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Conformational landscape surfing induced by off–on π–π stacking in a porphyrin–quinone dyad

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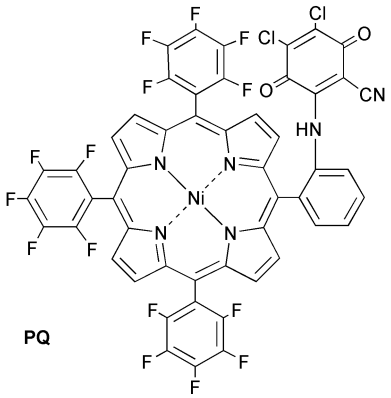
A covalently linked porphyrin–quinone dyad crystallizes with two orientations of the quinone, extended away from (off) and cofacial with the porphyrin macrocycle (on), which induce different conformations of the macrocycle and model the recently proposed structural effect of a nearby residue on the heme prosthetic group of a nitric oxide synthase.

Recent crystallographic determinations of heme proteins (nitric oxide synthases, cytochromes, cytochromes P_{450}, catalase and sulfite reductase)[1] as well as of photosynthetic antenna and reaction center complexes[2] have revealed that the porphyrinoid prosthetic groups and chromophores can adopt multiple non-planar macrocyclic conformations. In attempts to assess the physicochemical consequences of the non-planar distortions observed *in vivo*, conformationally designed porphyrins have been synthesized in which the introduction of multiple or bulky peripheral substituents enforces non-planarity which is retained in solution because of steric constraints and thus allows the (photo)physical and chemical effects of distortions to be documented.[3] These studies have established that non-planarity can significantly alter the optical, redox, radical, magnetic and excited state properties of porphyrins.[4] Although this approach has yielded novel synthetic chromophores with unusual properties, the methodology has been faulted recently[5] because the electronic and stereochemical effects of the peripheral substituents that induce the non-planarity may not be truly representative of the constraints imposed within a protein matrix where hydrogen bonding, axial ligation, aggregation and nearby residues determine the scaffolding that enforces non-planarity in *vivo*.[6] Indeed, Raman *et al.*[1] have recently suggested that even a single residue, Trp 180, which stacks with the heme surface in bovine endothelial nitric oxide synthase (eNOS), can force the porphyrin to adopt a non-planar conformation.

In support of the Raman proposal, we present here crystallographic results for **PQ**, a dyad comprised of a metalloporphyrin to which a quinone ('residue') is covalently anchored.† Within the *same* crystal, and obviously within the same dyad, the quinone orients in two different configurations, one in which it aligns perpendicular to and away from the porphyrin plane (off), and the other in which it stacks over the porphyrin plane in π–π contact (on) (Fig. 1). The 'on' configuration does indeed result in a more pronounced macrocyclic distortion with a concomitant shift from a combination of saddled and ruffled conformations‡ to a nearly pure ruffled one, a landscape frequently observed *in vivo*,[1,2] as well as in conformationally designed synthetic porphyrins.[3,4] These results also reinforce the evolving concept that non-planar porphyrins can readily traverse ('surf') multiple conformational landscapes which are separated by only small energy barriers.[8]

The crystal structure of **PQ** reveals that the asymmetric unit incorporates two different configurations of the dyad in which the quinone orients away from the porphyrin (off) and the other in which it aligns over and parallel to the macrocycle (on) (Fig. 1).§ In the latter, the closest approach of the quinone to the porphyrin is 2.9 Å, clearly indicative of π–π interactions. In the off configuration, the porphyrin adopts a combination of *sad*/*ruf* conformations (~2:3)‡ with a maximum C_{meso} out-of-plane displacement of 0.43 Å. In contrast, the on configuration results in an essentially pure *ruf* conformation with a maximum C_{meso} displacement of 0.61 Å, *i.e.* the presence of the quinone in π–π contact with the porphyrin has significantly altered the macrocyclic conformation.



