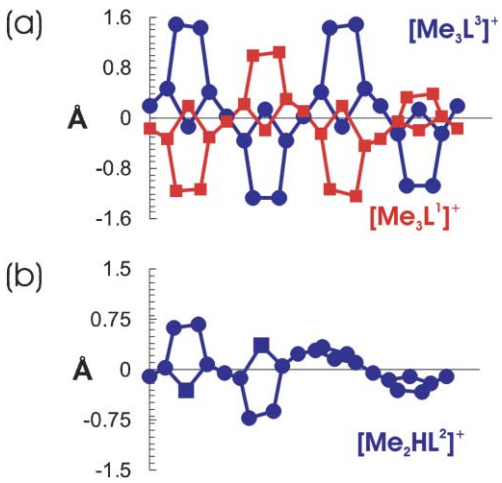


Fig. 10 Illustration of the macrocycle conformation in *N*-alkylporphyrin monocations. (a) Linear display of the skeletal deviations in $[Me_3\mathbf{L}^3][H_3CSO_4]$ (●, blue)[20a] *vs.* $[Me_3\mathbf{L}^1][F_3CSO_3]$ (■, red).[20c] (b) Linear display of the skeletal deviations in $[Me_2H\mathbf{L}^2][F_3CSO_3]$. Large ■ indicate *N*-methyl groups.[20a]

Physicochemical properties

As shown, significant changes in the conformation can be imposed on the porphyrin macrocycle by various means. But what does this imply for the physical and chemical properties of these non-planar systems? Several groups have been active in this area and thus I will only highlight the most prominent effects.[21] The most notable result of macrocycle distortion is a bathochromic shift of the absorption spectrum. In fact, the simplest classroom experiment on porphyrin non-planarity is using a standard (planar) porphyrin and adding a drop of acid to form the non-planar dications. The red solution immediately turns bright green. The red shifts are a result of a destabilization of the π system leading to a smaller HOMO–LUMO gap.[8d,22] Although discussed controversially over the years for most non-planar porphyrins such a (non-linear) correlation can be established between distortion and red shifts.[21a] For example, the Soret and Q_0 absorption bands in the *n*-butyl derivative $H_2\mathbf{L}^8$ are 417 and 659 nm compared to 446 and 691 in the *t*-Bu derivative $H_2\mathbf{L}^7$.[14a]

Naturally, an important question here is the correlation between solid state structural data and the conformation in solution. Shelnutt's group has employed resonance Raman spectroscopy and molecular mechanics calculations in numerous studies to show that similar distortions are found in solution.[4,9e] Likewise, EXAFS spectroscopy was used to determine the Ni–N bond lengths (which become shorter with increasing macrocycle distortion) in the highly ruffled $Ni^{II}\mathbf{L}^9$ and showed the same Ni–N bond lengths (1.87 Å) in solution and the crystalline state (see Fig. 11).[22] This compound also exhibited another well established consequence of macrocycle distortion, namely that non-planar porphyrins are easier to oxidize than their planar counterparts.[6c,8d,21b,22] This has important implications for applications in catalysis as such systems are capable of stabilizing metals in high oxidation states.

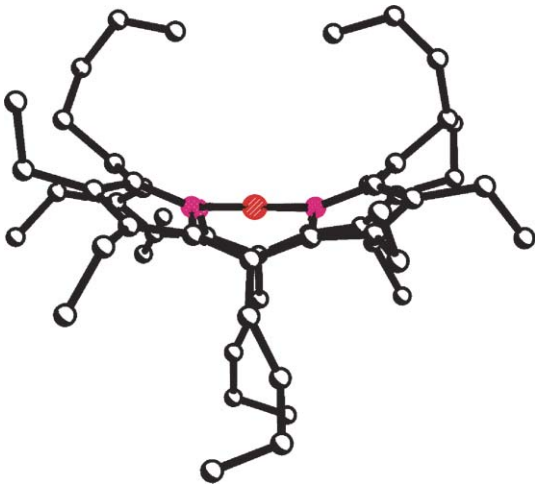


Fig. 11 Side view of the molecular structure of $Ni^{II}L^{9}$.[22]

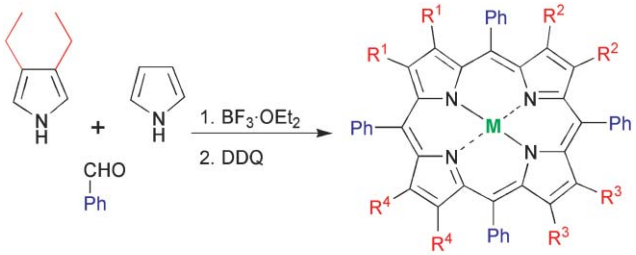
NMR studies have shown the presence of numerous dynamic processes (*e.g.*, rotation of aryl substituents and inversion of the macrocycle) and strong intramolecular N–H bonding as a result of core contraction in H_2L^7 where, in contrast to the *sad* distorted porphyrins, the pyrrole hydrogen atoms remain in the 4N plane.[21c] Intriguingly, despite the significant out-of-plane displacements observed in such systems the decrease in ring current of the aromatic system is only moderate.[21d] Time-resolved EPR of the photoexcited triplet states points towards multiple conformations in the excited state[21e,f] and similar indications have been found in many other photophysical studies by Holten and co-workers.[21g] Almost all photophysical parameters are directly affected by macrocycle distortion. In general terms, non-planar porphyrins have significantly lower fluorescence yields, large Stokes shifts, and shorter lifetimes of the lowest excited state. This is a result of faster intersystem crossing and internal conversion. These results clearly indicate that macrocycle distortion directly affects properties related to biological processes such as exciton transfer or redox reactions.

