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4,4,9,9-Tetraphenyl pyrroloindolizine: a structural analogue of calix[2]pyrrole†

K. C. Gowri Sreedevi,[a] Ajesh P. Thomas,[b] S. Ramakrishnan,[a] P. S. Salini,[a] M. G. Derry Holaday,[a] M. L. P. Reddy[c] and A. Srinivasan*[b]

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Synthesis, spectral and structural characterization of a pyrroloindolizine derivative having structural similarity with calix[2]pyrrole is described. Here, two pyrrole rings are connected with two *meso*-carbon atoms having an N,α-linkage and an α,β-linkage to afford the smallest analogue in the calixpyrrole family. Detailed NMR spectroscopic studies along with single crystal X-ray analysis confirm the assigned structure of the molecule.

Porphyrinoids, with their structural variations such as, *normal*, *contracted*, and *expanded* derivatives, are explored for applications in molecular recognition, catalysis, material science and medicine.[1] In particular, the *contracted* porphyrinoids have continued to gather much interest since the first synthesis of subphthalocyanines **1**,[2] the lower homologues of phthalocyanines formed by three instead of four N-fused 1,3-diiminoisoindole units, by Meller and Ossko in 1972,[2a] which represent fascinating examples of non-planar aromaticity with unique spectral and electronic features. Later, in 2005, Torres *et al*. reported subporphyrazines **2**,[3] by the removal of the three fused benzene rings from the subphthalocyanine. In sharp contrast, the first subporphyrin, tribenzosubporphine **3**, with a similar electronic structure to subphthalocyanines **1**, was prepared by the group of Osuka in 2006 as the B(III) complex under harsh reaction conditions (Fig. 1).[4] Subsequently, series of boron free subporphyrinoids, such as subpyriporphyrin,[5] [14]benzotriphyrin(2.1.1)[6] and β-substituted, *meso*-free[14]triphyrin(2.1.1)[7] have been reported. Very recently, our group reported a β-unsubstituted, *meso*-aryl [14]triphyrin (2.1.1) in its free-base form.[8] These set of compounds are found to be ideal candidates for the construction of supramolecular self assemblies in spite of the increased ring strain.[9]

In addition to regular porphyrinoids, mutations such as confusion and fusion are found to have a place in porphyrins since the discovery of N-confused porphyrins.[10] Recently, Furuta *et al*. reported a corrole isomer, "norrole" **4** with an N,β-link as a by-product from the oxidative ring closure of N-confused bilane and called a neo-confused derivative.[11] Subsequently, Lash *et al*. presented the first examples of neo-confused porphyrins **5** where a pyrrole nitrogen is connected to a *meso*-carbon (Fig. 1).[12]

On the other hand, calix[4]pyrrole, first prepared by Baeyer in 1886,[13] is a class of fully *meso*-substituted porphyrinogen-like macrocycles. As in the case of porphyrins, *normal*, *expanded* and *confused* structural variations of calixpyrroles are well known in the literature, which are widely used as receptors for various anions both in solution and in the solid state.[14] However, the corresponding *contracted* calixpyrroles are not known in the literature, probably due to the higher order ring strain in those derivatives. In 1958, Treibs and Kolm[15] reported a *meso*-free cyclic molecule **6**, by an acid catalyzed cyclo-condensation of ethyl 2-methyl-3-pyrrolecarboxylate with formaldehyde, where the two pyrrole rings are connected with the *meso*-carbon atoms through α,β-linkages (Fig. 1) and which fall into the category of pyrroloindolizine derivatives having valuable biological activities.[16] Herein, we report the synthesis, spectral and structural characterization of a 4,4,9,9-tetraphenyl pyrroloindolizine derivative, which is a structural analogue of calix[2]pyrrole (**7b**) with N,α- and α,β-linkages to the *meso*-carbon atoms.

The title compound is synthesized by acid-catalyzed condensation reaction, where 2-(diphenylhydroxymethyl) pyrrole **8**[17] in dichloromethane is allowed to stir for 2 h in the presence of $BF_3{\cdot}OEt_2$ as an acid catalyst (Scheme 1). The solvent is removed and the dark residue is then purified by column chromatography on silica gel using hexane as the eluent, to afford a white solid **7b** in 20% yield. The compound is soluble in common organic solvents. The identity of **7b** was confirmed by various spectroscopic methods, and finally by single crystal X-ray analysis, revealing the exact structure of the molecule.