The question arises as to why there are two such distinctly different orientations of the quinones in the same crystal. A likely explanation for the stabilization of the off configuration may lie in the hydrogen bond between the amino hydrogen

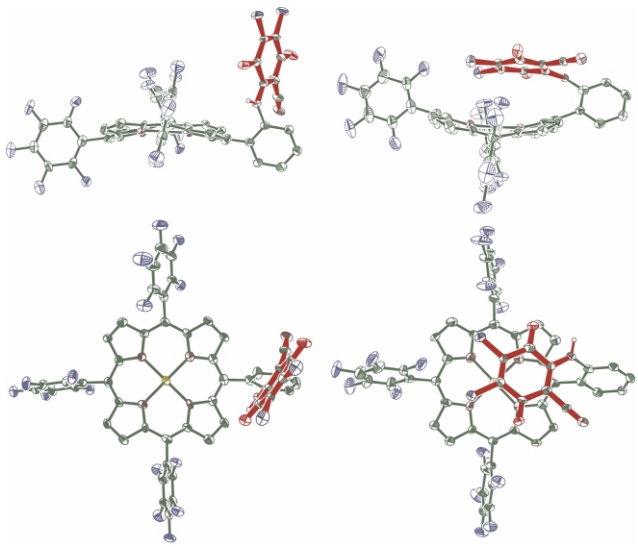


Fig. 1 Molecular structures of **PQ** in the off (left) and on (right) configurations with the quinone shown in red. Thermal ellipsoids enclose 30% probabilities.

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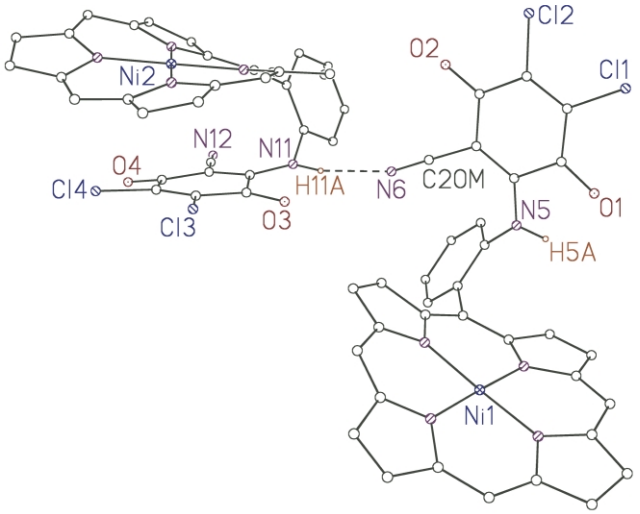

Fig. 2 Hydrogen bonding in the **PQ** crystal between the amine hydrogen (H11A) of the molecule in the on configuration with the cyano nitrogen (N6) of the molecule in the off configuration (C_6F_5 rings not shown). Selected distances (Å): N6–N11 2.868(12), N6–H11A 2.00(5), N11–H11A 0.91(2).

(H11A) of the molecule in the on configuration with the cyano nitrogen (N6) of the quinone in the off configuration (Fig. 2). If this explanation is correct, the simple **PQ** dyad thus also exemplifies the potential structural effects that the ubiquitous hydrogen bonds in proteins may induce *in vivo*.

These results thus demonstrate that a single neighboring 'residue' can indeed induce a more distorted conformational landscape in porphyrins, as suggested by Raman *et al.*,[1] for eNOS, and further illustrate the plasticity of the macrocycles as well as their acute sensitivity to their microenvironment increasingly observed both *in vitro* and *in vivo*.[1–4] These evidently facile interconversions and multiplicities of conformational surfaces ('surfing') also raise the caveat that site-directed mutations in proteins may not be structurally innocent by affecting the conformations and hence the properties of the porphyrinic prosthetic groups and chromophores.[3,4,8]