In order to clearly establish correlations between deformation and physical properties, series of porphyrins with graded degrees of distortion were needed. One example is the *meso*-alkylporphyrins mentioned above and another is a series of 5,10,15,20-tetraphenylporphyrins with an increasing number of β-ethyl groups prepared by us (XETPPs, Scheme 1).[23] Investigation of this series showed that chemical, redox, spin, static and dynamic optical properties change systematically with increased macrocycle distortion.[21f,23,24,25a]

This series also served to illustrate the importance of the regiochemical substituent arrangement on the macrocycle conformation. As shown in Fig. 12, having the four β-ethyl groups at the 2,3,7,8-positions (H_2L^{16} with 1 × Et–Ph–Et + 2 × Et–Ph–H *peri* interactions) leads to a more non-planar and unsymmetrical conformation than in the case of the 2,3,12,13-tetraethyl derivative (H_2L^{15}, 4 × Et–Ph–H).[23]

Chemical reactivity and conformation

Bending the porphyrin macrocycle not only alters its physicochemistry but also its chemical reactivity. The most



		M = 2H: λ_{max}/nm	Δ24/Å
ML^1	$R^1 = R^2 = R^3 = R^4 = H$	417, 647	0.05 (tricl.)
ML^{14}	$R^1 = Et, R^2 = R^3 = R^4 = H$	420, 645	0.10
ML^{15}	$R^1 = R^3 = Et, R^2 = R^4 = H$	426, 649	0.29
ML^{16}	$R^1 = R^2 = Et, R^3 = R^4 = H$	433, 672	0.38
ML^{17}	$R^1 = R^2 = R^3 = Et, R^4 = H$	444, 683	0.46
ML^3	$R^1 = R^2 = R^3 = R^4 = Et$	446, 686	0.54

Scheme 1 Synthesis of the XETPP series and main electronic absorption bands and Δ24 values for the free base porphyrins.[23]

fundamental consequences of large *sad* distortions are an increased basicity and faster metalation rates. In fact, some non-planar porphyrins can be protonated by water,[8a] while metalation rates can be several orders of magnitude faster.[26a] Thus, some standard metalation reactions can be performed by simply stirring the free base with metal salts for a few minutes at room temperature.[23] The latter effect has considerable relevance for ferrochelatase, where macrocycle distortion and out-of-plane tilting of the N–H vectors is believed to be a critical step of the reaction mechanism.[26b] Formation of the superstructured cavities above and below the porphyrin core also prevents some reactions that are observed for other porphyrins, *e.g.*, π–π aggregation or the formation of μ-oxo dimers. Similarly, the smaller core size of non-planar porphyrins aids the stabilization of small metal ions[26c] but results in lower stability for complexes with larger metal ions.[9b,26d]

As mentioned above, highly substituted porphyrins still undergo "normal" porphyrin reactions such as protonation, metalation, N-substitution, and standard β-substitution reactions.[27] Another example is the classic diimide reduction of non-planar porphyrins to chlorins (hydroporphyrins).[25] Reduction of the compounds shown in Scheme 1 gave all different regioisomers up to the hydrochlorins related to L^{17} (*e.g.*, **5** and **6** derived from H_2L^{16}).[25a] As indicated in Fig. 13, reduction often leads to an increase in non-planarity (compare chlorins in Fig. 13 with parent porphyrin H_2L^{16} in Fig. 12).

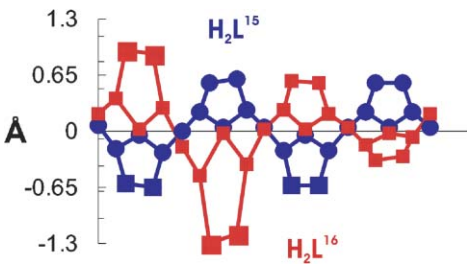


Fig. 12 Linear display of the skeletal deviations in H_2L^{15} (●, blue) *vs.* H_2L^{16} (■, red). Larger ■ indicate β-ethyl residues.[23]