The FAB mass spectrum showed a peak at *m*/*z* 464.29 pointing out the formation of the smallest self-condensed product between two units of **8** (*m*/*z* = 249) by the elimination of two

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[a] *Photosciences and Photonics Section, National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Trivandrum-695019, Kerala, India*
[b] *National Institute of Science Education and Research (NISER), Bhubaneswar-751005, Odisha, India. E-mail: srini@niser.ac.in*
[c] *Inorganic Chemistry Section, Chemical Sciences and Technology Division, National Institute for Interdisciplinary Science and Technology (NIIST-CSIR), Trivandrum-695019, Kerala, India*

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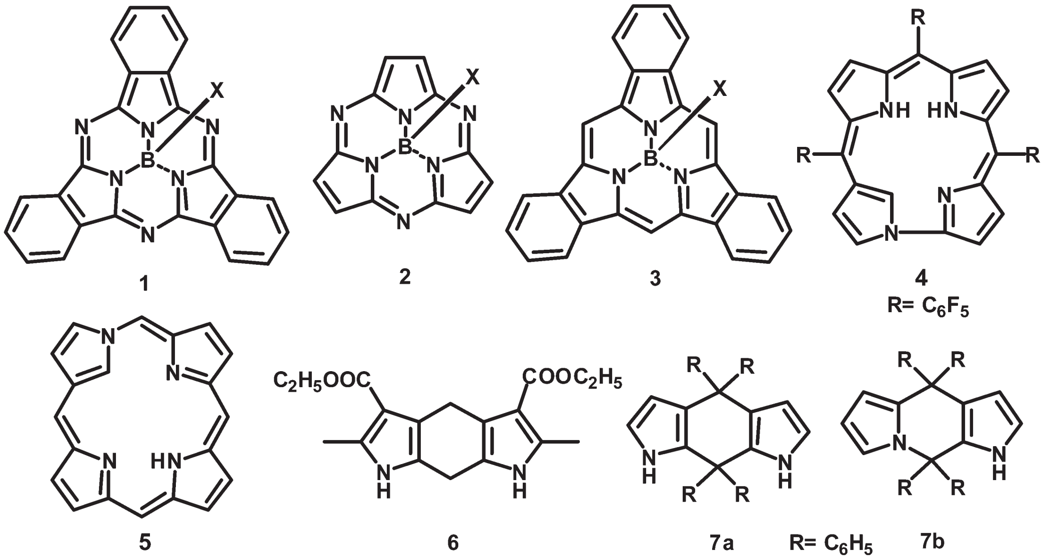
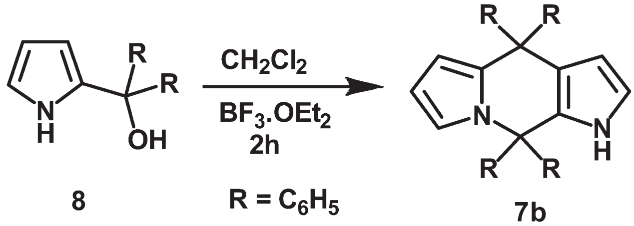


Fig. 1 Porphyrinoids



Scheme 1 Synthesis of **7b**.

water molecules. The expected structure of the compound is either **7a**, as seen by the group of Treibs and Kolm, or **7b**.

The ^{1}H NMR spectrum of the compound (**7**) in $CDCl_3$ at room temperature is shown in Fig. 2, which shows only one NH, twenty phenyl protons and five pyrrolic CH leading towards the asymmetric nature of the molecule, thus ruling out the possibility of **7a**. The NH proton resonates as a singlet at 7.60 ppm (a) and is confirmed by D_2O exchange experiment. The twenty phenyl protons appear as three sets in which six protons resonate at

