## PREPARATION AND MOLECULAR RECOGNITION BEHAVIOR OF A HEXAPUS AZAPARACYCLOPHANE

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Summary: The proton dissociation, iron-coordination, and molecular recognition behavior of a hexapus triaza[3.3.3]paracyclophane having three catechol moieties and six hydrocarbon chains was investigated in aqueous media.

In connection with the chemistry of 1,5,9-N,N',N''-tris(2,3-dihydroxybenzoyl)cyclotriazatridecane (CYCAM) which was developed by Raymond et al. as a siderophore model,<sup>1,2</sup> we prepared in this work a triaza[3.3.3]paracyclophane derivative having three catechol moieties and six hydrocarbon chains (1). The proton-dissociation and iron-coordination behavior of 1, as well as its molecular recognition capability toward hydrophobic guest molecules, was investigated in aqueous media. Hexapus azaparacyclophane 1 was prepared by following the reaction steps shown in Scheme 1.

A catechol derivative with two hydrocarbon chains (3) was prepared from the acid chloride of  $2^3$  and N,N-di(tetradecyl)amine<sup>4</sup>, and purified by gel-filtration chromatography on a column of Sephadex LH-20 with chloroform-methanol (1:1 v/v) as an eluant; a viscous and pale yellow liquid, yield 90.4 %. IR (neat)  $v_{C=0}$ (ester) 1740 cm<sup>-1</sup>; NMR (60 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$  0.90 [6H, t, (CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 1.25 [48H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 3.01 (4H, broad s, NCH<sub>2</sub>), 3.80 (9H, s, OCH<sub>3</sub>), 6.92 (1H, d, phenyl H), 7.45 (1H, d, phenyl H). Found: C, 74.36; H, 10.96; N, 2.18%. Calcd for C<sub>39</sub>H<sub>69</sub>NO<sub>5</sub>: C, 74.12; H, 11.00; N, 2.22%.





Compound 3 was hydrolyzed with sodium hydroxide in  $H_2O-CH_3OH$  (1:75 v/v), and the product (4) was purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as an eluant; a viscous and pale yellow liquid, yield 98.2 %. IR (neat)  $v_{C=0}$  (carboxylic acid) 1740,  $v_{C=0}$ (amide) 1640 cm<sup>-1</sup>; NMR (60 MHz, CD<sub>3</sub>OD)  $\delta_H$  0.95 [6H, t, (CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 1.21 [48H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 3.01 (4H, broad s, NCH<sub>2</sub>), 3.85 (6H, s, OCH<sub>3</sub>), 6.94 (1H, d, phenyl H), 7.73 (1H, d, phenyl H). Found: C, 73.68; H, 10.88; N, 2.32%. Calcd for C<sub>18</sub>H<sub>67</sub>NO<sub>5</sub>: C, 73.85; H, 10.93; N, 2.27%.

Compound 5 was prepared from the acid chloride of 4 and 2,11,20triaza[3.3.3]paracyclophane<sup>5</sup> in the presence of dry triethylamine, and purified by gel-filtration chromatography on a column of Sephadex LH-20 with chloroformmethanol (1:1 v/v) as an eluant; a colorless viscous liquid, yield 83.7 %. IR (neat)  $v_{C=0}$ (amide) 1640 cm<sup>-1</sup>; NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{\rm H}$  0.91 [18H, t, (CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 1.97 [144H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 3.19 [12H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>], 3.80 (9H, s, OCH<sub>3</sub>),

3.85 (9H, s, OCH<sub>3</sub>), 4.30 (12H, broad s, PhCH<sub>2</sub>N), 6.61-7.20 (18H, m, phenyl H). Found: C, 76.20; H, 10.17; N, 3.81%. Calcd for  $C_{138}H_{222}N_6O_{12}$ ·H<sub>2</sub>O: C, 76.19; H, 10.38; N, 3.86%.

Dimethylsulfide-borane reduced all the amide and methoxy groups of 5, and the product (6) was purified by gel-filtration chromatography on a column of Sephadex LH-20 with chloroform-methanol (1:1 v/v) as an eluant; a pale yellow solid, yield 90 %. IR (KBr)  $v_{C=0}$  disappeared; NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_{H}$  0.92 [18H, t, (CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 1.23 [144H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 3.02 [12H, broad s, NCH<sub>2</sub>(CH<sub>2</sub>)<sub>12</sub>], 3.70 (6H, s, OH), 4.19 (24H, s, NCH<sub>2</sub>), 7.23 (12H, m, phenyl H), 7.55 (3H, d, catechol H), 7.70 (3H, d, catechol H). Found: C, 67.70; H, 10.21; N, 3.53%. Calcd for C132H228N6O6.6HCl.7H2O: C, 67.92; H, 10.45; N, 3.60%.