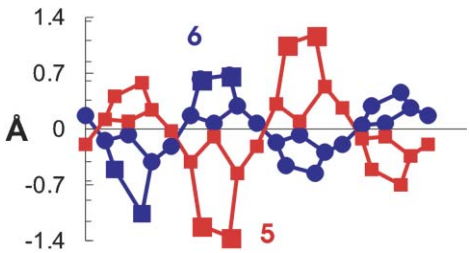
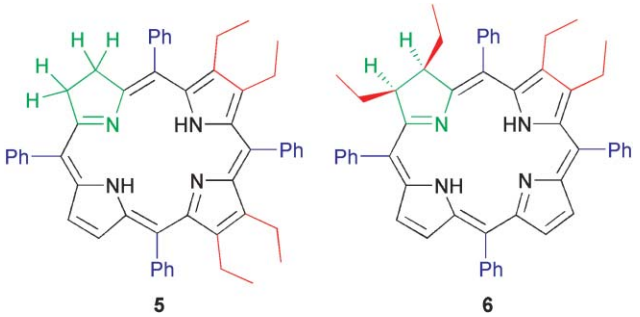
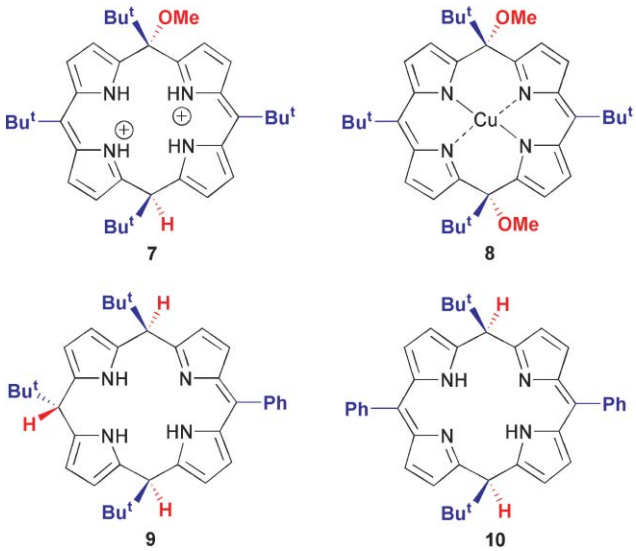


Fig. 13 Non-planar chlorins. Linear display of the skeletal deviations in **6** (●, blue) *vs.* **5** (■, red). Larger ■ indicate β-ethyl residues; reduction had occurred in the leftmost pyrrole ring.[25]

Chlorins generally show a higher degree of conformational flexibility than porphyrins.[3b,5d,7a] These structures again indicated the importance of the regiochemistry and substituent arrangement. For example, reduction of unsubstituted pyrrole rings led to more conformational distortion while reduction of β-ethyl substituted ring systems led to slightly less non-planarity compared to the porphyrins. The more non-planar porphyrins yield increasingly unstable chlorins. Similarly, simple *meso*-alkylporphyrins such as $H_2\mathbf{L}^8$ gave the respective chlorins and bacteriochlorins[25b] while reduction of $H_2\mathbf{L}^7$ resulted in the formation of the porphyrinogen (5,10,15,20,22,24-hexahydroporphyrin, "calixpyrrole").[25a]



The steric strain imposed on the systems also gives rise to novel, porphyrin atypical reactions, notably for porphyrins with very large *ruf* distortions. During our initial studies to crystallize tetra-*tert*-butylporphyrin in the presence of alcohols we noted the formation of porphodimethenes[28] ("calixphyrins").[14a] For example, an attempt to prepare the dication $[H_4\mathbf{L}^7]^{2+}$ by treating $H_2\mathbf{L}^7$ with $HClO_4$ in CH_3OH–$CHCl_3$ resulted in the quantitative formation of $[\mathbf{7}][ClO_4]_2$ in the crystallization tube. Here a methanol had been added to two opposite *meso* carbon atoms in a *syn* orientation under disruption of the aromatic system, effectively moving two *tert*-butyl groups as far out of the macrocycle plane as possible (Fig. 14). Similar structures were obtained from metalation experiments with $H_2\mathbf{L}^7$ in polar solvents. One example is the formation of **8** in a methanolic solution of $Cu(OAc)_2$. In contrast, the more planar porphyrins ($\mathbf{L}^8$) or *sad* distorted porphyrins such as $\mathbf{L}^3$ underwent "standard" porphyrin reactions. This increased reactivity is clearly a consequence of the steric strain at the *meso* positions and has recently been used by Neya and Funasaki to develop a new synthesis of unsubstituted porphyrin (porphine) *via* acid-catalyzed dealkylation of $H_2\mathbf{L}^7$.[29a] Other atypical reactions[30] of *meso*-alkylporphyrins have been found by Smith and co-workers during β-bromination reactions.[29b]



An influence of the conformation on the reactivity was also noted during the synthesis of highly ruffled porphyrins. Typically S_4 symmetric non-planar porphyrins have been prepared *via* standard acid-catalyzed pyrrole condensation reactions followed by oxidation, or alternatively *via meso*- or β-polyhalogenation or -nitration reactions.[2] However, attempts to synthesize sterically strained

