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Setsune, Jun-ichiro
Tsukajima, Aki
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(Citation)
Tetrahedron Letters,48(9):1531-1535

(Issue Date)
2007-02

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90000170

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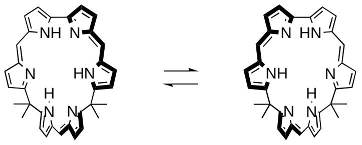
Jun-ichiro Setsune,* Aki Tsukajima, and Junko Watanabe

Department of Chemistry,

Faculty of Science, Kobe University

Nada-ku, Kobe 657-8501, Japan



(*M*)-**6** (*P*)-**6**

Pergamon

TETRAHEDRON
LETTERS

Synthesis and chiroptical property of C_2-symmetric cyclohexapyrrole

Jun-ichiro Setsune,* Aki Tsukajima, and Junko Watanabe

Department of Chemistry, Faculty of Science, Kobe University, Nada-ku, Kobe 657-8501, Japan

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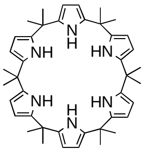
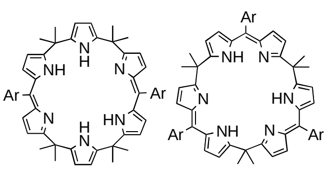
Abstract— Condensation reaction of *gem*-dimethyldipyrrylmethane-5,5'-dicarbinol and 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrole under the catalysis by trifluoroacetic acid gave a hexapyrrolic macrocycle **6** in 15% yield after DDQ oxidation. X-ray crystallography of **6** shows that three parts of highly planar dipyrrylmethene unit are assembled by two sp^3 hybridized *gem*-dimethyl carbon bridges and one direct linking at the pyrrole α-positions, leading to C_2 molecular symmetry. The complexation of **6** with (*S*)-(+)- and (*R*)-(-)-mandelic acid induced a CD Cotton effect at 461 and 650 nm.

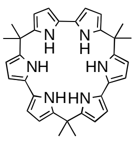
Hexapyrrolic macrocycles with bridging sp^3 carbon(s) have been synthesized and their unique structures with interrupted π-electron conjugation are in contrast to those of fully conjugated hexaphyrins.[1-3] Depending on the substitution pattern of the six bridging sp^3 carbons and pyrrole β-positions, calix[6]pyrrole changes its shape from hexagonal disc-like structure to trigonal cone structure and hexagonal column-like structure.[1] Calix[6]phyrins with combination of sp^3 and sp^2 bridging carbons and calix[3]bipyrrole with a little bit smaller cavity size have unique structural features.[2,3] Some of these cyclohexapyrroles are drawing great attention because of the anion binding properties. In contrast to these structure and function, this paper focuses on the new aspect of cyclohexapyrrole with bridging sp^3 carbons. A new cyclohexapyrrole having C_2 molecular symmetry is described with its application to supramolecular chirogenesis where optically active carboxylic acid regulates the chiral conformation of the macrocycle.[4]



