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Catalytic Hydrogenation of *meso*-Octamethylporphyrinogen (Calix[4]pyrrole)

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Abstract: Hydrogenation of *meso*-octamethylporphyrinogen (calix[4]pyrrole) with a number of heterogeneous catalysts under different experimental conditions has been investigated. GC-MS analyses of the reaction mixtures showed the formation of one to four products in low to moderate yields: three of them were diastereoisomers of the product derived from half-hydrogenation of the substrate, and displayed alternating pyrrolidine and pyrrole rings, while the fourth was the all-*cis* saturated product. An acidic medium was necessary to achieve hydrogenation. However, the use of too strongly acidic solvents or additives was detrimental to the stability of the substrate and/or the catalyst.

Keywords: calix[4]pyrrole · heterogeneous catalysis · hydrogenation · nitrogen heterocycles · porphyrinoids

Introduction

Many vital biological processes depend on the presence of macrocyclic metal porphyrin complexes, for example, the electron transport by cytochrome c, the transport of oxygen by myoglobin or hemoglobin, and most important of all the photosynthesis by chlorophylls.[1] These complexes are therefore known as "the pigments of life", and they are formed by condensation reactions of comparatively simple starting materials[2] in an early step of the biosynthetic pathway.[2a,c]

Many different chemical syntheses of nitrogen-containing macrocycles, such as triazacyclononanes, cyclens, cyclams, and obviously non-natural porphyrins, have hitherto been reported. Their chemical, catalytic, and structural properties have been extensively studied.[3] Metal complexes of aza-macrocycles and their derivatives have found interesting applications as sensors, as contrast agents in the detection and destruction of cancer cells, and as oxidation or bleaching catalysts.[4] A wide range of aza-macrocycles has been prepared to aid in the understanding of the function and mechanism of enzyme-catalyzed reactions by mimicking the active site with simpler artificial systems. The quest for high-valent iron or manganese oxo species is an important example of such studies.[4g,j,5] Other metal complexes have been synthesized with a view to performing challenging but inherently very useful transformations, such as selective oxidations of the small hydrocarbons methane, ethane, or propane.[4g,6] The properties of metal complexes of macrocyclic ligands such as porphyrins and porphyrinogens have been compared with those of linear chelating ligands such as salens and their derivatives.[7] White et al. beautifully demonstrated that rigidifying a linear tetradentate ligand restrains the geometry of the metal complex to one single conformation, thereby leading to a more stable metal complex and hence to more efficient catalysis.[7c] In another example, Ready and Jacobsen improved the catalytic activity of a linear salen derivative by transforming it to a macrocyclic analogue.[8]

The first *meso*-octaalkylporphyrinogen **1** was synthesized more than 120 years ago by Baeyer by mixing pyrrole and acetone in the presence of an acid.[9] First proposed by Chelintzev et al., the correct structure was definitively proven

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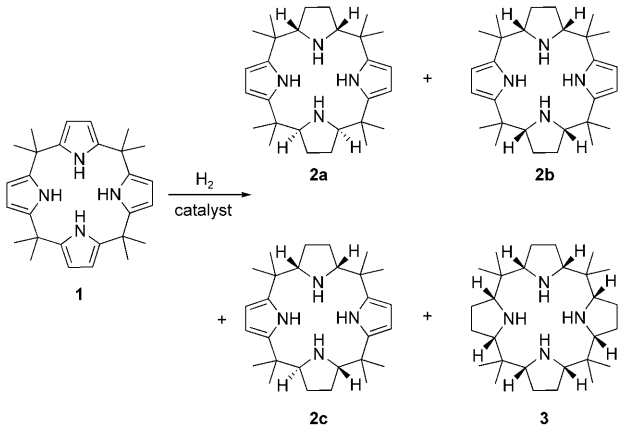
by Rothemund in 1955.[10] Forty years later, the X-ray structure determination of this compound revealed the alternating conformations of the pyrrole rings in the solid state,[11] with vicinal pyrrole rings pointing in opposite directions. The pyrrole rings opposite each other are nearly parallel, thus forming a cavity. The X-ray crystal structures of these macrocycles bound to anions such as fluoride and chloride revealed a significant change in their conformations,[11] with all of the NH groups being directed towards the anion, thereby creating a cone-like conformation similar to that observed for calixarenes.[19] Based on this observation and on the similarity of the Rothemund procedure[10b] for the synthesis of calixarenes to the Baeyer procedure, it was proposed to rename these macrocycles "calix[4]pyrroles".[11] In accordance with this proposal is the fact that *meso*-octaalkylporphyrinogens are not *bona fide* precursors of porphyrins.

