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Serendipitous one-pot synthesis of brand-new, bowl-shaped molecular architecture from phloroglucinol and ninhydrin

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Abstract—We prepared a brand-new, bowl-shaped molecular architecture in one step from the reaction of ninhydrin and phloroglucinol in acetic acid in excellent yield (95%) in a one-pot reaction and the bipolarofacial nature of this compound was confirmed by its X-ray structure.

Design and synthesis of artificial receptors for selective recognition of guest substrates have received much attention in recent years.[1–3] Especially the construction of container molecules such as bowl-shaped molecules is still an interesting topic in organic synthesis.[1,2] Of particular interest are bipolarofacial molecular entities for one of the faces of the molecule to be hydrophobic while the other is hydrophilic with interspersed recognition sites. In these contexts, during our recent studies on the ninhydrin chemistry,[4f–h,5] we made a serendipitous observation that bowl shaped bipolarofacial architectures can be constructed in a one-pot reaction of ninhydrin with phloroglucinol.

The synthesis of ninhydrin–phenol adduct can be done easily in acidic medium.[4] In acetic acid medium, the *ortho*-position of phenol reacts selectively with the carbonyl group at the 2-position of ninhydrin (**1**) followed by acid-catalyzed formation of cyclic hemiketal to form the tetracyclic skeleton finally. We decided to examine the reaction of ninhydrin and phloroglucinol (**2**). We reasoned that a 3:1 adduct of ninhydrin and phloroglucinol would result if three ninhydrin molecules could react successively with one molecule of phloroglucinol. We also reasoned that we could synthesize a new bowl-shaped compound if the three indanone moieties were positioned toward same direction during the formation of the 3:1 adduct presumably due to the favorable interactions such as H-bonding or hydrophilic–hydrophobic interactions.[6]

Thus, when ninhydrin was treated with phloroglucinol in a 3:1 ratio, we found that the three *ortho*-positions of phloroglucinol (**2**) reacted with three molecules of ninhydrin successively to give the bowl-shaped compound **3** in excellent yield (95%) in a one-pot reaction (**1**/**2** in a 3:1 ratio, AcOH, 80–90 °C, 12 h, Scheme 1).[7]

The structure of **3** was confirmed by its IR, ^{1}H, ^{13}C NMR, mass spectra, and eventually by its X-ray crystal structure (Fig. 1).[8] The six-hydroxy groups directed downwards relative to the central hexahydro-trioxatrindene ring. Intramolecular hydrogen bonding interactions between the hydroxy groups and between the hydroxy groups and the oxygen atoms of carbonyl moiety or the oxygen atoms of ethereal linkage may be present. Three indanone moieties directed upwards from the central hexahydro-trioxatrindene moiety. The six carbon atoms at the ring junction (between indanone and hexahydro-trioxatrindene) are tetrahedral carbon, and as a result, three indanone moieties positioned in a propeller shape.[3]

We found another interesting characteristic of the bowl compound in the solid structure. As can be seen in Figure 1, one of the three benzene rings of the indanone moiety was positioned at the center of the inner cavity of the other bowl compound. Several types of hydrogen

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Keywords: Bowl compound; Phloroglucinol; Ninhydrin; One-pot synthesis.