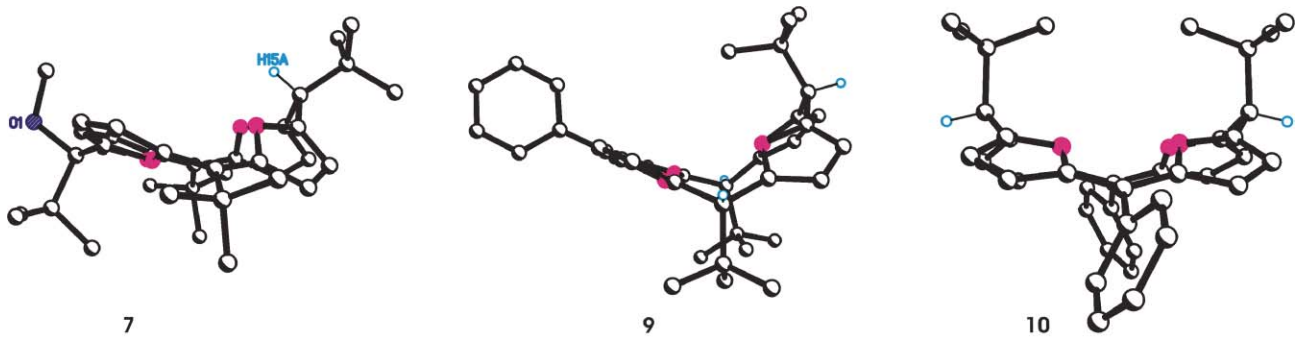


Fig. 14 Side views of the molecular structure of the porphodimethene **7** (dication ligand only),[14a,e] the porphomethene **9** and the porphodimethene **10**.[31]

dodeca*alkyl*porphyrins using condensation reactions either failed or resulted in the formation of porphodimethenes that could not be oxidized to porphyrins.[11a]

Even more surprising observations were later made by us during condensation reactions to yield *meso*-*tert*-butyl substituted porphyrins. While such condensation reactions worked well for the symmetric H_2**L**^{7}, the condensation of *t*-BuCHO plus a sterically *less* hindered aldehyde (*e.g.* PhCHO) with pyrrole to yield porphyrins with a mixed substituent pattern failed. Besides the S_4 symmetric porphyrins and porphyrins with one *t*-Bu group only, oxidation resistant porpho(di)methene macrocycles with mixed substituents (*e.g.*, **9** and **10**) were formed.[14c,31] The structures of **9** and **10** (Fig. 14) indicate that oxidation occurred easily in the sterically unhindered quadrants of the molecule while the *t*-Bu groups again are almost orthogonal to the mean plane.[31]

An excursion to synthesis

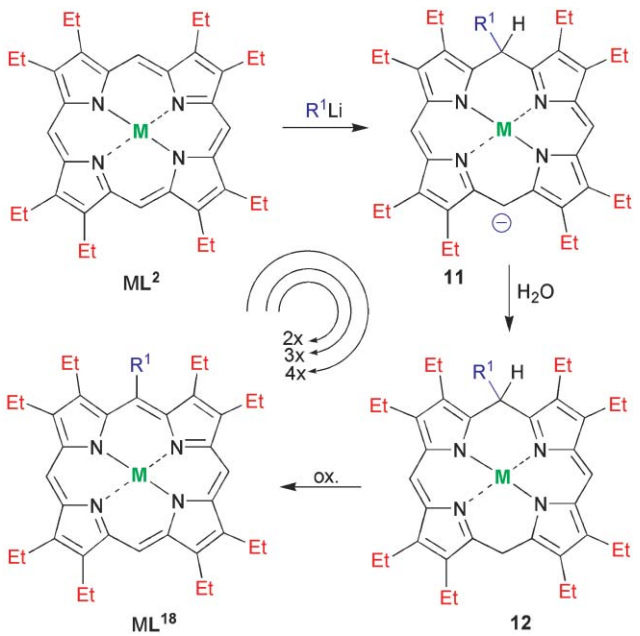
But we are getting ahead of the story. By 1998 I had been working at the FU Berlin for several years and we had more or less finished studies on the OETPP, OETNP, XETPP, and *meso*-alkylporphyrin series. Rather we concentrated on photosynthetic model compounds, namely electron transfer models[16c,32] and cofacial bischlorins as mimics for the special pair[16b] in photosynthesis. In the intervening years we had taken a first glance at the conformation of porphyrins with an intermediate degree of substitution/distortion and continued the conformational studies described above.[33] Nevertheless, we had reached an impasse with regard to novel studies on porphyrin non-planarity. Although we were keenly interested in studying sterically strained dodecaalkyl substituted porphyrins and non-planar porphyrins with different types and regiochemical arrangement of *meso*-substituents these were synthetically inaccessible. Macrocycles such as **L**^{19} with four different *meso*-substituents should show a mix of different distortion modes and be more akin to the situation found in natural unsymmetrical pigments with mixed distortion modes.[2–4,5b]

In the absence of any reliable syntheses for such compounds we decided to develop appropriate methodologies. Easier said than done, this occupied us for almost six years but ultimately led to a general concept for the preparation of a wide variety of different porphyrin types. To make a long story short, an investigation of organometallic coupling reactions showed the utility of RLi reagents for the substitution of unactivated porphyrins.[34]

We found that porphyrins react readily with organolithium reagents, preferentially at the *meso* positions. The overall reaction with OEP is a nucleophilic substitution and proceeds *via* initial reaction of the organic nucleophile with a *meso* carbon, yielding an anionic species **11** which is hydrolyzed to a porphodimethene (5,15-dihydroporphyrin, **12**), formally constituting an addition reaction to two C_m positions.[34b] Subsequent oxidation yields *meso*-substituted porphyrins M**L**^{18}. The reaction is highly versatile, is accomplished in high, often quantitative yields with various alkyl- or aryllithium reagents and can be applied to both free base porphyrins and a variety of metal complexes. Even more importantly, this reaction can be used in sequence for the introduction of 1, 2, 3 or 4 (different) *meso*-substituents giving an entry into almost any desired *meso*-substituted porphyrin including some unusual types of macrocycles (Scheme 2).[35,36]