The calix[4]pyrroles have been extensively studied with regard to their capacity to function as anion sensors through the formation of four pyrrole NH–anion hydrogen bonds.[12] In contrast to typical Werner-type complexes, the nitrogen lone pairs of calix[4]pyrroles are part of the aromatic π-system of the pyrrole ring and are therefore not available for the complexation of metal species. However, the metallation of calix[4]pyrroles to give the tetra-anion allows the introduction of metal ions.[13] This procedure is experimentally challenging and requires the use of strong bases and strict exclusion of oxygen and water.

The reduction of calix[4]pyrrole to give the corresponding "calix[4]pyrrolidine" opens a new route to macrocycles capable of complexing metal cations. The reduction of pyrrole and its substituted derivatives has been widely studied and different procedures have been developed. The electrochemical and Birch reductions have been used rather infrequently.[14] Ciamician[15] and Knorr and Rabe[16] described the use of zinc under acidic conditions for the reduction of pyrrole to give a mixture of 2- and 3-pyrrolidines.[17] Heterogeneous catalytic hydrogenation remains one of the most powerful reduction processes,[18] and has been widely applied in the reduction of pyrroles[19] to obtain the corresponding pyrrolidines with high *cis* stereoselectivity.[20]

We have recently reported the results of a preliminary study of the heterogeneous catalytic hydrogenation of calix[4]pyrrole, **1** (Scheme 1).[21] After a brief survey of the efficacies of a few heterogeneous catalysts (Pd/C, Raney nickel, and Rh/Al_2O_3) under different experimental conditions, we recently found that the use of 10% Pd/C in acetic acid at 100°C under a hydrogen pressure of 100 atm gave the highest conversion of the starting material to a mixture of half-reduced and fully reduced compounds, from which only **2b** and **3** could be isolated in respective yields of 29.4 and 7.4%. A survey of the metal-coordinating properties of compound **3** showed that it formed complexes with Cu^{II}, Ni^{II}, and Pd^{II} salts, while maintaining its anion-binding ability through the hydrogen-bond network.

To the best of our knowledge, reduction of calix[4]pyrroles with preservation of the macrocyclic skeleton had not been reported prior to our initial publication. Only one previous publication describing the reduction of calix[4]pyrrole has been reported; in that case, very forcing conditions were applied, which caused its fragmentation to a mixture of pyrrole, 2-isopropyl-1*H*-pyrrole, 2-isopropyl-pyrrolidine, and 2,5-diisopropyl-pyrrolidine.[10b] The authors were able to deduce the structure of the macrocycle from these results.



Scheme 1. Catalytic hydrogenation of calix[4]pyrrole, **1**.

Results and Discussion

We report here on the outcome of a thorough study of the catalytic hydrogenation of calix[4]pyrrole **1** performed using common as well as novel heterogeneous catalysts based on transition metals (Pd, Rh, Ru) supported on solid matrices (carbon, graphite, alumina). During our studies, we have been able to isolate and identify two novel half-hydrogenated products, **2a** and **2c**, although the yield of the fully hydrogenated product **3** could not be improved. It is noteworthy that no other diastereoisomers of compound **3** were detected in the crude reaction mixtures.

Before starting the screening of the hydrogenation catalysts under different experimental conditions (solvent, temperature), we developed an easy and fast analytical protocol that allowed a qualitative and quantitative determination of the compositions of the reaction mixtures. GC analysis using the internal standard methodology proved to be the best tool:[22] *n*-eicosane was used as the internal standard (IS), which was added in accurate amounts to each reaction mixture before running the hydrogenation.

GC-MS analyses of the reaction mixtures were indicative of the formation of four major compounds: according to their molecular weights, three of them were diastereoisomers of the half-reduced product **2**, and the fourth was the fully reduced compound **3** (Scheme 1). In particular, the diastereoisomers **2a** and **2c** of the half-reduced product, which have previously not been detected, could be isolated in pure form.