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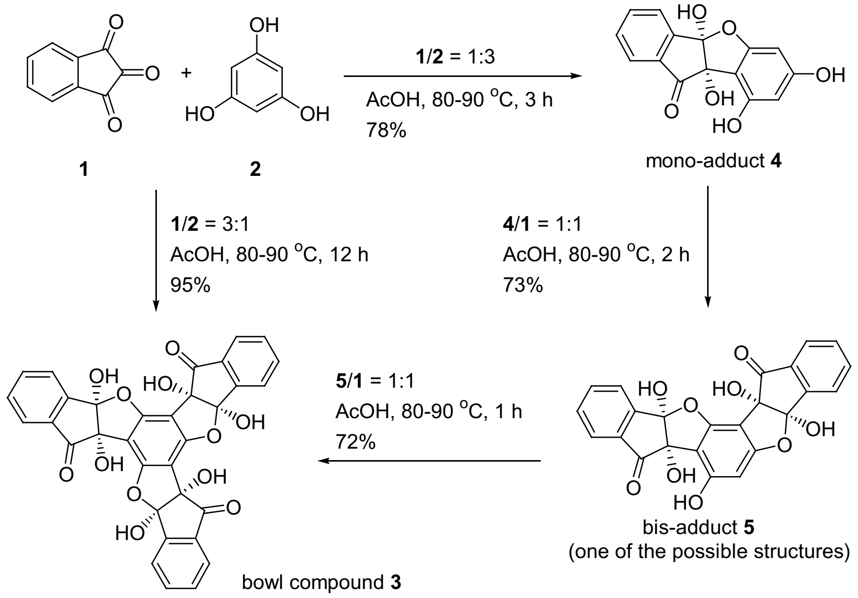

Scheme 1. Synthesis of bowl compound **3**.

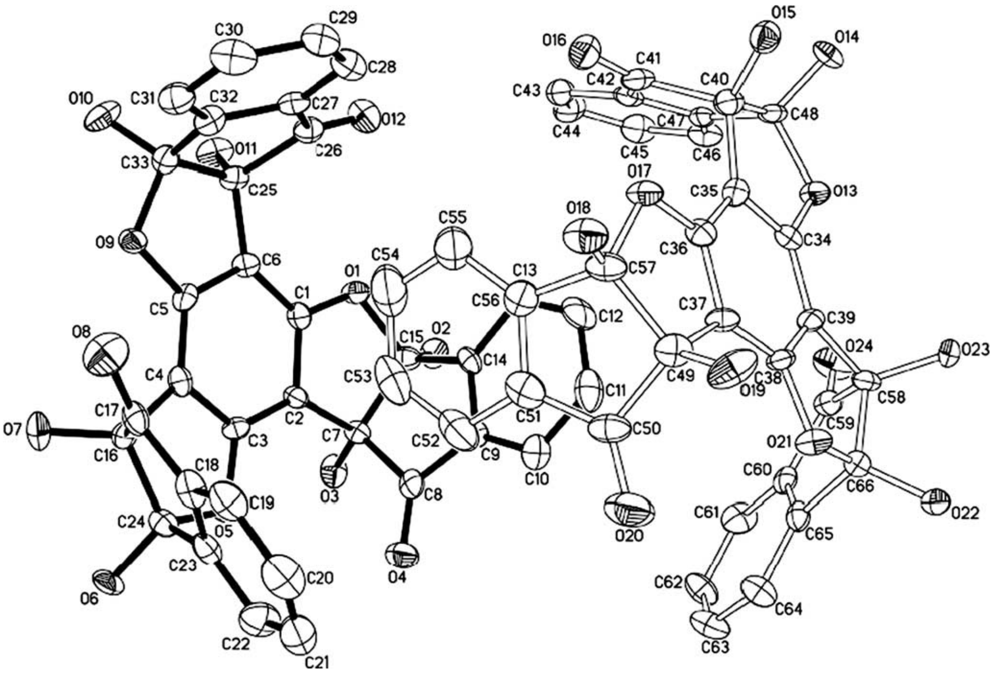

Figure 1. X-ray crystal structure of the bowl compound **3**.

bonding act inter- and intra-molecularly around the bottom portion of the bowl compound. Due to such hydrophilic interactions, the upper portion (the indanone moiety) gets together by weak π–π interactions. In the self-assembled structure (Fig. 1), the benzene moiety positioned in the inner cavity has two π–π interactions with the two benzene rings of the partner bowl compound.

