Toward calix[2]-type macrocycles: Synthesis and structural analysis of cyclic tetraketone and highly strained furanophane

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ABSTRACT: Recent progress in the synthesis of calix[3]pyrrole has proven that cyclic polyketones composed of 3,3-dialkylated pentane-2,4-diones as the repeating unit are promising precursors for strained calix-type macrocycles. Toward the synthesis of calix[2]pyrrole and calix[2]furan, which are the most strained congeners among the possible calix[*n*]pyrroles and calix[*n*]furans, we report synthesis of cyclic dimer of 3,3-dimethylpentane-2,4-dione and its furanophane derivative. These compounds were produced from a linear tetraketone precursor. Single crystal X-ray diffraction analysis revealed that furan ring in the furanophane was highly strained with deformation angles α and β of 3.69º and 16.00º, respectively. These deformation angles were the largest in the series of 1,4-diketone-linked oligofuran macrocycles. Although these two macrocyclic compounds are likely the most promising precursors for calix[2]-type macrocycles, Paal–Knorr-type pyrrole or furan ring formation did not proceed under standard conditions used for calix[3]pyrrole or calix[3]furan. Theoretical calculations indicated that the second aromatic ring formation on the cyclic tetraketone is a highly uphill process whose activation energy cannot be overcome by standard thermal reactions.

KEYWORDS: calixpyrrole, Paal–Knorr, strained macrocycle, polyketone

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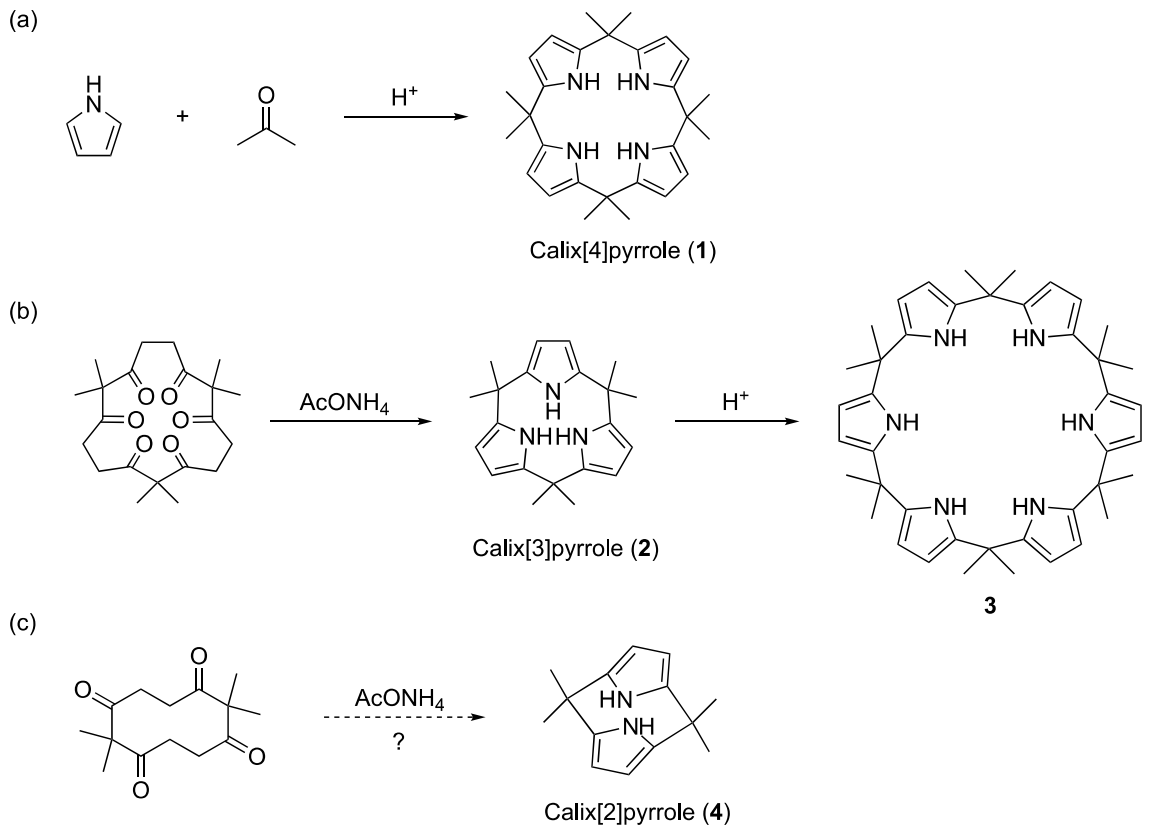
INTRODUCTION