The crude reaction mixture obtained by performing the hydrogenation of **1** (0.47 mmol) under the previously de-

scribed conditions (34 mol% of 10% Pd/C, AcOH, 100 atm of H_2 pressure, 100°C) was first analyzed. The three diastereoisomers **2a–c** (in order of GC elution) were detected in a total yield of 79%, together with the fully reduced compound **3**, which was formed in 16% yield (Table 1, entry 1). Compound **2b** was the prevalent component of the mixture. Reducing the relative amount of catalyst to a 17 mol% metal loading resulted in lower yields of both products **2** and **3**. The ratio of products **2** and **3** and the diastereoselectivity of the reduction were comparable with those of the first trial (entry 2).

Table 1. Catalytic hydrogenations of calix[4]pyrrole **1**.[a]

Entry	Catalyst	**2a**/**2b**/**2c**[b]	**3**[b]
1	10% Pd/C	25:40:14	16
2	10% Pd/C[c]	23:35:11	12
3	10% Pd/C[d]	29 (2)[e]:35 (24)[e]:13	12 (8)[e]
4	5% Rh/Al_2O_3	40:33:11	8
5	$C_{24}Rh$	43:31:12	9
6	$C_{24}Ru$	36:39:19[f]	5
7	$C_{16}Pd$	27:34:17	6

[a] The reactions were performed in an autoclave on a 0.47 mmol scale in acetic acid at 100°C for 24 h under 100 atm of H_2 pressure using a catalyst loading of 34 mol% of metal. [b] Yields (%) were calculated by GC analysis using the internal standard methodology. [c] Catalyst loading: 17 mol% of metal. [d] The reaction was performed on a 4.70 mmol scale. [e] Isolated yield. [f] Traces of **1** were detected.

The hydrogenation under the conditions of entry 1 was then carried out on a larger scale (4.7 mmol of **1**), which allowed the isolation of all of the reaction products. The product ratio was comparable to that determined for the small-scale reaction (entry 3). The tetraacetate form of **2b** precipitated from the crude mixture after evaporation of the solvent and addition of dichloromethane. The free-base **2b** was obtained in 24% yield by treatment with aqueous NaOH. Crystallization from ethyl acetate gave pure **2b** in 23% yield. Compound **2c**, incorporating one *cis*- and one *trans*-2,5-disubstituted pyrrolidine ring, was isolated from impure **2b** by repeated crystallizations. The relative configuration of **2c** is compatible with the asymmetry reflected in the ^1H and ^{13}C NMR spectra. Product **3** was recovered in 8% yield from the dichloromethane mother liquor after treatment with aqueous Na_2CO_3, evaporation of the solvent, and addition of ethyl acetate. This caused separation of **3** as an insoluble solid, and then compound **2a** could be isolated from the mother liquor as a solid by evaporation of the solvent and column chromatography (Al_2O_3) of the residue. Compound **2a** was purified by crystallization (EtOAc) and the relative configuration of the stereocentres was determined by an X-ray diffraction study (Figure 1).

Compound **2a** crystallized with three independent molecules per asymmetric unit.[22] In one of the molecules the pyrrolidine rings occupy two alternative positions. However, the overall structures of the three independent molecules are very similar. The N···N distances between the adjacent nitrogens are also similar, with three distances being shorter

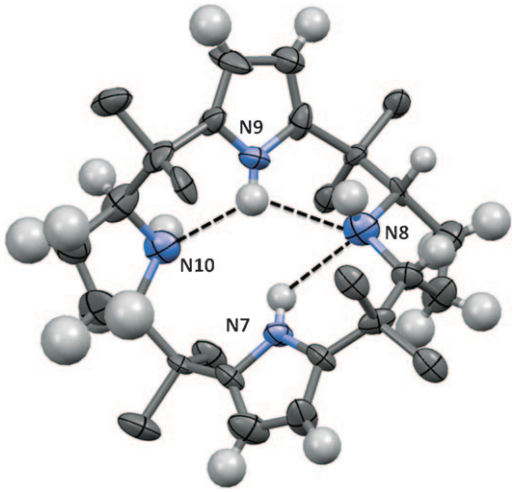


Figure 1. Molecular structure of one of the independent molecules of compound **2a**,[22] with the thermal ellipsoids drawn at the 50% probability level (the hydrogens of the CH_3 groups are omitted for clarity). N–H···N hydrogen bonds are shown as black dashed lines.