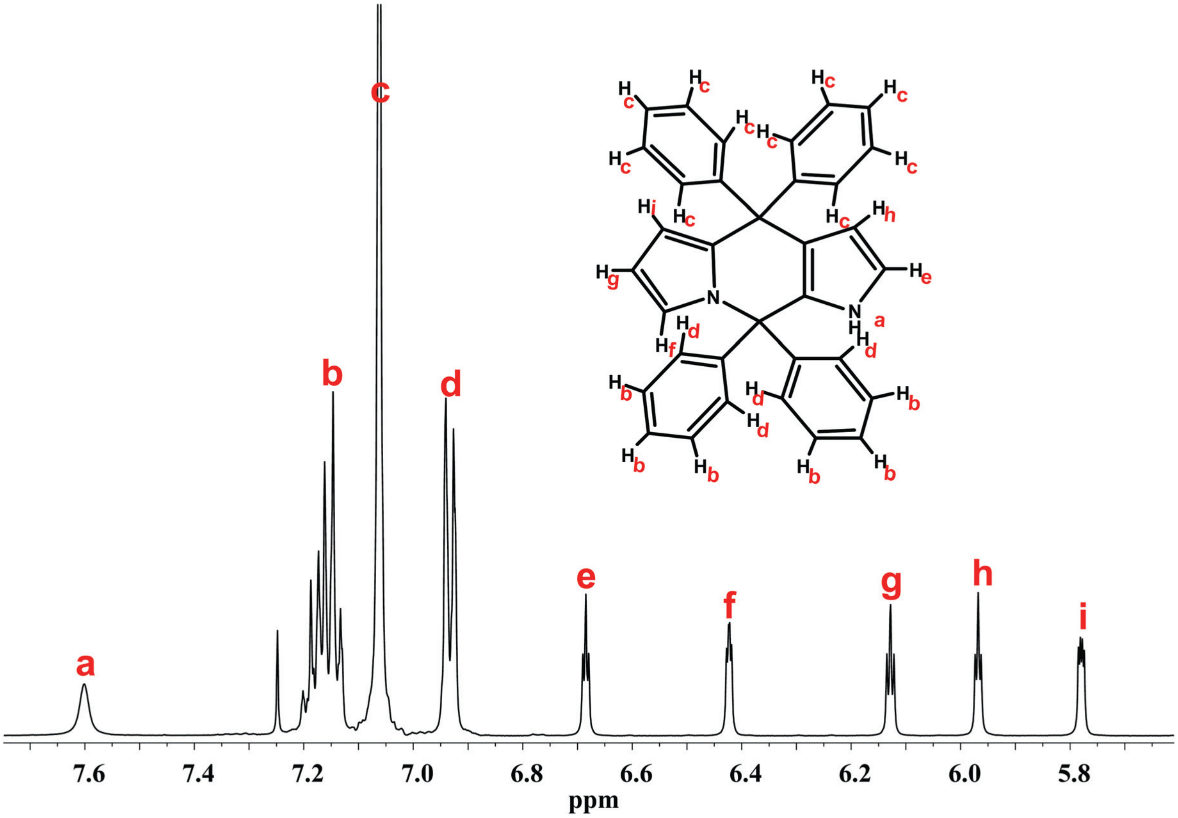


Fig. 2 ^{1}H NMR spectrum of **7b** in $CDCl_3$.