Thus, one of the first studies involved the synthesis of M**L**^{19} with different numbers and regiochemical arrangements of butyl groups. The Ni^{II} porphyrins Ni^{II}**L**^{20}–Ni^{II}**L**^{23} were prepared by successive reaction with BuLi and in the last step gave the dodecaalkyl substituted porphyrin Ni^{II}**L**^{9} mentioned earlier.[22,34a] Similar to the mostly *sad* distorted XETPP series, this gave a range of compounds with increasing *ruf* distortion accompanied by bathochromic shifts of the absorptions bands. Again, the 5,10-substituted derivatives exhibited a larger degree of non-planarity than the 5,15-derivatives. Fig. 15 shows the conformation of Ni^{II}**L**^{9} and indicates the significant *meso* displacements encountered in such porphyrins. The type and degree of distortion is very similar to those found for **L**^{3} (see Fig. 6).

In addition to opening a new route to *meso*-substituted porphyrins these studies revealed another example of the influence of the tetrapyrrole conformation on the reactivity. For example, reaction of the Ni^{II}OEP derivatives Ni^{II}**L**^{2},



Scheme 2 S_NAr reaction of porphyrins with RLi. The reaction sequence can be repeated until all *meso* positions are substituted.[34]

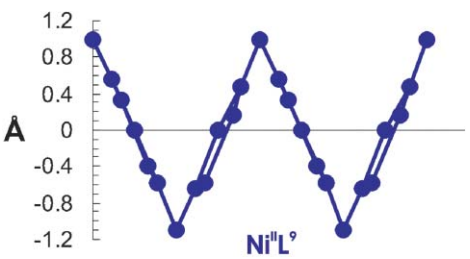
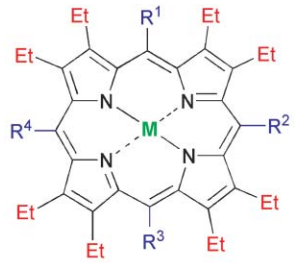
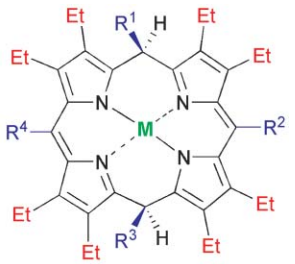


Fig. 15 Linear display of the skeletal deviations in Ni^{II}**L**^{9}.[34a]





ML^{19}
ML^{20} $R^1 = Bu$, $R^2 = R^3 = R^4$
ML^{21} $R^1 = R^3 = Bu$, $R^2 = R^4 = H$
ML^{22} $R^1 = R^2 = Bu$, $R^3 = R^4 = H$
ML^{23} $R^1 = R^2 = R^3 = Bu$, $R^4 = H$
ML^{9} $R^1 = R^2 = R^3 = R^4 = Bu$
ML^{24} $R^1 = R^3 = Ph$, $R^2 = Bu$, $R^4 = H$
ML^{25} $R^1 = R^2 = Ph$, $R^3 = R^4 = H$

ML^{26} $R^1 = R^2 = R^3 = R^4 = Bu$
ML^{27} $R^1 = R^2 = R^3 = Bu$, $R^4 = H$
ML^{28} $R^2 = R^4 = H$
ML^{29}

$Ni^{II}L^{20}$–$Ni^{II}L^{22}$ with BuLi at −80 °C generally proceeds with excellent yields. However, introduction of the fourth *meso*-butyl residue, *i.e.*, conversion of the undecasubstituted porphyrin $Ni^{II}L^{23}$ to the dodecasubstituted porphyrin $Ni^{II}L^{9}$ gave only a yield of 50% and was accompanied by the formation of the porphodimethene $Ni^{II}L^{26}$ in 40% yield.[34a] Similarly, when the reaction temperature for the preparation of $Ni^{II}L^{23}$ was raised to −30 °C, the porphodimethene $Ni^{II}L^{27}$ was formed instead in quantitative yield. All these calixphyrins were isolated as products despite the presence of oxidants (DDQ) in the reaction mixture. These compounds are stable against common oxidants and their structure is characterized by a roof-type conformation[28a] with the two *meso*-hydrogen atoms at the sp^3 hybridized centers in a *syn* diaxial orientation (Fig. 16).

Another example involves thermodynamic control of double substitution reactions. For simple, sterically unhindered porphyrins we had shown that the intermediary Meisenheimer complex **11** can be trapped *in situ* with electrophiles resulting in the introduction of two substituents (one from RLi, one from the electrophile).[37] Treatment of Ni^{II}OEP with R^1Li and R^3I at low temperatures yielded mono- or disubstituted porphyrins in the presence of DDQ. In contrast, similar reactions using elevated temperatures and longer reaction times gave the *meso*-disubstituted porphodimethenes ML^{28} in yields ranging from 20–60%. Use of the conformationally strained decasubstituted porphyrins (*e.g.*, NiL^{21}) gave the dodecasubstituted calixphyrins ML^{29} in considerably higher yields (60–80%).[38]