The six nitrogen atoms of 6 were methylated with methyl iodide, and the product was applied on an ion-exchange column of Amberlite IRA-401 to replace the counterions by bromide ions. The product (1) was purified by gel-filtration chromatography on a column of Sephadex LH-20 with methanol as an eluant; a pale yellow solid, yield 98 %. NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 0.87 [18H, t, (CH<sub>2</sub>)<sub>12</sub>CH<sub>3</sub>], 1.25 [144H, broad s,  $NCH_2(CH_2)_{12}CH_3$ ], 1.86 [9H, broad s,  $(C_6H_4)CH_2N^+CH_3CH_2(C_6H_4)$ ], 3.15 (21H, broad s, CH<sub>2</sub>N+CH<sub>3</sub>CH<sub>2</sub>), 4.44 (24H, m, NCH<sub>2</sub>), 7.29 (18H, m, phenyl and catechol H). Found: C, 62.49; H, 9.01; N, 3.39%. Calcd for C138H240Br6N6O6.5H2O: C, 62.57; H, 9.31; N. 3.17%.

0.1M KOH at an ionic strength of 0.10 with KNO<sub>3</sub> and at 25.0 °C under argon atmosphere (Figure 1A). The acid dissociation constants for the first three protons (refer to equations 1, 2, and 3) were evaluated from the titration curve: pKa(H<sub>6</sub>L), 5.18; pKa(H<sub>5</sub>L), 5.96; pKa(H<sub>4</sub>L), 6.54. The corresponding values for an enterobactin model (CYCAM) were reported to be 7.86, 8.65, and 9.26, H The present values are respectively.<sup>1</sup> somewhat smaller in pKa relative to those for CYCAM, most likely due to overlapped effects: an electrostatic effect exerted by positive charges placed in the proximity portions of the catechol moieties; formation of strong hydrogen bonds among the catechol moieties as

$$H_{6}L \xrightarrow{Ka(H_{6}L)} H_{5}L^{-} + H^{+} \quad (1)$$

$$H_5L^ H_4L^{2-} + H^+$$
 (2)

$$H_4L^{2-}$$
  $\frac{Ka(H_4L)}{L_3}$   $H_3L^{3-} + H^+$  (3)

Potentiometric titration of hexapus cyclophane 1 was carried out by adding



Figure 1. Potentiometric titration curves for hexapus azaparacyclophane 1 in aqueous solution ( $\mu$  0.10 with KNO<sub>3</sub>) by adding 0.10 M aqueous KOH at 25.0 °C under argon atmosphere: a, moles of base added per mole of ligand; A, 1 (1.0 x  $10^{-4}$  M); B, 1 + Fe<sup>3+</sup> (1:1; 1.0 x  $10^{-4}$  M each).



PAN

caused by hydrophobic association of the six hydrocarbon chains. The coordination interaction of 1 with ferric ions was investigated by potentiometric titration under the identical conditions (Figure 1B). There is a clear inflection at a=6, which indicates that a single species is formed upon complete dissociation of all the catechol protons. This means that all the catechol moieties are coordinated to the ferric ion at 1:1 molar ratio of 1 to Fe<sup>3+</sup> above pH 6.

Molecular recogntion behavior of hexapus cyclophane 1 toward hydrophobic guests was investigated in aqueous buffer of 2-[4-(2hydroxyethyl)piperazinyl]ethansulfonate (0.01 M, pH 8.0;  $\mu$  0.10 with KCl) by electronic spectroscopy in a manner as described previously.<sup>6</sup> Anionic and nonionic guests, OG and PAN, respectively, were incorporated into the host with the binding constants, 6.67 x 10<sup>5</sup> and 7.46 x 10<sup>5</sup> M<sup>-1</sup>, respectively. However, a cationic guest, QR, was not recognized by the host. Consequently, the present host recognizes hydrophobic guests in aqueous media on the basis of hydrophobic and electrostatic effects in a manner comparable to that observed with octopus cyclophanes (refer to 7).<sup>6</sup>



QR

Studies on molecular recognition by iron complexes of 1 are in progress in our laboratories.

## References

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