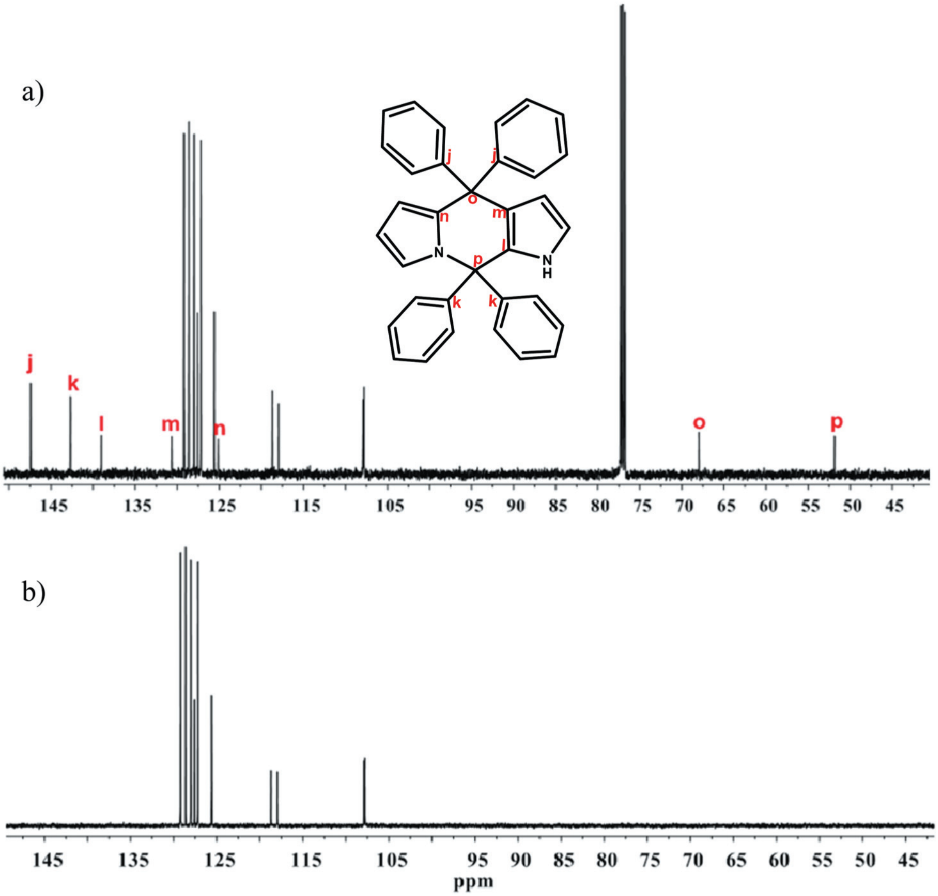


Fig. 3 (a) ^{13}C NMR spectrum of **7b** in $CDCl_3$ and (b) DEPT 45 spectrum of **7b** in $CDCl_3$.

7.16 ppm as multiplet, ten protons resonate as a singlet at 7.06 ppm and other four protons at 6.92 ppm as a doublet (b, c and d) thus confirming that the chemical environment of the two *meso*-carbon atoms are different. The α- (e and f) and β-pyrrolic CH protons (g, h and i) resonate as a triplet and multiplets at 6.68, 6.42, 6.13, 5.96 and 5.77 ppm, respectively. All together, the asymmetric chemical environment around the *meso*-carbon and the presence of only one pyrrolic NH proton with five pyrrolic CH protons prove the composition is **7b** having N,α- and α,β-linkages with *meso*-carbons instead of **7a**. However, this mode of linkage is different from those found in the neo-confused and N-confused porphyrin systems, where the pyrrole units are connected with the *meso*-carbon atoms through N,β- and α,β′-linkages to form the macrocycles respectively.[11,12]

The spatial orientations of hydrogen atoms were assigned by 2D ^{1}H–^{1}H correlation spectroscopy.[18] There are two sets of homonuclear coupling correlations observed in the COSY spectrum. The first correlation is between the α and β-pyrrolic CH protons (f, g and i as in Fig. 2) and the other is between the pyrrolic NH with CH protons (e and h).

The fusion of the pyrrolic rings to the *meso*-carbon atoms in **7b** is further supported by the ^{13}C NMR and DEPT 45 spectral analysis as shown in Fig. 3. The peaks at 67.97 and 51.86 ppm (o and p) in the ^{13}C NMR spectrum (Fig. 3a) unambiguously explain the different chemical environments for the two *meso*-carbon atoms, which indicates one of the pyrrolic nitrogens is fused to a *meso*-carbon atom and is responsible for the shielding of that particular carbon in the ^{13}C NMR spectrum. The *ortho*-protons of the corresponding phenyl rings are thus largely shielded compared to other phenylic protons and split into a multiplet and doublet as observed in the ^{1}H NMR spectral analysis. The seven quaternary carbons present in **7b** can be correctly assigned by subtracting the DEPT 45 (Fig. 3b) from ^{13}C NMR signals. The peaks at 147.42 and 142.70 ppm (j and k) correspond to the quaternary carbon atoms of the phenyl groups, which are attached to two different *meso*-carbons resonating at 67.97 and 51.86 ppm (o and p) respectively as shown in Fig. 3a. The peaks observed at 139.02, 130.64 and 125.13 ppm (l, m and n) represent the remaining three quaternary pyrrolic carbon atoms. Thus, both ^{1}H and ^{13}C NMR data validate the self-condensation of **8** leading to the formation of **7b**.