Calix[4]pyrrole (**1**) is a porphyrinogen-like macrocycle constructed with four pyrrole units linked by dialkylated methylene bridges. The *meso*-octamethyl analogue is a prolific macrocycles that is readily obtained by acid-catalyzed condensation of acetone and pyrrole (Scheme 1a) [1]. Calix[4]pyrrole macrocycle is characterized by conformational flexibility and a convergent hydrogen-bonding site, which is advantageous for anion binding [2]. Thus, various materials for anion sensing [3], exchange [4], and extraction [5] have been developed based on calix[4]pyrroles. As anion selectivity changes in response to cavity size, ring-expanded analogues such as calix[*n*]pyrroles ($n \geq 5$) [6,7] have also been explored. Recently, our group reported the synthesis of calix[3]pyrrole (**2**) [8], a ring-contracted tripyrrolic congener, using a Paal–Knorr-type pyrrole ring formation reaction [9] with a cyclic hexaketone. While **2** showed poor anion binding properties compared with calix[4]pyrrole (**1**), a strain-induced ring-expansion reaction resulting in the quantitative formation of calix[6]pyrrole (**3**) [10] was observed under acidic Rothemund–Lindsey conditions [11], which are frequently used in porphyrinoid synthesis (Scheme 1b). These findings have demonstrated the importance of synthetic investigations of contracted calixpyrrole macrocycles to discover hidden reactivities that derives from macrocyclic ring strain.

Calix[2]pyrrole (**4**) is the smallest analogue possible among the calix[*n*]pyrrole family, and is still missing in the porphyrin chemistry. Only calix[2]pyrrole-like compound linked at N, α- and α,β-positions of pyrrole units have been reported previously [12]. Given the distorted structure of known calix[3]pyrrole (**2**) [8], it is easy to imagine that **4** may have an extremely high strain energy. This situation provides a new challenge for synthetic chemists to elucidate whether calix[2]-type macrocycles are accessible or not. While most of pyrrole-containing macrocycles have been synthesized by acid-catalyzed condensation of pyrrole precursors, such approaches are no longer applicable for highly strained contracted calix-type macrocycles. As shown by calix[3]pyrrole, acid-catalyzed strain-induced ring-expansion immediately (within 10 seconds) occurs to completely consume such macrocycles even if they are generated *in situ*. In this sense, a Paal–Knorr reaction approach using cyclic polyketone precursors would be the first strategy to be investigated (Scheme 1c), as the macrocyclic strain energy would be compensated for by aromatic stabilization during the final pyrrole ring formation process. Here, we report synthesis, reactivity, and strain energy analysis of cyclic tetraketone **9** and furanophane **7** that are plausible precursors for calix[2]pyrrole and calix[2]furan, respectively.



Scheme 1. (a) Conventional synthesis of calix[4]pyrrole (**1**). (b) The synthesis of calix[3]pyrrole (**2**) and its strain-induced ring-expansion reaction to **3**. (c) A plausible approach to calix[2]pyrrole (**4**).

EXPERIMENTAL

Materials and Reagents

Compounds **5** and **6** in Scheme 2 were synthesized according to the literature [13]. Detailed synthetic procedures for compounds **7**, **8**, **9**, and **12** are available in the Supporting Information. All the solvents and reagents were purchased from WAKO Pure Chemical Industries Ltd. or TCI Co. and used without further purification unless otherwise mentioned.