(2.687(12)–2.893(13) Å) than the fourth (3.174(12)–3.246(11) Å). Three intramolecular hydrogen bonds between the pyrrolic N–H bonds and the lone pairs of the neighbouring pyrrolidines are present. These hydrogen bonds fix the relative position of the adjacent pyrrole ring with respect to the neighbouring pyrrolidine ring and define two planes; the pyrrole rings are mutually inclined by 69.4(6)–71.2(6)°, and the best mean planes of the pyrrolidine rings are mutually inclined by 26.0(9)–26.8(6)°. The majority of the pyrrolidine rings have twisted conformations, leading to alternative positions of the quaternary carbons. Two of the quaternary carbons are situated above the average plane of the macrocycle and the other two are situated below. The positions of the quasi-axial methyl groups also alternate, with two above the plane and two below. Compound **2b** has been described previously[21] and possesses crystallographic C_2 symmetry. Its pyrrole rings are mutually inclined by 71.3(1)°, while its pyrrolidine rings have twisted conformations and their best mean planes are mutually inclined by 85(2)°. In the macrocycle of **2b** there are two short (2.802(16) Å) and two long (3.1174(17) Å) N···N distances between adjacent nitrogens.

X-ray structure determination of various metal complexes of compound **3** have been reported previously.[21] Here, we report on the crystal structure of compound **3** obtained by crystallization from methanol (Figure 2). The molecule in the crystal has pseudo-C_2 symmetry rather than C_4 symmetry.[22] The compound presents an average plane defined by the four nitrogen atoms. All of the NH groups point towards the same point, slightly above the average plane of the macrocycle, on the same side as the N–C–H hydrogen atoms. Four of the eight methyl groups bonded to the *meso* carbons are arranged in quasi-axial positions, whereas the other four point away from the macrocycle in quasi-equatorial positions. Two opposite pyrrolidine rings, involving atoms N2 and N4, have envelope conformations with the nitrogen at

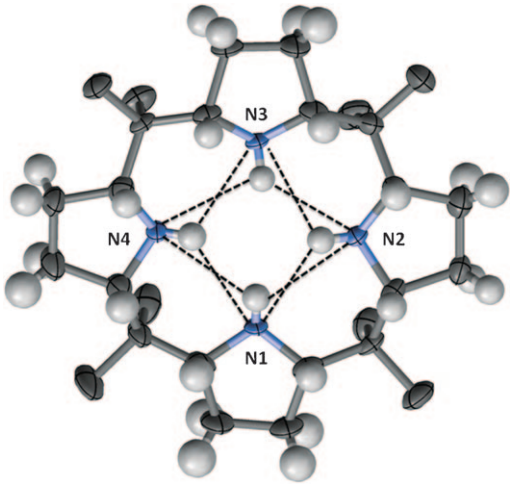


Figure 2. Molecular structure of compound **3**, with thermal ellipsoids drawn at the 50% probability level (the hydrogens of the CH_3 groups are omitted for clarity). N–H···N hydrogen bonds are shown as black dashed lines.

the flap, whereas the other two pyrrolidine rings, involving atoms N1 and N3, have twisted conformations. Here, the N···N distances between adjacent nitrogens vary much less, in the range 2.999(4)–3.109(4) Å, and eight hydrogen bonds are present. It is noteworthy that the free ligand adopts a similar conformation to that observed in the metal complexes, except that the NH groups in the complexes are in quasi-axial positions and on the opposite side with respect to the N–C–H hydrogen atoms.

Having identified and isolated all of the products that were detected by GC and GC-MS analysis, we started the screening of different catalysts under the same experimental conditions, aiming to increase the relative amount of the fully reduced product **3**. The use of commercially available 5% Rh/Al_2O_3 under the same conditions resulted in a slight increase in the total yield of the partially reduced products **2a–c** and a concomitant decrease in the yield of the fully reduced product **3** (Table 1, entry 4). Moreover, inversion of the diastereoselectivity occurred in the formation of the partially reduced products **2**, favouring instead the diastereoisomer **2a**.

One of us (D.S.) has been involved in the past years in the preparation of highly active zero-valent transition metals dispersed on the surface of graphite by the reduction of metal salts with potassium graphite C_8K, an intercalation compound of graphite.[23] Recently, rhodium on graphite ($C_{24}Rh$) has been prepared and used as a catalyst for the hydrogenation of aromatic compounds, including pyrrole derivatives.[24] When this catalyst was applied to the hydrogenation of calix[4]pyrrole **1**, a slightly increased yield of **2** (86%) and almost the same diastereoselectivity were observed. The amount of **3** did not increase significantly (entry 5). We then prepared a new catalyst, $C_{24}Ru$, in 97% yield by reduction of anhydrous $RuCl_3$ with three equivalents of C_8K. $C_{24}Ru$ showed comparable activity to $C_{24}Rh$ and predominantly **2a** and **2b** were obtained in almost the same amounts (entry 6). Finally, we observed that palladium on graphite, $C_{16}Pd$,[25] was slightly less effective than 10% Pd/C for the complete reduction of **1** to **3** (entry 7).