The explicit structure of the calix[2]pyrrole (**7b**) has come from the single crystal X-ray diffraction analysis (Fig. 4).[19] The good quality single crystals were grown by slow evaporation of *n*-hexane into CH_2Cl_2 solution. As confirmed by the spectral analysis, out of the two pyrrole rings, one of the pyrrolic rings is in an N,α-linkage with the *meso*-carbon atom whereas the second pyrrole ring connects to the *meso*-carbon atom through an α,β-linkage (Fig. 4a). Unlike the parent calix[4]pyrrole unit,[1] the two pyrrole rings, in order to reduce the steric repulsion, were found to be in the same plane with two *meso*-carbon atoms

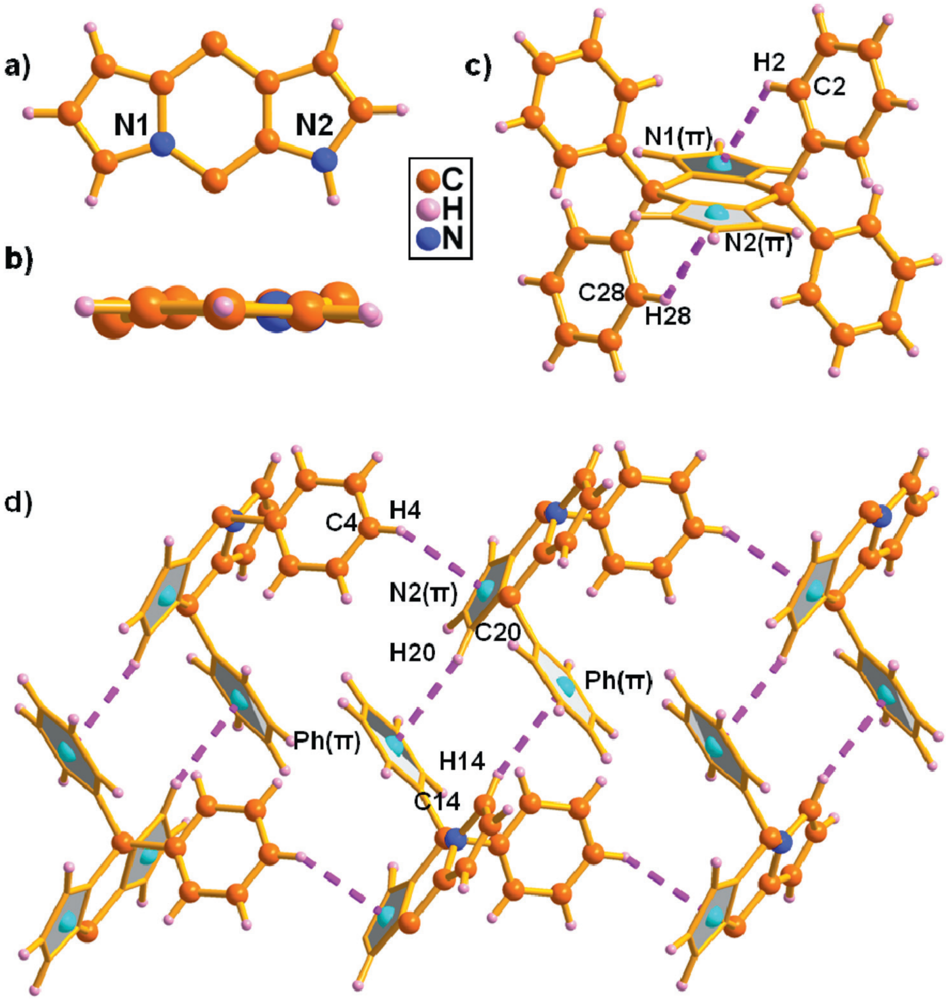


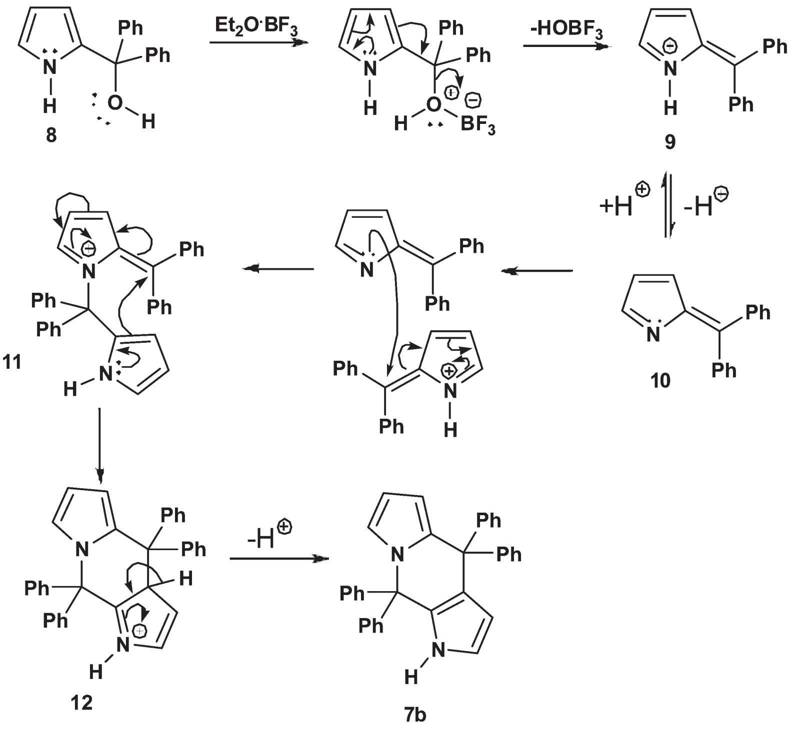
Fig. 4 Single crystal X-ray structure of **7b**. (a) Top view, (b) side view, (c) top view with intramolecular hydrogen bonding interactions and (d) 2D array. The *meso*-diphenyl groups in (a, and b) and the phenyl groups which are not involved in hydrogen bonding interactions in (d) are omitted for clarity.