Instrumentation

All ^{1}H and ^{13}C NMR spectra were recorded using JEOL JMN-ECS400 spectrometer and chemical shifts were reported in parts per million (ppm) relative to an internal standard tetramethylsilane (δ = 0.00 ppm for ^{1}H NMR in $CDCl_3$) or a solvent residual peak (δ = 77.16 ppm for ^{13}C NMR in $CDCl_3$). Infrared spectra were measured using a JASCO Co. FT/IR-4600. ESI-TOF-MS spectra were recorded on a Thermo Scientific Executive spectrometer. Elemental analyses were carried out using an Exceter Analytical, Inc. CE440 or MICRO CORDER JM10. Thin layer chromatography was performed on a silica gel sheet, MERCK silica gel 60 F254. Preparative scale separations were performed by means of gravity column chromatography over silica gel (Wakosil® 60. 64 ~ 210 μm). Single crystal X-ray diffraction data were obtained using

Rigaku XtaLAB P200 diffractometer equipped with a PILATUS200K detector, which uses a multilayer mirror (MoK_α radiation λ = 0.71073 Å) or a Rigaku XtaLAB Synergy-R/DW instrument equipped with a HyPix-6000HE detector, which uses a monochromated mirror.

Theoretical calculations

Theoretical calculations were performed with Gaussian 16 Rev. C01 [14]. Structures of the macrocycles were optimized at the B3LYP/cc-pVTZ level of theory with Grimme's D3BJ dispersion correction [15], referring to their single crystal X-ray structures (CCDC deposition numbers: 2223944, 2223945, 2080603, 2127626, and 1151802 for compounds **7**, **9**, **14**, **15** and **16**, respectively) as the initial structures. The initial structures of compounds **4** (calix[2]pyrrole), **18** (calix[2]furan), and **19** (cyclic diketone-1-pyrrole) were modified from the crystal structure of cyclic tetraketone **9**, and structural optimizations were attempted under the same conditions as above. In the same process, the crystal structure of cyclic octaketone **16** was modified to optimize the structure of compound **17** (cyclic hexaketone-1-furan). Optimized structural coordinates are listed in the Supporting Information. After optimization, the destabilization energy (ΔE) between cyclic oligoketones and its related products was evaluated using following equations:

$$Furan\ system\ \Delta E = -\{E_{all-Ketone} - (E_{nFuran} + nE_{H2O})\}$$

$$Pyrrole\ system\ \Delta E = -\{(E_{all-Ketone} + nE_{NH3}) - (E_{nPyrrole} + 2nE_{H2O})\}$$

where $E_{all\text{-}Keton}$ is the energy of the optimized cyclic ketone, E_{H2O} is the energy of the optimized water molecule, E_{nFuran} is the energy of the optimized cyclic ketone-*n*-furan, E_{NH3} is the energy of the optimized NH_3 molecule, and $E_{nPyrrole}$ is the energy of the optimized cyclic ketone-*n*-pyrrole. Note: NH_3 and water molecules were included for stoichiometry to evaluate the destabilization of furan/pyrrole ring formation, although the ring formation conditions in the real systems are different from the evaluation scheme above.

