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Retro-Diels–Alder reaction using bicyclo[2.2.2]octatriene-fused pyrrole during porphyrin synthesis

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Abstract—Porphyrin synthesis using 4,7-etheno-4,7-dihydro-2*H*-isoindole and tripyrranedicarbaldehyde gave a porphyrin derivative bearing no bicyclo[2.2.2]octatriene moiety as well as the targeted bicyclo[2.2.2]octatriene-fused porphyrin.

1. Introduction

Many excellent and reliable methods have been reported for the preparation of porphyrins and their analogues involving the naturally occurring porphyrinoids. Lindsey, MacDonald, and their related methods are commonly used in the preparations of a wide variety of porphyrins required for material chemistry due to their versatility, efficiency, and applicability.[1] In all these preparation methods of porphyrins, two chemical steps are involved: The first step is the construction of the macrocyclic ring skeletons by a cyclotetramerization or condensation reaction, and then the intermediary macrocyclic compounds are converted to the targeted porphyrin derivatives by treatment with oxidizing reagents such as quinones and oxygen. Among the macrocyclic intermediates, porphyrinogen (Fig. 1) is the most important intermediate with the lowest oxidation state, and has been synthesized and investigated by many groups from both synthetic and mechanistic points of view.[2] Other possible intermediates with higher oxidation states such as porphomethene, porphodimethene, phlorin, and isophlorin (Fig. 1) are also recognized, and were prepared in certain cases that they could resist the oxidation to porphyrins.[3] During our investigation for creation of new porphyrinoids, we found the intramolecular hydrogen transfer from the macrocyclic ring to the acetylenic *meso*-substituents affording *meso*-alkenyl-substituted porphyrins,[4] and became aware of an important role of the intermediates. In this Letter, we will reveal another example showing the importance of these intermediates in the porphyrin synthesis: In the preparation of bicyclo[2.2.2]octatriene-fused porphyrins, unusual porphyrin compounds bearing no

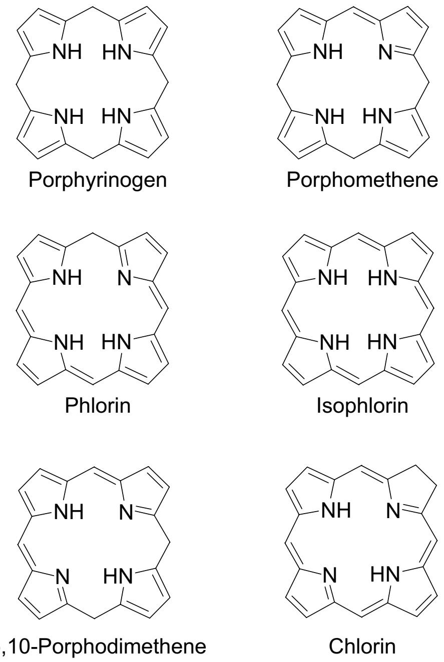

Figure 1. Intermediary compounds during porphyrin synthesis.

Keywords: Porphyrin synthesis; Retro-Diels–Alder reaction; Bicyclo[2.2.2]octatriene.

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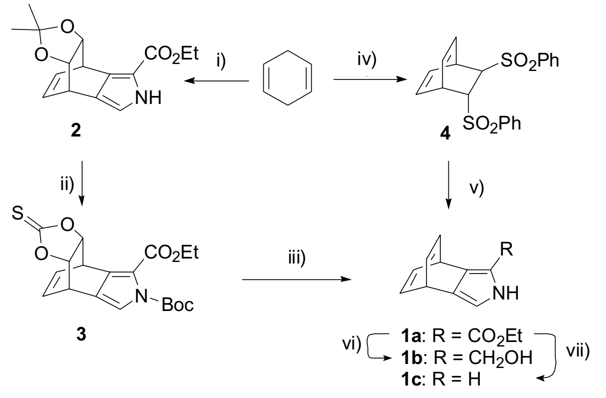
bicyclo[2.2.2]octatriene moiety were formed by the retro-Diels–Alder reaction.