All stable porphodimethenes isolated so far have the configuration shown for ML^{29}. It should be remembered that porphyrin (bio)synthesis generally involves condensation to a non-aromatic porphyrinogen, which is then oxidized by successive removal of six hydrogen atoms to the fully aromatic porphyrin. Porpho(di)methenes are typical intermediates of this sequence. Clearly, the configuration and conformation of the intermediary hydroporphyrins have a crucial impact on their transformation into the aromatic porphyrins. Apparently thermodynamic control of the substitution reactions or using sterically hindered educts favors formation of the intermediary porphodimethene in a *syn* diaxial configuration that is more difficult to oxidize than the normal intermediate (presumably *anti*) of standard porphyrin synthesis.[34b,c]

A closer look—mixing distortion modes

The S_NAr methodology described above allowed the quick generation of a variety of compounds with different types, numbers and regiochemical arrangements of substituents. This put us in a position to study the effects of intermediate degrees of distortion in more detail and validate the hypotheses made earlier.[34] It also made it finally possible to study compounds with mixed substituent pattern.[39]

Indeed a substituent-induced mixing and changing of distortion modes is possible. For example, the conformation of the macrocycles $Ni^{II}L^{23}$ (three *meso*-butyl groups) is mostly *ruf*. However, exchange of two *meso*-substituents to phenyl results in a macrocycle with a considerable degree of *sad* distortion while still retaining an overall ruffled macrocycle ($Ni^{II}L^{24}$, Fig. 17).[39] Clearly, statements like "the porphyrin is ruffled" or has a "saddle conformation" can give only a sense of the overall structure but fail to describe the conformation in sufficient detail.

In reality, except for some symmetric compounds, almost no porphyrin exhibits a conformation with a single type of distortion mode. The attentive reader will have noticed that

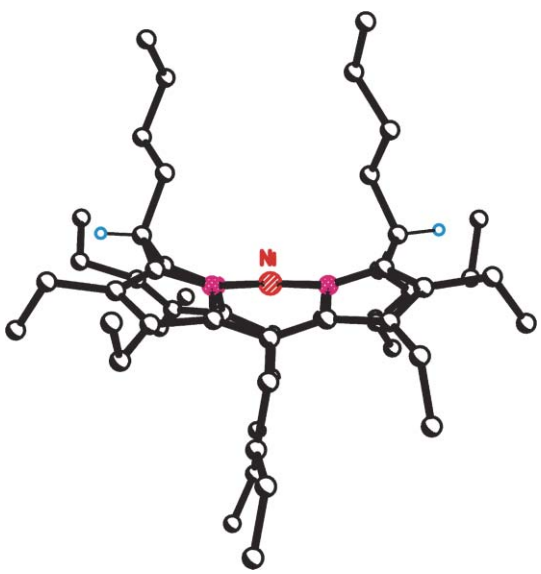


Fig. 16 Side view of the molecular structure of the porphodimethene $Ni^{II}L^{26}$.[34a]

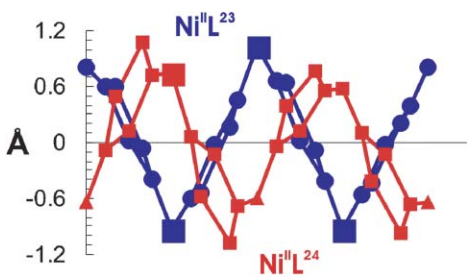
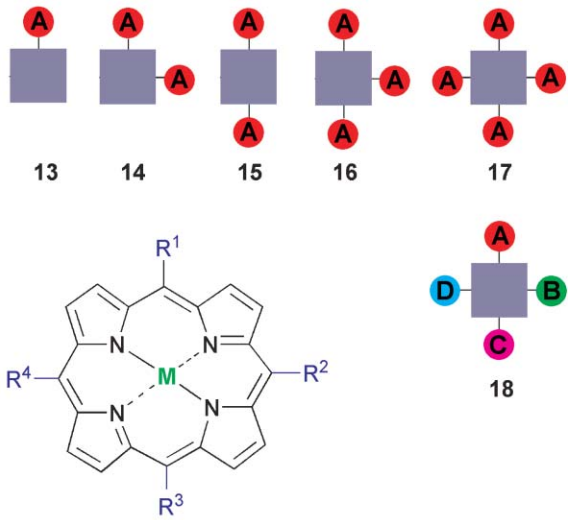


Fig. 17 Linear display of the skeletal deviations in $Ni^{II}L^{23}$ (●, blue) *vs.* $Ni^{II}L^{24}$ (■, red). Large ■ indicate *meso*-Bu, ▲ a *meso*-Ph residue.[39]

basically every skeletal deviation plot shown in this article indicates the presence of more than one distortion mode even in symmetrically substituted porphyrins [*e.g.*; Fig. 5(c) and 9(c)]. The situation is even more pronounced in unsymmetrically substituted porphyrins [Fig. 10(b), 13, and 17]. Natural porphyrin cofactors always show mixed distortion modes. This is not only the result of their asymmetric structure but also a result of the protein scaffold which imposes an unsymmetrical spatial environment on the macrocycle. There are many examples for alterations in the mix and degree of distortion modes affected through covalent or non-covalent pigment–protein interactions. Especially changes in axial ligand coordination and hydrogen bonding pattern have biological relevance.[1b,2,4,5] Thus, a comparison of the relationship between cofactors from different porphyrin–protein complexes requires an analysis of the contribution of individual distortion modes to the overall conformation, preferably using Shelnutt's NSD method.[4,15] For a typical example of a graphical representation see Fig. 19.