Next, we investigated changing the reaction medium. For this study, we selected the three catalysts (10% Pd/C, $C_{24}Rh$, 5% Rh/Al_2O_3) that gave the best results under the previously adopted experimental conditions (Table 2). First, we sought to determine the effect of the acidity of the medium using the Pd/C catalyst without changing the other experimental conditions. We performed the hydrogenation with 10% Pd/C as the catalyst in 95:5 mixtures of acetic/sulfuric acids and acetic/trifluoroacetic acids. In neither case was any hydrogenation product formed, possibly because of catalyst deactivation. The starting material **1** could be quantitatively recovered (entries 1 and 2). Decomposition occurred in neat trifluoroacetic acid (TFA) at 70°C using either Pd/C or Rh/Al_2O_3 (entries 3 and 4), whereas the use of $C_{24}Rh$ under the latter conditions selectively afforded **2b** in 55% yield (entry 5).

Table 2. Catalytic hydrogenations of calix[4]pyrrole **1** in different media.[a]

Entry	Catalyst	Solvent/Additive	T [°C]	**2a/2b/2c**[b]	**3**[b]
1	10% Pd/C	$AcOH/H_2SO_4$ 95:5	100	–[c]	–
2	10% Pd/C	AcOH/TFA 95:5	100	–[c]	–
3	10% Pd/C	TFA	70	–[c]	–
4	5% Rh/Al_2O_3	TFA	70	–[c]	–
5	$C_{24}Rh$	TFA	70	0:55:0	–
6	10% Pd/C	THF/AcOH 1:1	55	16:26:9[d]	6
7	5% Rh/Al_2O_3	THF/AcOH 1:1	55	32:20:8[e]	4
8	$C_{24}Rh$	THF/AcOH 1:1	55	23:14:11[e]	0.4
9	10% Pd/C	MeOH/AcOH 1:1	55	18:17:4[d]	2
10	5% Rh/Al_2O_3	MeOH/AcOH 1:1	55	21:12:5[e]	–
11	$C_{24}Rh$	MeOH/AcOH 1:1	55	9:5:3[e]	–
12	10% Pd/C	$AcOH/H_2O$ 8:2	100	36:57:0[e]	–

[a] The reactions were performed in an autoclave using a catalyst loading of 34 mol% of metal under 100 atm of H_2 pressure for 24 h. [b] Yields (%) were calculated by GC analysis using the internal standard methodology. [c] Decomposition of the starting material **1** was observed. [d] Traces of **1** were detected. [e] Starting material **1** largely accounted for the remaining percentage.

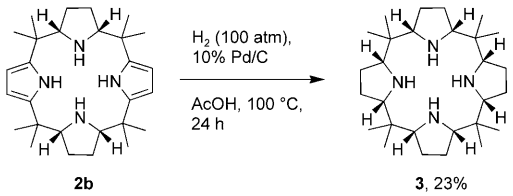
On the other hand, in a 1:1 tetrahydrofuran/acetic acid mixture at 55°C, the formation of both the half-reduced products **2a–c** and the fully hydrogenated product **3** was observed when using any of the three catalysts (entries 6–8). Similar results were obtained in a 1:1 methanol/acetic acid mixture (entries 9–11). However, the total yields of the reduced products and the diastereoselectivities among the respective compounds **2** were low in all cases. It is surprising that compound **3** was obtained in higher yield in a less acidic medium and at lower temperatures.

The poor solubility of **1** and/or **2** in the solvent mixtures is probably responsible for the low yields obtained. The choice of solvent appears to be crucial to achieve satisfactory results.[26] Surprisingly, we finally observed that performing the reaction with Pd/C in an 80:20 acetic acid/water mixture at

100 °C afforded compounds **2a** and **2b** in yields of 36 and 57 %, respectively.

Kuwano and co-workers have reported the enantioselective catalytic hydrogenation of *N*-Boc-pyrroles to pyrrolidines using a chiral homogeneous ruthenium catalyst.[27] Our attempt to hydrogenate the calix[4]pyrrole **1** by an analogous ruthenium-based procedure avoiding the presence of chiral ligands was unsuccessful.