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Notes and references

† *PQ synthesis*: condensation of pyrrole (4 eq.), pentafluorobenzaldehyde (3 eq.), and 2-nitrobenzaldehyde (1 eq.) in refluxing acetic acid gave 5-(2-nitrophenyl)-10,15,20-tri(pentafluorophenyl)porphyrin (**1**) in 6% yield[7] [^{1}H NMR, $CDCl_3$: δ −2.77 (s, 2H, NH), 7.99 (m, 2H, phenyl H), 8.25, 8.52 (m, 1H each, phenyl H), 8.78, 8.84 (d, 2H each, C_β H), 8.93 (br, 4H, C_β H); ^{19}F NMR, $CDCl_3$: δ 3.84 (m, 6F, F_{meta}), 13.82 (m, 3F, F_{para}), 28.52 (m, 2F, F_{ortho}), 28.71 (m, 1F, F_{ortho}), 29.15 (m, 1F, F_{ortho}), 29.44 (m, 2F, F_{ortho}); Vis. λ/nm: 412 (100), 510 (7.2), 542 (1.1), 586 (2.3), 642 (0.4), mp > 260 °C]. Nickel insertion into **1** with Ni(II) acetylacetonate (20 eq.) in refluxing xylenes afforded Ni(II) nitroporphyrin **2** in 91% yield [^{1}H NMR, $CDCl_3$: δ 7.96, 7.98 (m, 1H each, phenyl H), 8.19, 8.43 (m, 1H each, phenyl H), 8.69, 8.66 (d, 2H each, C_β H), 8.76 (br, 4H, C_β H);^{19}F NMR, $CDCl_3$: δ 3.86 (m, 6F, F_{meta}), 13.74 (m, 3F, F_{para}), 28.51 (m, 2F, F_{ortho}), 28.71 (m, 1F, F_{ortho}), 29.15 (m, 1F, F_{ortho}), 29.44 (m, 2F, F_{ortho}), Vis. λ/nm: 404 (100), 526 (7.4), 560 (5.1), mp > 260 °C]. Under an atmosphere of $H_{2(g)}$, **2** was stirred with palladium on carbon in CH_2Cl_2 and yielded a mixture of reduced macrocycle Ni(II) 5-(2-aminophenyl)-10,15,20-tri(pentafluorophenyl)porphyrinoids (**3**). Under inert atmosphere, this mixture was reacted with an excess of DDQ in CH_2Cl_2 and afforded **PQ** in 18% yield from **2** [**PQ**: ^{1}H NMR, $CDCl_3$: δ 7.48 (s, 1H, amino H, exchangeable with D_2O), 7.60 (d, 1H, phenyl H), 7.91 (m, 2H, phenyl H), 8.33 (d, 1H, phenyl H), 8.75 (m, 6H, C_β H), 8.88 (d, 2H, C_β H); ^{19}F NMR, $CDCl_3$: δ 4.61 (m, 6F, F_{meta}), 14.43 (t, 3F, F_{para}), 28.65 (m, 2F, F_{ortho}), 28.86 (m, 1F, F_{ortho}), 29.28 (m, 1F, F_{ortho}), 29.57 (m, 2F, F_{ortho}); Vis. λ/nm: 406(100), 525(10.1), 556(8.1); Maldi TOF LRMS, *m/z*: observed 1158.5; mp > 260 °C].

‡ In a saddled (*sad*) conformation the pyrrole rings alternately tilt up and down relative to the 24-atom porphyrin plane while the meso carbons remain in plane. In a ruffled (*ruf*) conformation the pyrrole rings twist about the axis that bisects opposing nitrogen atoms and the meso carbons alternately shift up and down out-of-plane; L. Sun, W. Jentzen, J. A. Shelnutt, The Normal Coordinate Structural Decomposition Engine (http://jasheln.unm.edu).

§ *Crystallographic details*: $2[C_{51}H_{13}Cl_2F_{15}N_6NiO_2]\cdot1.5[C_6H_{14}]$, M = 2468, monoclinic, space group $C2/c$, a = 31.037(5), b = 22.693(4), c = 30.799 Å, β = 100.047(4)°, V = 21359(6) Å^3, Z = 8. Data were collected on a Bruker SMART 1000 diffractometer [λ(Mo-Kα) = 0.71073 Å] at 91(2) K to $2\theta_{max}$ = 63° [total measured reflections = 121513, ($\pm h$, $\pm k$, $\pm l$)]. A $2\theta_{max}$ cutoff of 45° was applied affording 13875 independent data (R_{int} = 0.238) of which 9065 had $I > 2\sigma(I)$. The structure was solved by direct methods and refined (based on F^2) by full matrix least-squares methods with 1248 parameters (Bruker SHELXTL V. 5.10). Hydrogens were generated by idealized geometry with the exception of the lone amino hydrogen on each of the two **PQ** molecules in the asymmetric unit; these were found on a difference map and refined freely with their bond lengths fixed at 0.91(2) Å. Final R factors were $R1$ = 0.123 (observed data), w$R2$ = 0.349 (all data) and GooF = 1.111. CCDC 194212. See http://www.rsc.org/suppdata/cc/b2/b209238g/ for crystallographic data in CIF or other electronic format.

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