Less is more—A_x and ABCD porphyrins

After having prepared highly substituted porphyrins using the S_NAr methodology it became obvious that this method might be useful for the preparation of β-unsubstituted porphyrins as well. Although a multitude of porphyrin studies was performed with derivatives of so-called A_4-type porphyrins **17**, *e.g.* TPP, studies on the other members of the A_x series (**13–17**) have been scarce.[40] Especially the mono-5- (A, **13**) and 5,10-disubstituted (5,10-A_2, **14**) were almost inaccessible. Nevertheless, such compounds would be extremely valuable for studies on the influence of individual substituents on the structure, spectroscopy and physicochemical properties of the parent porphyrin macrocycle.



ML[30] $R^1 = R^2 = R^3 = R^4 = H$
ML[31] $R^1 = R^2 = Ph$, $R^3 = R^4 = H$
ML[32] $R^1 = Bu$, $R^2 = R^3 = R^4 = H$
ML[33] $R^1 = Bu^t$, $R^2 = R^3 = R^4 = H$

Using the acid-catalyzed dealkylation[29a] of H_2**L**[7] we generated porphyrin H_2**L**[30] and *in situ* reacted it with RLi to yield either the A- (**13**) or the 5,10-A_2-type (**14**) porphyrins depending on the reaction conditions. Alternatively these compounds could also be prepared *via* condensation reactions using either a [2 + 1 + 1] condensation with dipyrromethane (for **13**) or a [3 + 1] condensation using tripyrrane (for **14**).[41] Based on these methods complete series of the A_x porphyrins and the unsymmetrical ABCD-type **18** porphyrins are now accessible.[41b]

Although comparative structural studies on these compounds are just beginning we can look at two examples. Fig. 18 shows the first example of a 5,10-A_2 porphyrin, the diphenylporphyrin H_2**L**[31].[41,42] Its crystal structure exhibits an unsymmetrically distorted macrocycle with noticeable *sad* and *ruf* distortions although no significant *peri* interactions are present.[43] This is quite different from the Ni^{II} complexes of the 5,15-derivatives for which a gable-type conformation akin to the porphodimethenes was predicted.[44a] Thus, the symmetry of the porphyrin and the regiochemical arrangement of the substituents play an important role in the conformational manifestations of porphyrins with only few substituents. The structure is yet another example for the inherent flexibility of the porphyrin system. This becomes evident when comparing it with the structure of the related β-octaethyl derivative H_2**L**[25].[39] The latter is much more non-planar as a result of the increased *peri* interactions but has less relative *ruf* contribution. It is also another example for the utility of conformationally designed porphyrins to bind small molecules in the core cavity (here a methylene chloride of solvation, Fig. 18).

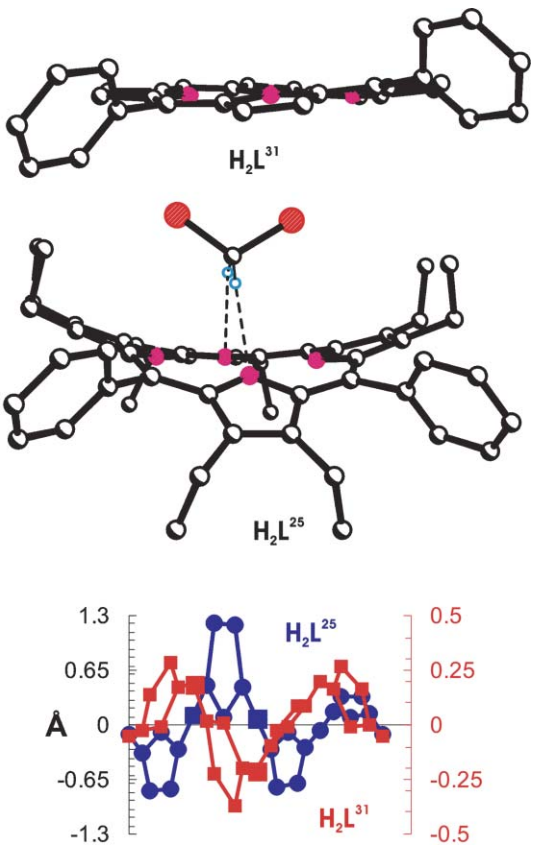


Fig. 18 Side views of the molecular structures of H_2**L**[25] and H_2**L**[31]. Linear display of the skeletal deviations in H_2**L**[25] (●, blue) *vs.* H_2**L**[31] (■, red). Large ■ indicate *meso*-Ph residues.[39,43]

The degree of non-planarity in $H_2\mathbf{L}^{31}$ is much lower than in the highly substituted porphyrins mentioned above but is comparable to that found in natural pigments. While the majority of porphyrin cofactors in porphyrin–protein complexes are non-planar, their out-of-plane displacements rarely exceed 0.5 Å. Natural pigments are either of the β-octasubstituted (protoporphyrin derivatives) or of the nona- (chlorophylls) or decasubstituted (some bacteriochlorophylls) type (phytochlorins). Their non-planar conformations are mainly the result of core coordination and/or an apoprotein effect.[2–5]