The key starting pyrrole **1** was prepared from 1,4-cyclohexadiene as shown in Scheme 1. First, we planned to utilize Corey–Winter olefination[5] for the introduction of a double bond by conversion of the known isopropylidenedioxy-substituted ethanoisoindole **2** to the target pyrrole **1**. According to the literature, ethanoisoindole **2** was prepared in good yield.[6] The conversion of isopropylidenedioxy to thiocarbonate groups and then Boc protection of pyrrolic NH gave **3** in 87% yield. The olefination of **3** with 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[7] followed by deprotection gave the targeted pyrrole **1a** in 62% yield. From thermogravimetric analysis of pyrrole **1a**, no decomposition was observed under 200 °C and sublimation with decomposition occurred above 215 °C.

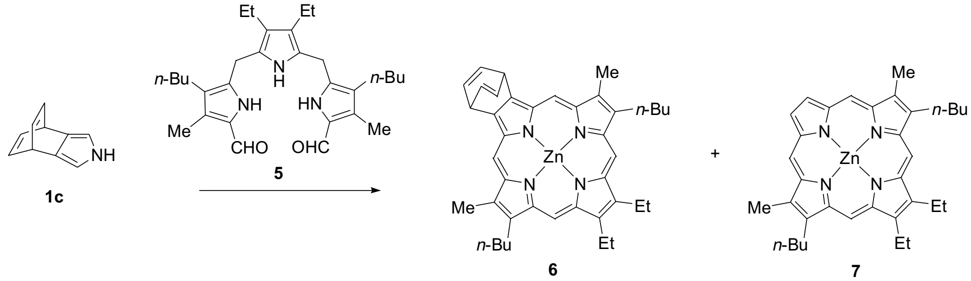


Scheme 1. Reagents, conditions, and yields: (i) Ref. 6; (ii) 1 M aq HCl, THF, 65 °C; thocarbonyldiimidazole, THF, 80 °C; $(Boc)_2O$, NaH, DMF, 80 °C; 87%; (iii) 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, toluene 125 °C; 62%; (iv) Ref. 8; (v) ethyl isocyanoacetate, *t*-BuOK, THF, 77%; (vi) $LiAlH_4$, THF, 0 °C, 89%; (vii) KOH, ethylene glycol, 200 °C.

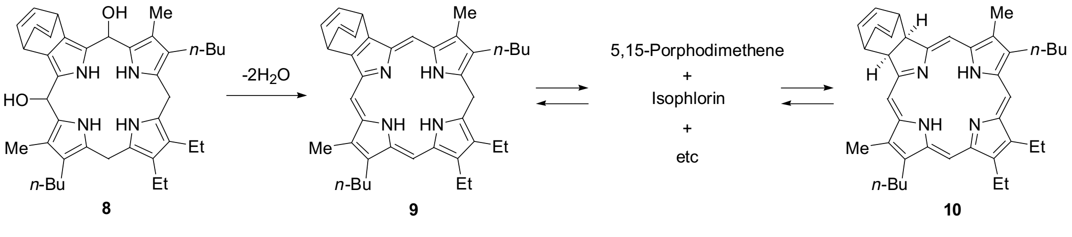
The shorter and more efficient synthesis of **1a** was achieved via the known bicyclo[2.2.2]octadiene **4**, which was prepared from 1,4-cyclohexadiene in very good overall yield according to the literature.[8] The modified Barton–Zard reaction of **4** with ethyl isocyanoacetate gave **1a** in 77% yield. The ester moiety of **1a** was converted to a hydroxymethyl group to give **1b** in 89% yield. Removal of the ester group in **1a** was quantitatively achieved by treatment with KOH in ethylene glycol at 200 °C to give **1c**.

First, we aimed at the preparation of porphyrins with one bicyclo[2.2.2]octatriene moiety in order to utilize the double bonds for porphyrin-ring construction.[9] Thus, the reaction of **1c** with tripyrranedicarbaldehyde **5** (3 mM concentration) was conducted in a 0.23 M solution of TFA in $CHCl_3$ at room temperature for 2 h under an inert atmosphere. After neutralization with triethylamine, oxidation with chloranil followed by complexation with $Zn(OAc)_2$ afforded two porphyrinic products, which were obtained as a mixture by silica-gel column chromatography. The products were successfully separated by preparative GPC, and the targeted porphyrin **6** and simple porphyrin **7** were obtained in 40% and 7% yields, respectively. A similar result was obtained by changing the oxidizing reagent from chloranil to DDQ (Scheme 2).