each having phenyl groups pointing above and below the mean plane[18] (Fig. 4b and 4c), and the distortion between the four phenyl units and the mean plane is 74.38°, 72.35°, 74.72°, 71.71°, respectively.

Two of the phenyl rings form intramolecular hydrogen bonding interactions with the pyrrolic π-cloud (C2–H2⋯N1(π) and C28–H28⋯N2(π)) with distances and angles of 2.81 Å, 127° and 2.83 Å, 127° (Fig. 4c). In addition, **7b** also generates weak intermolecular interactions, where three molecules of **7b** are involved to generate two one-dimensional arrays. The first array is formed between one of the *meso*-phenylic C–Hs and the N2 pyrrolic π-cloud [C4–H4⋯N2(π)], while the *meso*-phenylic π-cloud interacts with the N1 pyrrolic α-CH [C14–H14⋯Ph(π)] and N2 pyrrolic β-CH [C20–H20⋯Ph(π)] with distances and angles of 2.92 Å, 129°; 2.98 Å, 143° and 2.99 Å, 142°, respectively, to generate the second one-dimensional array.[18,20] Combining these two one-dimensional arrays, **7b** generates a two-dimensional supramolecular assembly in the solid state as shown in Fig. 4d.

The formation of **7b** can mechanistically be explained as illustrated in Scheme 2. In the presence of a Lewis acid catalyst, **8** may undergo $BF_3{\cdot}OEt_2$ assisted hydrolytic cleavage to form the 2-(diphenylmethylene)pyrrolium intermediate **9** which can lose a proton to afford 2-(diphenylmethylene)pyrrole **10**. In the next step, the lone pair electrons of the nitrogen atom in **10** assists [3 + 3] cycloaddition with **9** to form a cyclic intermediate **12**, which rapidly undergoes aromatization to yield the more stable compound **7b**.

In summary, we have demonstrated the synthesis, spectral and structural characterization of a 4,4,9,9-tetraphenyl pyrroloindolizine derivative, which is a structural analogue of calix[2]pyrrole. The molecule can be considered as the smallest congener of the corresponding porphyrinogen family, containing only two pyrrole rings connected through *meso*-carbon atoms substituted with bulky phenyl groups. In addition to the spectroscopic evidence, single crystal X-ray analysis reveals the assigned structure of the molecule. We hope this example will pave the way towards the synthesis of *meso*-octaaryl calix[4]pyrroles and similar porphyrinoids which are unprecedented in the literature. Attempts towards the synthesis of these macrocycles and studies to explore the biological activities of the pyrroloindolizine derivative are currently under way in our group.



Scheme 2 Mechanistic rationale for the formation of **7b**.

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18 See the ESI.†

19 Crystal data for **7b** (from CH_2Cl_2–hexane): $C_{34}H_{26}N_2$, M_w = 462.21, monoclinic, a = 9.0197(6), b = 8.1267(7), c = 16.7735(14) Å, α = 90, β = 103.407(4), γ = 90°, V = 1196.00(16) Å^3, T = 293 (2) K, space group Pn, Z = 2, D_c = 1.284 mg m^{-3}, μ(Mo-Kα) = 0.075 mm^{-1}, 10540 reflections collected, 3958 unique (R_{int} = 0.0275), R_1 = 0.0391, wR_2 = 0.0963, GOF = 1.052$\{I > 2\sigma(I)\}$. CCDC 855537 contains the supplementary crystallographic data for **7b**.

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