We sought to ascertain whether compound **2b** could be converted to the fully hydrogenated compound **3** (Scheme 2), which would elucidate the hydrogenation pathway. Hydrogenation of **2b** with the Pd/C catalyst under the originally applied experimental conditions afforded compound **3** in 23 % GC yield, and the starting compound **2b** was recovered in 54 % GC yield. Apparently, decomposition of **2b** in the acidic medium occurred at a constant rate. The use of any other catalysts and different experimental conditions, including the addition of Lewis acids, resulted in no conversion to **3**. These results demonstrate that compound **2b** is rather resistant to hydrogenation, probably because of the increased steric hindrance introduced by the pyrrolidine rings. We believe that the isomers **2a** and **2c** are even less reactive than **2b**, as otherwise diastereoisomers of **3** would have been produced from them. It should also be pointed out that compound **3** could be formed from **1** through reaction pathways not involving **2b** as an intermediate. It is possible that after the hydrogenation of the first pyrrole ring of **1**, the next reduction proceeds on an adjacent pyrrole ring and that the resulting hypothetical half-hydrogenated intermediate, which has not been detected, undergoes a relatively fast hydrogenation ultimately affording the saturated compound **3**.



Scheme 2. Catalytic hydrogenation of compound **2b**.

Conclusion

GC analyses of the mixtures obtained following heterogeneously catalyzed hydrogenation reactions of *meso*-octamethylporphyrinogen (calix[4]pyrrole, **1**) have allowed the determination of the product compositions. As a function of the reduction conditions, one to four different reduction products could be isolated. Three of them, **2a–c**, were diastereoisomers of the partially reduced compound and displayed alternating pyrrole and pyrrolidine rings. Compounds **2a** and **2c**, which had not been detected during our previous work, have been isolated and their relative configurations have been assigned through single-crystal X-ray diffraction (**2a**) and spectroscopic (**2c**) studies. A single, all-*cis*, fully hydrogenated compound **3** could be obtained in low yields only under drastic reaction conditions (100 atm of hydrogen pressure at 100 °C in acetic acid).

Attempts to increase the yield of the saturated compound **3** using a variety of common as well as novel heterogeneous catalysts under diverse reaction conditions were unsuccessful. However, the half-hydrogenated compounds **2a** and **2b** could be obtained in increased overall yield (87 %) in an approximately 2:3 ratio by employing the same catalyst in an 80:20 AcOH/H_2O mixture, all other experimental conditions being identical. On the other hand, **2b** was selectively obtained in 55 % GC yield using rhodium-graphite, $C_{24}Rh$, in trifluoroacetic acid at 70 °C under a hydrogen pressure of 100 atm.

Experimental Section

The preparations of palladium-graphite $C_{16}Pd$,[25] rhodium-graphite $C_{24}Rh$,[24b] and calix[4]pyrrole **1**[21] have been reported elsewhere. Compounds **2b** and **3** have been described previously.[21]

Preparation of ruthenium-graphite ($C_{24}Ru$): Graphite (0.694 g, 57.8 mmol) was placed in a three-necked flask equipped with a condenser, a dropping funnel, an argon inlet, and a magnetic stirring bar and the flask was heated under argon at 150 °C for 10 min. Freshly cut potassium (0.282 g, 7.2 mmol) was slowly added to the stirred graphite while maintaining heating at 150 °C. After all of the potassium pieces had melted and a bronze-coloured powder of potassium-graphite (C_8K) had formed, the flask was allowed to cool to room temperature and the C_8K was covered with anhydrous THF (15 mL) without stirring. Then, a suspension of anhydrous $RuCl_3$ (0.50 g, 2.4 mmol) in a mixture of THF (20 mL), 1,2-dimethoxyethane (DME) (25 mL), and hexamethylphosphoramide (HMPA) (5 mL) was slowly added with stirring. The resulting mixture was heated at reflux temperature for 3 h, then cooled at 0 °C, whereupon water (10 mL) was slowly added. After stirring for 30 min, the solid was collected by filtration and washed with water, MeOH, and Et_2O (30 mL of each). The solid was dried at room temperature under vacuum (0.1 mmHg) for 6 h to give 0.895 g (96 %) of $C_{24}Ru$ as a dark-black powder.