Formation of porphyrin **7** could be rationalized by the retro-Diels–Alder reaction of intermediary chlorin derivative **10**, which had the same oxidation state as 5,10-porphodimethene **9**, phlorin, and isophlorin. These intermediary compounds could be formed by acid-promoted dehydration and isomerization of the initial condensation product **8** (Scheme 3). In fact, a chlorin zinc



Scheme 2. Inverse [3+1] porphyrin synthesis of bicyclo[2.2.2]octatriene-fused pyrrole **1c** with tripyrranedicarbaldehyde **5**.

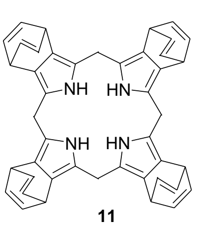


Scheme 3. Possible intermediates giving porphyrin **7**.

complex was formed with the aid of $Zn(OAc)_2$ from an equilibrium mixture of porphodimethene and phlorin species, which was obtained by the condensation of dipyrromethane and dipyrromethanedicarbaldehyde derivatives.[10] In this case, the divalent zinc metal greatly favored the chlorin formation over other species due to its valence and requisite for square planar ligand alignment. In order to investigate the isomerization, the acid-treatment period was changed, because the porphyrin synthesis was not so easily controlled by changing the proton concentration and strength. As the starting materials disappeared around 30 min under the reaction conditions, the acid condensation was stopped after 30 min stirring. After oxidation and complexation with zinc, bicyclo[2.2.2]octatriene-fused porphyrin **6** and retro-Diels–Alder porphyrin **7** were isolated in 43% and 0.4% yields, respectively. On the other hand, the formation of retro-Diels–Alder porphyrin **7** greatly increased and the yield became 17% in addition to bicyclo[2.2.2]octatriene-fused porphyrin **6** (58%), when the acid treatment period was elongated to 48 h.

Next, cyclotetramerization of α-hydroxymethylpyrrole **1b** was examined. Treatment of **1b** with *p*-TsOH gave a crude mixture of porphyrinogen **11** (Fig. 2), which was then subjected to oxidation with chloranil followed by treatment with $Zn(OAc)_2$. Quadruply bicyclo[2.2.2]-octatriene-fused porphyrin **12** was predominantly obtained in 74%, and retro-Diels–Alder product **13** was isolated only in a trace amount (0.4%). The similar result was obtained in the reaction using DDQ as the oxidizing reagent instead of chloranil; the yield of **13** was 0.3%. On the other hand, the product ratio of **13**/**12** greatly increased to be 1/4 when porphyrinogen **11** was oxidized in refluxing chloroform by slow addition of chloranil, although the total yield became lower due to the formation of unidentifiable materials.

Once porphyrin **12** was formed, no extrusion of any benzene molecule occurred. The thermal fragmentation of **12** afforded tetrabenzoporphyrinato zinc (TBP–Zn) as a sole product. This thermal behavior of zinc porphyrin **12** was examined by thermogravimetric analysis (TG, 10 °C/min). Figure 3 shows the TG curves of zinc porphyrin **12** as well as the corresponding bicyclo[2.2.2]-octadiene-fused zinc porphyrin (TBCODP–Zn). Fast weight loss of **12** started at much higher temperature (252 °C) than that of TBCODP–Zn (134 °C). This is well understood by the difference of extruding molecules (ethylene for TBCODP–Zn and acetylene for **12**). In both cases, more than theoretical amounts of their weights (theoretical: 16.4%) were lost during the fragmentation. This would be due to the inclusion of solvent molecules such as water. In fact, single crystals of **12** with two molecules of chlorobenzene were obtained from a chlorobenzene/methanol recrystallizing solvent system. Obviously, the last extrusion of acetylene in the fragmentation of **12** occurred more slowly between 265 and 280 °C than other three fragmentation steps. Close inspection of the TG curve of TBCODP–Zn revealed the similar phenomenon. The similar retardation in the final fragmentation step was observed in the thermolysis of TBCODP–H_2 and its core-modified derivatives with sulfur.[11] This phenomenon is well rationalized by the contribution of the major porphyrin 18π-electron system and local 6π-benzene aromaticity: In the last step, only the local aromaticity of 10π-isoindole not 6π-benzene is gained.