calix[6]-
pyrrole



calix[6]phyrins



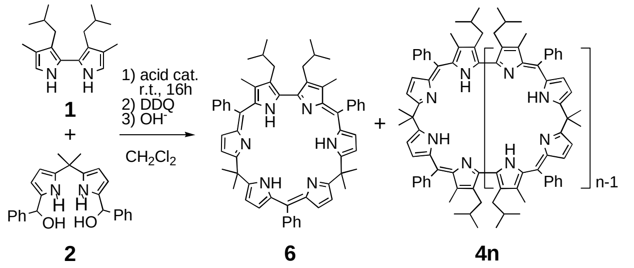
calix[3]-
bipyrrole

The acid catalyzed condensation reactions between 2,2'-bipyrrole and dipyrrylmethane-5,5'-dicarbinol have been reported to give corrole and octaphyrin(1.1.1.0.1.1.1.0) after oxidative work-up.[5] We examined here a similar [2+2]-type cyclization of 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrole **1** and *gem*-dimethyldipyrrylmethane-5,5'-dicarbinol **2**, which generated isocorrole and the higher homologues after DDQ oxidation. The presence of alkyl substituents at the 2,2'-bipyrrole β-positions and at the dipyrrylmethane central position in our case significantly changed the distribution and yield of the cyclooligomers in comparison with the previous works.[5] If scandium triflate (Sc(OTf)$_3$) or trifluoroacetic acid (TFA) was used as an acid catalyst in 1 mmol dm^{-3} concentration with reactant concentration of 30 mmol dm^{-3}, isocorrole **4**, cyclooctapyrrole **8** and the higher homologues **12**, **16**, **20**, **24**, **28** were obtained in ca. 50% total yields as shown in Table 1 (run 1 and 2). We used here much smaller amount of catalyst and solvent in comparison with the literature reaction where 25% yield of octaphyrin(1.1.1.0.1.1.1.0) was obtained using 10 mmol dm^{-3} concentration of Yb(OTf)$_3$ with 2.5 mmol dm^{-3} reactant concentration.[5a] The product distribution and yield in these reactions of **1** and **2** are similar to those observed in the reaction of **1** and bis(azafulvene) **3**, a doubly dehydrated product from **2**.[6] However, the present acidic reaction conditions gave rise to cyclohexapyrrole **6**[7] that was absent in the reaction of **1** and **3** under neutral conditions.

Keywords: porphyrinoids, calixphyrin, porphyrin, hexaphyrin, chirality, induced CD

*Corresponding author.

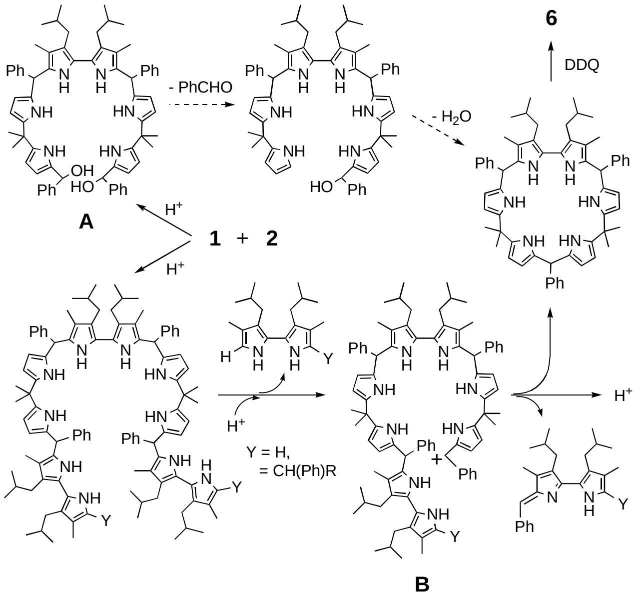
Table 1. Synthesis of cyclopolypyrroles **6** and **4n** (n = 1 ~ 7)



Run	Catalyst	Molar ratio[a)]		Yield / %			
		cat./**1**	**2**/**1**	**6**	**4**	**8**	**12 – 28**[b)]
1	Sc(OTf)$_3$	0.034	1.0	2.1	7.6	25.1	21.1
2	TFA	0.033	1.0	tr	4.6	12.4	28.5
3	TFA	0.22	1.0	15.1	5.3	-	-
4	TFA	0.25	2.0	3.2	1.1	-	-

[a]The concentration of **1** is in the range of 0.027-0.032 mol dm^{-3}. [b]The sum of higher homologues **12**, **16**, **20**, **24**, and **28**.

Increasing the amount of TFA from 0.033 molar equivalents (1 mmol dm^{-3}) to 0.22 molar equivalents (7 mmol dm^{-3}) caused formation of **6** in 15% yield with complete disappearance of the higher homologues (Table 1, run 3). Since **6** is made of one bipyrrole and two *gem*-dimethyldipyrrylmethanes, 1:2 molar ratio of **1** and **2** in the reactant composition was expected to give a better yield of **6**. However, this was not the case and the yield of **6** was significantly decreased. (Table 1, run 4). Therefore, it seems unlikely that the hexapyrrole-α,ω-dicarbinol (**A**) may lead to **6** by the acid catalyzed release of benzaldehyde followed by the dehydration as shown in Scheme 1. The pyrrolylphenylmethyl cation intermediates (**B**) produced during the acid catalyzed decomposition of the big cyclooligopyrroles or long chain oligopyrroles may lead to **6**. This protonolysis reaction of the C_{meso}-$C_{pyrrole\text{-}\alpha}$ bond is known to give rise to the scrambled macrocycles in the porphyrinoid synthesis,[8] and seems to promote the transformation to **6** in the present case under the strongly acidic reaction conditions.