Nevertheless, the synthesis of bowl compound **3** was carried out in a stepwise manner, albeit with moderate yield, initially (Scheme 1). The reaction of ninhydrin (**1**) and phloroglucinol (**2**) gave the mono-adduct **4** in 78% yield (**1/2** in a 1:3 ratio, AcOH, 80–90 °C, 3 h).[7] The reaction of **4** and ninhydrin afforded the bis-adduct **5** in 73% yield (**4/1** in a 1:1 ratio, AcOH, 80–90 °C, 2 h).[7] However, we could not assign the structure of the bis-adduct.[9] But, the next reaction of the bis-adduct **5** and ninhydrin gave the desired bowl compound **3** in 72% yield (**5/1** in a 1:1 ratio, AcOH, 80–90 °C, 1 h). The overall yield for the stepwise synthesis of **3** reached 41%. Irrespective of the structure and stereochemistry of the bis-adduct **5**,[9] we obtained the bowl compound **3** at last. The bowl compound might be formed via the sequential opening and closure of cyclic hemiketal ring[4] in order to produce the most thermodynamically stable bowl compound. During the formation of the bowl compound, hydrophilic and hydrophobic interactions might act to make the upper part (three indanone moieties) as hydrophobic and the lower part (six hydroxyl groups) as hydrophilic nature.

In summary, we synthesized a new bowl compound in excellent yield by a simple one-pot reaction from the reaction of ninhydrin and phloroglucinol. The modification of the bowl compound and study of potential guest molecules are currently underway.

Acknowledgements

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7. Experimental procedures and spectral data of the bowl compound **3**, mono-adduct **4** and bis-adduct **5** are as follows.

   One-pot synthesis of the bowl compound **3**: A stirred mixture of ninhydrin (1000 mg, 5.61 mmol) and phloroglucinol dihydrate (295 mg, 1.82 mmol) in glacial AcOH (25 mL) was heated to 80–90 °C for 12 h. During the reaction white solid was deposited in the reaction mixture. After cooling the reaction mixture to room temperature solid materials were filtered and washed successively with cold AcOH and ether to afford the desired compound as a white solid, 1048 mg (95%). Analytically pure sample was obtained by recrystallization in ethanol/benzene.

   Spectroscopic data of the bowl compound **3**: 95%; white solid, mp 230–232 °C (EtOH/benzene, dec); IR (KBr) 3572, 3413, 1724, 1635, 1146 cm^{-1}; ^{1}H NMR (CDCl$_3$ + three drops of THF-d_8) δ 7.40 (td, $J = 7.5$ and 1.2 Hz, 3H), 7.53 (d, $J = 7.5$ Hz, 3H), 7.60 (br s, 3H, OH), 7.63 (br s, 3H, OH), 7.68 (td, $J = 7.5$ and 1.2 Hz, 3H), 7.89 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (CDCl$_3$ + three drops of THF-d_8) δ 80.73, 101.31, 114.39, 123.56, 125.36, 131.35, 134.47, 136.60, 147.66, 157.35, 196.65; LCMS *m*/*z* 606.0 (M$^+$, $C_{33}H_{18}O_{12}$); HRMS (MALDI-TOF): for $C_{33}H_{18}O_{12}$, calcd 606.0798, found 606.0901, for $C_{33}H_{18}O_{12}$+Na, calcd 629.0696, found 629.0653.