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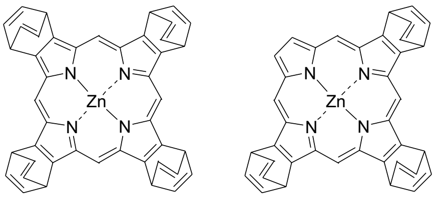

12 13

Figure 2. Cycloteramerization of bicyclo[2.2.2]octatriene **1b**.

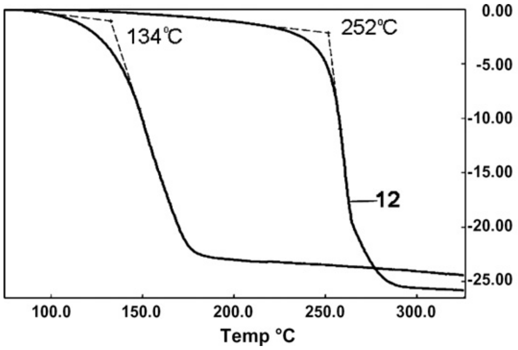

Figure 3. TG curves of **12** (right) and TBCODP–Zn (left).

In conclusion, we found an unusual retro-Diels–Alder reaction from the intermediary chlorin derivative in the synthesis of bicyclo[2.2.2]octatriene-fused porphyrins. Even in the absence of a metal template such as a zinc ion, the chlorin derivative was formed in the equilibrium between macrocyclic intermediates formed by the [3+1] porphyrin synthesis. The similar decomposition occurred in a very little extent during the oxidation of the porphyrinogen to the porphyrin with chloranil or DDQ. The bicyclo[2.2.2]octatriene-fused pyrrole can be used as a pyrrole equivalent for the porphyrin syntheses without oxidation.

2. Selected experimental data

2.1. Compound 1a

A white powder; 113.2–113.8 °C; ^1H NMR ($CDCl_3$) δ 1.38 (3H, t, $J = 6.8$ Hz, CH_2CH_3), 4.31 (2H, q, $J = 7.3$ Hz, CH_2CH_3), 4.76 (1H, m, bridge head), 5.22

(1H, m, bridge head), 6.48 (1H, d, $J = 2.5$ Hz, CHNH), 6.92 (4H, m, CH=CH), and 7.84 (1H, br, NH); ^{13}C NMR (CDCl$_3$) δ 14.5, 41.5, 41.9, 60.0, 112.3, 114.6, 136.5, 140.6, 141.0, 141.6, and 161.3; IR (KBr) $\nu_{\max}$/cm^{-1}: 3346, 1676, 1421, 1321, 1279, and 1124; MS (FAB) *m*/*z* 216 (M+1); Anal. Calcd for $C_{13}H_{13}NO_3$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.25; H, 6.02; N, 6.52.

2.2. Compound 6

A red powder, >233 °C (decomp); ^{1}H NMR (CDCl$_3$) δ 1.12 (6H, t, $J = 7.3$ Hz, (CH$_2$)$_3$CH_3), 1.76 (4H, m, (CH$_2$)$_2$CH_2CH$_3$), 1.93 (6H, t, $J = 7.6$ Hz, CH$_2$CH_3), 2.29 (4H, m, CH$_2$CH_2CH$_2$CH$_3$), 3.68 (6H, s, CH$_3$), 4.06–4.13 (8H, m, CH_2(CH$_2$)$_2$CH$_3$, CH_2CH$_3$), 6.59 (2H, m, bridge head), 7.65 (1H, d, $J = 3.4$ Hz, bridge), 7.66 (1H, d, $J = 3.4$ Hz, bridge), 10.11 (4H, s, meso), and 10.24 (4H, s, meso); ^{13}C NMR (CDCl$_3$) δ 11.0, 14.2, 18.6, 19.9, 21.0, 23.0, 26.3, 29.8, 35.5, 44.6, 45.6, 77.6, 97.1, 98.5, 141.5, 144.0, 156.8, 174.2, and one carbon was not found; MALDI-TOF MS 645 and 619; UV–vis (CHCl$_3$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) 403 (5.47), 533 (4.20), and 573 (4.20); HRMS (EI): calcd for $C_{40}H_{44}N_4Zn$, 644.2857; found, 644.2854.