Scheme 1: Plausible mechanism for formation of **6**.

The X-ray crystallography of **6**[9] shows that three dipyrrylmethene units are assembled by two sp^3 hybridized *gem*-dimethyl carbon bridges and one direct linking at the pyrrole α-positions, which leads to a beautiful C_2-symmetric molecular shape (see Figure 1). The C_2 rotational axis passes through C(15) and the midpoint of the bipyrrole 2,2'-bond C(1)-C(1A). The torsion angles N(1)-C(4)-C(5)-C(6) and C(4)-C(5)-C(6)-N(2) which are diagnostic of the planarity of the N(1)-C(5)-N(2) dipyrrylmethene unit are 0.58° and 2.39°. The corresponding torsion angles N(3)-C(14)-C(15)-C(14A) and C(14)-C(15)-C(14A)-N(3A) for the N(3)-C(15)-N(3A) dipyrrylmethene are 2.95° and 2.95°. Two dipyrrylmethene units are connected by a hinge-like bipyrrole 2,2'-bond with the N(1)-C(1)-C(1A)-N(1A) torsion angle of 54.51°. The mean plane of each dipyrrylmethene was defined by eleven sp^2 atoms and the angles between these three dipyrrylmethene mean planes are 98.29°, 98.29°, and 58.93°. These highly planar dipyrrylmethene units indicate that **6** is almost free from the ring strain of the macrocycle and the conformational freedom of the macrocycle is limited.

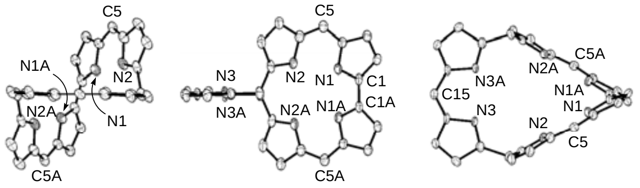


Figure 1. Ortep drawings of **6** with a numbering scheme: a front view (left), a side view (center), and a top view (right). Peripheral substituents are omitted for clarity. N(1A), N(2A), N(3A), C(1A), and C(5A) are at equivalent positions (-x, y, 0.5-z) of N(1), N(2), N(3), C(1), and C(5), respectively.

A pair of methyl doublets at 0.76 and 0.70 ppm due to the *iso*-butyl group and a pair of methyl singlets at 1.77 and 1.54 ppm due to the *gem*-dimethyl group were observed in the ^{1}H NMR in tetrachloroethane-d_2 at 20 °C. Since the latter signals were coalesced at 90 °C, the interconversion between the enantiomeric forms of **6** is taking place on the NMR time scale. The energy barrier ($\Delta G^{\ddagger}_{363}$) for the racemization estimated on the basis of the coalescence temperature and the chemical shift difference between the *gem*-dimethyl signals is 76 kJ mol^{-1}. This barrier is in the range where optical resolution is not easy. The major UV-vis band of **6** appears at an intermediate wavelength (453 nm) between **4** (420 nm) and **8** (541 nm) and it shifted to 457 nm on protonation. A broad visible region band of **6** centered at 611 nm was shifted to 714 nm at the same time by protonation as seen in Figure 2 (line a and b). While the CD spectrum of free base **6** in CH_2Cl_2 solution (1.1×10^{-5} mol dm^{-3}) is silent, addition of (*S*)-(+)-mandelic acid (200 equiv) in methanol solution (1.65×10^{-1} mol dm^{-3}) induced a positive CD Cotton signal at 461 nm and a negative CD Cotton signal at around 650 nm (Figure 2, line b*). A mirror image CD spectrum was observed by using (*R*)-(-)-mandelic acid (Figure 2, line b**). These observations clearly indicate that the carbon center asymmetry of the carboxylic acid induced the axis asymmetry of **6** by the complex formation. The further UV-vis spectral change was observed by adding more amount of (*S*)-(+)-mandelic acid. A shoulder band at 500 nm increased and a broad visible region band shifted to 685 nm at the addition of 3300 equiv of (*S*)-(+)-mandelic acid (Figure 2, line c), when the 461 nm CD band almost disappeared and new CD bands at 393 (positive), 501 (positive), and 620 (negative) nm (Figure 2, line c*) appeared. This indicates that polyprotonation of **6** does not change the helicity of the π-conjugated tetrapyrrolic moiety.