   Synthesis and spectroscopic data of the mono-adduct **4**: A solution of ninhydrin (250 mg, 1.40 mmol) and phloroglucinol (680 mg, 4.20 mmol) in acetic acid (4 mL) was heated to 80–90 °C for 3 h. After removal of acetic acid, the reaction mixture was diluted with ethyl acetate (40 mL), and washed with water (20 mL). The combined organic layers were dried over MgSO$_4$, filtered, concentrated, and purified by flash column chromatography (hexanes/ethyl acetate = 1:3) to give the mono-adduct **4** as a white solid (312 mg, 78%); mp 217–219 °C; IR (KBr) 3460, 3232, 1712, 1631, 1142 cm^{-1}; ^{1}H NMR (CDCl$_3$ + two drops of DMSO-d_6) δ 5.79 (br s, 1H, OH), 5.89 (d, $J = 2.0$ Hz, 1H), 6.02 (d, $J = 2.0$ Hz, 1H), 6.39 (br s, 1H, OH), 7.21 (br s, 1H, OH), 7.55 (td, $J = 7.5$ and 0.9 Hz, 1H), 7.76–7.82 (m, 2H), 7.95 (d, $J = 7.5$ Hz, 1H), 8.87 (br s, 1H, OH); ^{13}C NMR (CDCl$_3$ + two drops of DMSO-d_6) δ 82.85, 90.74, 97.13, 102.31, 110.37, 124.07, 125.21, 130.94, 133.80, 136.92, 149.20, 156.13, 158.81, 162.33, 199.87; Mass (70 eV) *m*/*z* (rel intensity) 51 (53), 69(85), 76 (100), 77 (68), 104 (52), 153 (63), 268 (47), 286 (M$^+$, 41).

   Synthesis and spectroscopic data of the bis-adduct **5**: A solution of **4** (220 mg, 0.77 mmol) and ninhydrin (137 mg, 0.77 mmol) in acetic acid (3 mL) was heated to 80–90 °C for 2 h. After cooling to room temperature the solid was

filtered and washed with acetic acid and methylene chloride to give the bis-adduct as a white solid (252 mg, 73%); mp 198–202 °C; IR (KBr) 3618, 3421, 3251, 1720, 1701 cm^{-1}; Mass (70 eV) *m*/*z* (rel intensity) 104 (95), 153 (52), 268 (87), 286 (100), 428 (28), 446 (M$^+$, 31); HRMS (MALDI-TOF): for $C_{24}H_{14}O_9$+Na, calcd 469.0534, found, 469.0116.

Synthesis of bowl compound **3** *from the reaction of* **5** *and* **1**: A mixture of **5** (200 mg, 0.45 mmol) and ninhydrin (80 mg, 0.45 mmol) in acetic acid (2 mL) was heated at 80–90 °C for 1 h. After cooling to room temperature the solid was filtered and washed with a few drops of acetic acid and methylene chloride successively to give the bowl compound **3** as a white solid (196 mg, 72%). The melting points and all spectroscopic data were identical with the bowl compound prepared from the one-pot reaction.

8. Crystal data of bowl compound: solvent of crystal growth (ethanol/benzene); empirical formula $C_{33}H_{27}O_{16.50}$, Fw = 687.55, crystal dimensions 0.30 × 0.20 × 0.20 mm^3, triclinic, space group $P-1$, $a = 13.8093(15)$ Å, $b = 14.8536(16)$ Å, $c = 15.4644(17)$ Å, $\alpha = 83.471(3)°$, $\beta = 70.508(2)°$, $\gamma = 83.332(2)°$, $V = 2960.5(6)$ Å^3, $Z = 4$, $D_{\text{calcd}} = 1.543$ mg/m^3. $F_{000} = 1428$, Mo Kα ($\lambda = 0.71073$ Å), $R_1 = 0.0759$, $wR_2 = 0.1579$ ($I > 2\sigma(I)$). The crystal structure of the bowl compound contained nine molecules of water per two bowls. Thus the empirical formula is $C_{33}H_{27}O_{16.5}$ (Fw = 687.55). We omitted water molecules and hydrogen atoms for clarity (Fig. 1). The X-ray data has been deposited in CCDC with number 258764.
9. The ^{1}H NMR spectrum of the bis-adduct **5** showed broad and complex peaks and we could not assign correctly. The reason for the rather complex and broad pattern might be due to the presence of regioisomeric and/or stereoisomeric and/or partial ring-opened compounds. But, fortunately, the mass and elemental analysis data demonstrated the compound must be a bis-adduct.