2.3. Compound 7

A red powder, >207.0 °C (decomp); ^{1}H NMR (CDCl$_3$) δ 1.12 (6H, t, $J = 7.3$ Hz, (CH$_2$)$_3$CH_3), 1.74 (4H, m, (CH$_2$)$_2$CH_2CH$_3$), 1.89 (6H, t, $J = 7.3$ Hz, CH$_2$CH_3), 2.22 (4H, m, CH$_2$CH_2CH$_2$CH$_3$), 3.48 (6H, s, CH$_3$), 3.92 (4H, t, $J = 7.3$ Hz, CH_2(CH$_2$)$_2$CH$_3$), 4.02 (4H, q, $J = 7.3$ Hz, CH_2CH$_3$), 9.24 (2H, s, β-pyrrole), 9.84 (2H, s, meso), and 9.88 (2H, s, meso); ^{13}C NMR (CDCl$_3$) δ 11.6, 14.3, 18.6, 19.8, 23.1, 26.1, 35.4, 96.8, 101.2, 130.3, 136.6, 141.2, 142.4, 147.6, 147.8, and 148.4; MALDI-TOF MS 569; UV–vis (CHCl$_3$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) 401 (5.45), 532 (4.15), and 569 (4.12); HRMS (FAB$^+$): calcd for $C_{34}H_{41}N_4Zn+H^+$, 569.2623; found, 569.2624.

2.4. Compound 12

A red powder, >242 °C (decomp); ^{1}H NMR (CDCl$_3$) δ 6.64 (8H, m, bridge head), 7.64 (8H, d, $J = 2.9$ Hz, CH=CH), 7.65 (8H, m, $J = 2.9$ Hz, CH=CH), and 10.41 (4H, s, meso); ^{13}C NMR (CDCl$_3$) δ 45.7, 98.8, 141.5, 144.0, 157.8; MALDI-TOF MS 677, 650, 625, 599, and 573; UV–vis (CHCl$_3$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) 404 (5.31), 533 (4.21), and 569 (3.93). X-ray analysis, **12** · 2PhCl: $C_{56}H_{38}Cl_2N_4Zn$; FW = 903.23, red prism, 0.40 × 0.35 × 0.15 mm, monoclinic, *C*2/*c* (#15), $Z = 4$ in a cell of dimensions $a = 21.871(5)$ Å, $b = 9.436(2)$ Å, $c = 20.619(5)$ Å, $\beta = 104.7830(10)°$, $V = 4114.4(15)$ Å^3, $D_{\text{calc}} = 1.458$ g cm^{-3}, Mo Kα, $F(0\,0\,0) = 1864$, $T = 150$, 4723 unique reflections, 4287 with F^2 $2\sigma(F^2)$. The final $R_1 = 0.051$, $wR_2(\text{all}) = 0.117$, goodness-of-fit = 1.09 for 289 parameters refined on F^2, CCDC No. 652718.

2.5. Compound 13

A red powder, >213 °C (decomp); ^{1}H NMR (CDCl$_3$) 6.59 (2H, m, bridge head), 6.65 (4H, m, bridge head), 7.66 (12H, m, CH=CH), 9.57 (2H, s, β-pyrrole), 10.40 (2H, s, meso), and 10.45 (2H, s, meso); ^{13}C NMR (CDCl$_3$) 45.7, 45.7, 77.6, 77.6, 98.9, 101.9, 131.7, 141.8, 143.9, 144.0, 144.0, and 148.9; MALDI-TOF MS 601, 575, and 549; UV–vis (CHCl$_3$): $\lambda_{\max}$ ($\log_{10}\varepsilon$) 403 (5.26), 532 (4.13), and 567 (3.84).

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