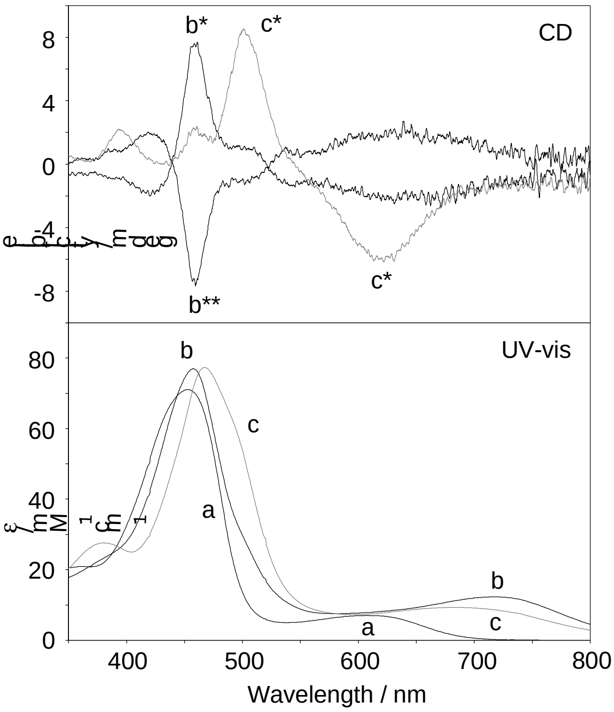
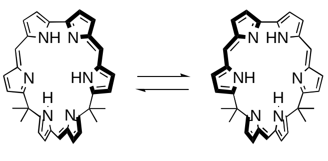
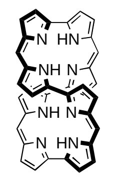


Figure 2. UV-vis (bottom) spectra of **6** (1.1×10^{-5} mol dm^{-3}) in CH_2Cl_2 (3 ml) (a); adding MeOH (40 μl) and (*S*)-(+)-mandelic acid (200 equiv) (b); adding MeOH (200 μl) and (*S*)-(+)-mandelic acid (3300 equiv) (c). The CD (top) spectra of **6** in the presence of 200 equiv (b*) and 3300 equiv (c*) of (*S*)-(+)-mandelic acid; in the presence of 200 equiv of (*R*)-(-)-mandelic acid (b**).

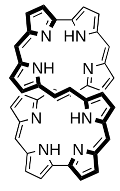
The intensity of the CD Cotton effect is dependent on the diastereoselectivity in the complexation of **6** with mandelic acid. We have recently reported that induced CD bands appear at 630–650 nm for 2,3,6,7,11,12,15,16,20,21,24,25,29,30,33,34-hexadecaethyl-9,18,27,36-tetraphenyl[32]octaphyrin(1.0.1.0.1.0.1.0) **8a** upon addition of various optically active carboxylic acids.[4] This phenomenon may be applied to the direct determination of the absolute configuration of optically active carboxylic acids. The induced CD bands seem to originate from the helical chirality in the π-conjugated tetrapyrrolic moiety in **8a**. In fact, Vogel and co-workers separated the [36]octaphyrin(2.1.0.1.2.1.0.1) free base **8b** having a similar π-conjugated tetrapyrrolic moiety into enantiomers and observed a negative CD Cotton effect at 630 nm for (*P,P*)-**8b**.[10] The same helical π-conjugated tetrapyrrolic moiety is present in **6**. The CD Cotton effects based on helical chirality in the π-conjugated tetrapyrrolic moiety have been known for biliverdins, bilindiones, and bilinones.[11] In addition, exciton coupling between the non-conjugated dipyrrylmethene units in **6** causes CD Cotton effects.[12] A similar exciton coupling between dipyrrolic units was used to empirically explain the sign of CD Cotton effects observed for bilirubins and double-helicate metal complexes of bis(dipyrromethene)s.[13] The left-handed chirality (-) is expected for the relative orientations of the electric dipole transition moments of a couple of dipyrrylmethene chromophores connected by a sp^3 carbon bridge in the case of (*P*)-**6**. Although corelation between the stereochemistry of the mandelic acid complex of **6** and the sign of the CD Cotton effect has remained unknown at present, the molecular framework of **6** illustrates appropriate molecular design for inducing simple CD response to chiral guest molecules.