The last example concerns the influence of a single substituent on the macrocycle. This first crystal structure of a monosubstituted porphyrin, $Ni^{II}\mathbf{L}^{33}$, was reported in 1998 by Shelnutt and co-workers.[44b] It exhibited a highly *ruf* distorted conformation with minor *dom*, *wav*(*x*), and *wav*(*y*) contributions, C_m displacements of up to 0.9 Å and an average Ni–N bond length of 1.901 Å. The in-plane distortions were mainly of the *bre* (A_{2g}) type. But is this conformation the result of the small Ni^{II} ion or a result of peripheral steric interactions, or both? With the advent of a rational synthesis for the A-type porphyrins comparative analyses are now possible. The crystal structure of the respective free base $H_2\mathbf{L}^{33}$ also shows an overall ruffled macrocycle albeit with smaller maximum C_m displacements of 0.5 Å.[41b] Here the relative contributions of *dom*, *wav*(*x*) and *wav*(*y*) are larger, a small *sad* contribution is present, and the main in-plane distortion mode is now of the B_{2g} (*m-str*) type. A very similar conformation was found for the copper complex $Cu^{II}\mathbf{L}^{33}$.[43] Thus, the bulky *t*-Bu residue exerts a significant conformation strain on the macrocycle while the small Ni^{II} significantly adds to the distortion and the relative mix of distortion modes. The data shown in Fig. 19 illustrate the close conformational relationship between the three compounds. In comparison the structure of the related $Ni^{II}\mathbf{L}^{32}$, with an *n*-butyl group, is planar with a $\Delta 24 = 0.0082$ Å and an average Ni–N bond length of 1.955 Å.[43] Thus, more data from such compounds are needed to clearly delineate the relative contributions of metal and substituent effects.

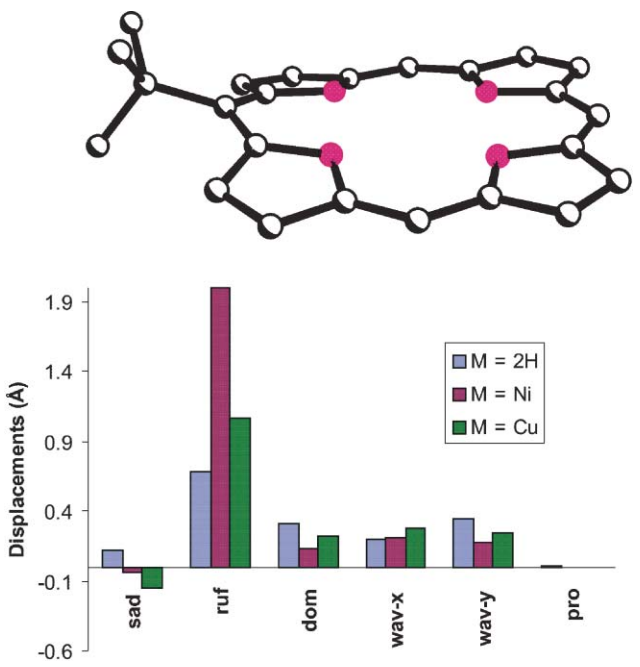


Fig. 19 View of the molecular structure of $H_2\mathbf{L}^{33}$ and out-of-plane normal-coordinate structural decomposition results for the free base, Ni^{II} and Cu^{II} complexes of $\mathbf{L}^{33}$.[41b,43,44b]

Outlook

Where to now? Clearly, the basic mechanisms and principles of porphyrin distortion have been established. The further analysis of the interrelationship between conformation and function will have implications for a wide range of biological processes and for the efforts now devoted to biomimetic solar energy conversion, catalysis, cancer therapy, as well as for studies on the basic mechanisms of electron transfer.

Much work remains to be done on the simple porphyrin systems mentioned at the end of this article and on studying metal complexes of biological relevance (esp., Fe and Mg).[24b,45] Such compounds will help to deepen our understanding of the reaction mechanisms of peroxidases and other enzymes involving high-valent metalloporphyrin intermediates. Likewise, potential exists to utilize the non-planar porphyrins for studies on ferrochelatase inhibitors, as enzyme mimics, specific DNA binding, for drug development, or to design novel donor–acceptor systems for directional electron transfer.

The progress made in synthetic methods to prepare unsymmetrically (highly) substituted porphyrins now makes it possible to utilize specific macrocycle conformations as a design principle for chromophores or receptors with tailor made properties. This will involve fine-tuning the optical properties of chromophores in intelligent photochromic and electrooptical materials, use as NLO materials, novel sensors, and building blocks in supramolecular chemistry and nanomaterials.[46] In the short term catalysts of practical utility for the enantioselective activation of unactivated C–H and N–H bonds are within reach. Probably enantioselective catalysis and molecular recognition with chiral, conformationally designed porphyrins will feature prominently in applications.[47] Nevertheless, the new understanding about the conformational flexibility of the tetrapyrroles also mandates another look at the pigment behavior *in vivo* to clearly identify the forces and structural principles in protein complexes that control the cofactor conformations and, at least in part, the biological function.

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