General procedure for the small-scale hydrogenation reaction: Calix[4]-pyrrole **1** (0.200 g, 0.47 mmol), *n*-eicosane (0.0266 g, 0.094 mmol), and 10 % Pd/C (0.170 g, 0.16 mmol of Pd) were placed in a test tube (125 × 15 mm) containing a small cross stirring bar. AcOH (5 mL) was added and the test tube was placed inside an autoclave vessel containing AcOH (25 mL). The reaction mixture was kept under a hydrogen pressure of 100 atm at 100 °C. After 24 h, the autoclave was cooled to room temperature and the reaction mixture was filtered through a pad of Celite, which was washed with AcOH (2 × 20 mL) and CH_2Cl_2 (3 × 15 mL). The combined filtrate and washings were concentrated under reduced pressure to give a colourless slurry, to which CH_2Cl_2 (25 mL) and 5 % aqueous NaOH (15 mL) were added. The resulting mixture was stirred for 5 min. The organic layer was then separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were washed with brine (25 mL), dried over K_2CO_3, and concentrated under reduced pressure to give 0.206 g of a white solid. This was redissolved in EtOAc for GC analysis [Agilent 6850 A, column HP-1, length 3 m, I.D. 0.32 mm, film 0.25 μm; temperature program: 220 °C (2 min), then heating (5 °C min^{-1}) to 300 °C, holding for a further 6 min]. The yields of the products were calculated according to the calibration curve (see the Supporting Information).

Large-scale hydrogenation of calix[4]pyrrole (1): A glass cylinder inside an autoclave vessel was charged with acetic acid (100 mL), calix[4]pyrrole

1 (2.00 g, 4.70 mmol), *n*-eicosane (0.266 g, 0.94 mmol), and 10% Pd/C (1.70 g, 1.6 mmol of Pd). The autoclave was closed, put under magnetic stirring, filled with hydrogen (100 atm), and heated at 100 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through Celite and the solid was washed with AcOH (2×20 mL) and CH_2Cl_2 (2×20 mL). The combined filtrate and washings were concentrated to give a slurry residue, which was dried under high vacuum. A small amount of this residue was redissolved in CH_2Cl_2 (5 mL), and this solution was washed with 2 M aqueous NaOH (5 mL) prior to GC injection. Addition of CH_2Cl_2 (50 mL) to the stirred reaction product led to the formation of a suspension. The solid was filtered off, then the solid and the solution were treated as appropriate (vide infra) to obtain compounds **2b** and **2c** from the solid and compounds **3** and **2a** from the solution.

Compound 2b:[21] The precipitate was dissolved in water (30 mL) and NaOH pellets were added until pH 14 was reached, whereupon a white solid was formed. The whole was extracted with CH_2Cl_2 (4×30 mL). The organic layers were collected, dried over anhydrous K_2CO_3, and filtered, and then the solvent was evaporated to leave a white solid (0.501 g, 24%), from which **2b** (0.489 g, 23%) was obtained in pure form by crystallization from EtOAc.

Compound 3:[21] The previously obtained filtered solution was treated with 10% aqueous Na_2CO_3 (4×20 mL) and brine (50 mL). Extraction with CH_2Cl_2 (4×30 mL) and standard work-up gave a yellow oil, from which a solid precipitated upon addition of EtOAc. Filtration afforded compound **3** (0.164 g, 8%) as a white solid. Alternatively, **3** could be purified by column chromatography on neutral alumina eluting with CH_2Cl_2/EtOAc mixtures (0–100% gradient of CH_2Cl_2).

Compound 2a: The filtered solution obtained following the precipitation of compound **3** (see the above procedure) was concentrated to remove CH_2Cl_2. Further EtOAc (5 mL) was then added, whereupon compound **2a** precipitated. Alternatively, the previous filtered solution could be submitted to column chromatography on neutral alumina eluting with a CH_2Cl_2/MeOH mixture (99:1) to give pure **2a** (80 mg, 2%) as a white solid. M.p. 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (br s, 2H; pyrrole NH), 5.79 (d, J = 2.6 Hz, 4H; pyrrole), 3.11–3.04 (m, 4H; pyrrolidine CHN), 1.76–1.66 (m, 6H; pyrrolidine CH_2 and NH), 1.48–1.39 (m, 4H; pyrrolidine CH_2), 1.25 (s, 12H; CH_3), 1.22 ppm (s, 12H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 102.6, 68.5, 37.3, 28.3, 26.5, 23.3 ppm; IR (KBr): $\tilde{\nu}$ = 3269, 3147, 2968, 1660, 1469, 1376, 1331, 963, 815, 730, 662 cm^{-1}; MS (ES): m/z: 437.27 $[M+H]^+$, 459.53 $[M+Na]^+$; MS (EI): m/z: 286 (100), 152 (96), 202 (84), 269 (46), 219 (41), 162 (34), 108 (33).