(*M*)-**6** (*P*)-**6**



(*P,P*)-**8a**



(*P,P*)-**8b**

In summary, we have found that the condensation of 2,2'-bipyrrole and *gem*-dimethyldipyrrylmethane-5,5'-dicarbinol afforded novel cyclohexapyrrole under strongly acidic conditions. X-ray crystallography of the cyclohexapyrrole showed C_2-symmetric molecular structure. Since the pyrrole NH protons are not in a convergent arrangement, the compound **6** may not be appropriate for an anion binding host. However, this unusual C_2-symmetric cyclohexapyrrole can be applied to a chirality sensing device as illustrated by the CD signal induction at visible region by optically active carboxylic acid. The scope and limitation of this novel chirality probe is now extensively studied in our laboratory.

Acknowledgments

This work was supported by Grant-in-Aid for Scientific Research (No.16350023 and No.18033240) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The author is also grateful to the CREST program (the Japan Science and Technology Agent) and the VBL project (Kobe University). We thank Dr. Juha M. Lintuluoto (Kobe University) for valuable discussion.

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7. Trifluoroacetic acid (5.2 □g, 0.046 mmol) was added to a dry CH_2Cl_2 (18 ml) solution of 4,4'-dimethyl-3,3'-di-*iso*-butyl-2,2'-bipyrrole **1** (58.1 mg; 0.213 mmol) and *gem*-dimethyldipyrrylmethane-5,5'-dicarbinol **2** (81.7 mg; 0.211 mmol) and the mixture was stirred for 16 h at room temperature under argon. DDQ (134 mg, 0.589 mmol) was then added to the reaction mixture and stirring was continued for additional 2 h at room temperature. The resulting blue-green solution was passed through Celite that was washed with CH_2Cl_2 and then with acetone. The organic solution was evaporated and the residue was dissolved CH_2Cl_2. The combined organic solution was shaken with 2% aqueous $HClO_4$ solution, water, and 0.5% aqueous NaOH solution, sequentially. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on Al_2O_3 (activity II-III). The first green band was eluted with CH_2Cl_2 to give isocorrole **4** in 5.3 % yield. The second green band was eluted with CH_2Cl_2-acetone 100:1 and recrystallization from CH_2Cl_2-methanol gave **6** in 15.1% yield. UV-vis (λ_{max} nm (logε) in CH_2Cl_2) 453 (4.85), 611 (3.84). ^{1}H-NMR (δ-value in $CDCl_3$) 14.0 (br, 2H, NH); 13.3 (br, 1H, NH); 7.52~7.30 (m̤15H, *meso*-Ph-H); 6.46, 6.40, 6.38, 6.01 (d×4, 2H×4, J=4.3 Hz, β-py-H); 2.34 (m, 4H, -C*H*$_2$CHMe); 1.86 (s, 6H, β-py-CH_3); 1.61, 1.39 (s×2, 6H×2, *gem*-CH_3); 1.70 (m, 2H, -CH_2C*H*Me); 0.83, 0.75 (d×2, 6H×2, J=6.6 Hz, -CH_2CH*Me*$_2$). ESI-MS (found/calcd for $C_{61}H_{62}N_6 + H^+$) 879.48/879.51. Analysis calcd. for $C_{61}H_{62}N_6$: C, 83.37; H, 7.11; N, 9.56. Found: C, 83.33; H, 7.05; N, 9.59.
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9. Recrystallization from CH_2Cl_2/hexane gave crystals of **6**. Crystal data: $C_{61}H_{62}N_8$, M = 879.17, monoclinic, space group *C2/c*, a = 12.146(2), b = 22.439(6), c = 20.212(4) Å, . = 97.953(4)°, V = 5456(2) Å^3, Z = 4, D_{calc} = 1.070 Mg/m^3, μ(Mo-Kα) = 0.063 mm^{-1}, T = 90(2) K, crystal size 0.30 × 0.20 × 0.10 mm. A total of 5506 unique reflections were collected ($3.6 < 2\theta < 54.4°$) using graphite-monochromated Mo-Kα radiation. The structure was solved by the direct method using a SHELX97 package. 435 parameters were refined with all non-hydrogen atoms anisotropically. All hydrogen atoms were found on a difference Fourier map and refined. R_1 = 0.0752, wR_2 = 0.1662 for 3046 reflections with $I > 2.00\sigma(I)$; R_1 = 0.1468, wR_2 = 0.2016 for all data. GOF (on F^2) = 1.020. CCDC reference number 632014.
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