Compound 2c: Compound **2c** accompanied isolated **2b** as an impurity. Impure **2b** (11.5 mmol, 5 g) was subjected to crystallization from EtOAc (150 mL) to give 4 g of pure **2b**. The mother liquor from the crystallization was concentrated under reduced pressure to give a white solid (1 g) composed of **2b** and **2c** (92:8). This was crystallized from EtOAc (50 mL) to give pure **2b** (0.6 g). The mother liquor was concentrated to give 0.4 g of a white solid again composed of **2b** and **2c** (68:32). This was recrystallized from EtOAc (50 mL) to give almost pure **2c** (0.15 g, 3%), which was washed with several portions of EtOAc. M.p. 147 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 6.83 (d, J = 1.6 Hz, 1H; pyrrole), 6.31 (d, J = 3.5 Hz, 1H; pyrrole), 6.21 (d, J = 3.5 Hz, 1H; pyrrole), 6.02 (d, J = 1.6 Hz, 1H; pyrrole), 3.68–3.56 (m, 4H; pyrrolidine CHN), 2.20–2.07 (m, 5H; pyrrolidine CH_2), 1.82–1.75 (m, 1H; pyrrolidine CH_2), 1.55 (s, 3H; CH_3), 1.47 (s, 6H; CH_3), 1.46 (m, 1H, pyrrolidine CH), 1.45 (s, 3H; CH_3), 1.44 (s, 3H; CH_3), 1.41 (s, 3H; CH_3), 1.30 (m, 1H; pyrrolidine CH_2), 1.29 ppm (s, 6H; CH_3); ^{13}C NMR (100 MHz, CD_3OD): δ = 134.2, 133.7, 133.5, 125.1, 119.3, 110.3, 109.9, 109.2, 70.5, 70.4, 70.1, 69.5, 38.5, 38.4, 38.1, 37.2, 29.0, 28.9, 28.1, 27.3, 27.1, 27.0, 26.5, 26.2, 25.8, 25.4, 24.7, 24.6 ppm; IR (KBr): $\tilde{\nu}$ = 3642, 3293, 3147, 2967, 2882, 2676, 1474, 1415, 1377, 1259, 814, 654 cm^{-1}; MS (ES): m/z: 437.27 $[M+H]^+$.

General procedure for the hydrogenation of 2b: The reaction was performed on 0.205 g (0.47 mmol) of **2b** according to the procedure previously described for the small-scale hydrogenation.

Crystal data for 2a: $C_{28}H_{44}N_4$, M_r = 436.67 g mol^{-1}; triclinic, $P\bar{1}$; T = 173(2) K; a = 15.2705(15), b = 15.304(4), c = 18.041(2) Å, α = 87.913(1), β = 64.964(1), γ = 85.060(1)°, V = 3805.8(11) Å^3; Z = 6; $F(000)$ = 1440; ρ = 1.143 g cm^{-3}; $\mu(Mo_{K\alpha})$ = 0.067; reflections measured 38671; unique reflections 14449; R_{int} = 0.1551; 866 parameters; wR_2 = 0.2147; S = 0.934 (all data); R_1 = 0.1038 for 5639 observed reflections [$I > 2\sigma(I)$]. Largest diffraction peak/hole +0.429/−0.298 Å^{-3}.

Crystal data for 3: $C_{28}H_{52}N_4$, M_r = 444.74 g mol^{-1}; monoclinic, $P2_1/c$; T = 173(2) K; a = 20.825(2), b = 6.3318(4), c = 21.0507(19) Å, β = 108.302(11)°, V = 2635.3(4) Å^3; Z = 4; $F(000)$ = 992; ρ = 1.121 g cm^{-3}; $\mu(Mo_{K\alpha})$ = 0.066; reflections measured 13510; unique reflections 3423; R_{int} = 0.074; 309 parameters; wR_2 = 0.1224; S = 1.021 (all data); R_1 = 0.0993 for 2363 observed reflections [$I > 2\sigma(I)$]. Largest diffraction peak/hole +0.732/−0.298 Å^{-3}. Further details and a description of the molecular structures of **2a** and **3** are available in the Supporting Information. CCDC-756401 (**2a**) and CCDC-756402 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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