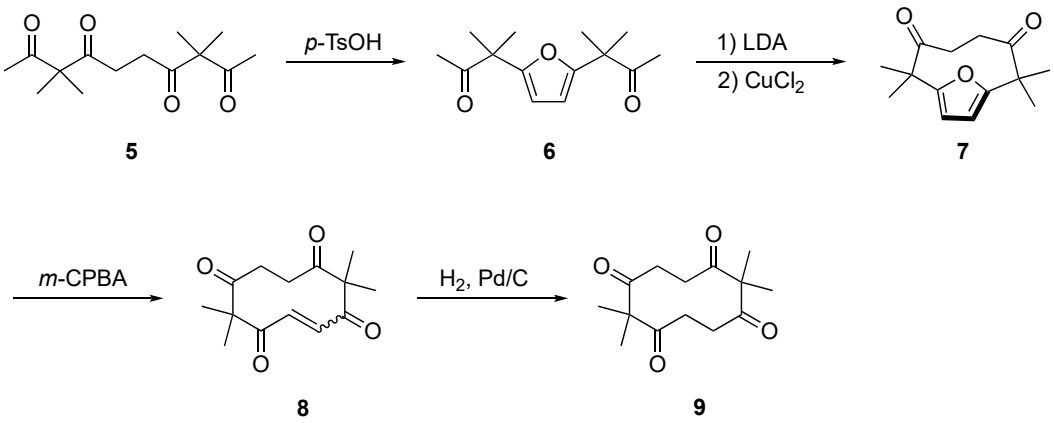
RESULTS AND DISCUSSION

Synthesis

Plausible precursors for calix[2]-type macrocycles were synthesized by intramolecular cyclization of linear tetraketone **5** as shown in Scheme 2. The internal 1,4-diketone unit of **5** was converted to furan compound **6** according to the reported procedure [13]. After double lithiation of **6** using an excess amount of lithium diisopropylamide (LDA), intramolecular cyclization was accomplished by addition of copper(II) chloride to give furanophane **7** in 12% yield. Although we examined various cyclization conditions using copper(II) triflate, iodine, and nickel(II) chloride to increase the yield, only a trace amount of product **7** was obtained with these oxidants. Oxidative furan ring-opening reaction of **7** proceeded by treatment with *m*-chloroperbenzoic acid (*m*-CPBA) at 0 ºC to give **8** in 69% yield. However, subsequent reduction of the C=C double bond in **8** using zinc powder [8,16] gave a complicated mixture. Formation of byproducts was suppressed using Pd/C catalyzed hydrogenation of **8**, and desired cyclic tetraketone **9** was obtained in 43% yield. Cyclic tetraketone **9** exhibited

two singlet signals in the ^{1}H NMR spectrum at 2.69 and 1.30 ppm assignable to the ethylene and methyl protons, respectively. High-resolution electrospray ionization time-of flight (ESI-TOF) mass of **9** showed peaks at *m/z* = 275.1247, which was assigned as the sodium adduct $[M+Na]^+$ (simulated value for $C_{14}H_{20}O_4Na^+$ = *m/z* 275.1254).

With precursor **9** in hand, we examined a Paal–Knorr-type reaction aiming at generating calix[2]pyrrole. When a solution of **9** and ammonium acetate in absolute ethanol was heated to reflux for 1.5 h, complicated mixtures that exhibited many proton signals around 2–3 ppm in ^{1}H NMR spectrum were obtained. This NMR spectrum suggested that intramolecular aldol-type condensation reactions had occurred to produce various byproducts. It is worth noting that the cyclic hexaketone precursor in Scheme 1b did not form such byproducts during the synthesis of calix[3]pyrrole (**2**) under similar conditions. Despite our repeated attempts using different reaction conditions, formation of calix[2]pyrrole (**4**) was not confirmed. There was no reaction when furanophane **7** was subjected to Paal–Knorr conditions. Furan ring formation with **9** was also unsuccessful, and even mono-furan intermediate **7** was not observed by the ^{1}H NMR spectroscopy. These differences in the reactivities of the cyclic ketone precursors may be attributable to the changes in macrocyclic strain energy during aromatic ring formation. Therefore, we analyzed the structures and strain energies of related compounds in the following sections.



Scheme 2. Synthesis of furanophane derivative **7** and cyclic tetraketone **9**.

Structural analysis and deformation angles

Single crystal X-ray analysis of cyclic tetraketone **9** revealed its C_i-symmetric conformation in which two 1,4-diketone units adopted a gauche conformation with a torsion angle of 60.7º (Figs. 1a and S2). A similar gauche conformation is commonly observed for other cyclic polyketones (such as cyclic hexaketone **14** and octaketone **16** in Fig. 2). When other structural parameters such as bond lengths and angles around the carbonyl groups were compared with larger cyclic polyketones, unusual distortion was not found for macrocycle **9**.

Furanophane **7** was considered as a possible intermediate in the synthesis of calix[2]furan from **9**. While compound **7** was a stable solid, single crystal X-ray analysis showed a highly strained structure around the furan ring (Fig. 1b). Deformation angles α and β [17] around the furan ring of **7** that are defined by the deviation angles between the mean planes of O−C(3)−C(4) and O−C(2)−C(3), and the mean plane O−C(2)−C(3) and a C(2)−C(*meso*) bond, were

calculated to be 3.69º and 16.00º, respectively (Fig. S4). These deformation angles were the largest among the known calix[*n*]furan macrocycles and precursors such as **10** and **12** in Table 1. The ethylene unit in **7** adopted an almost eclipsed conformation so that distortion around the rigid furan part was reduced (Fig. S1). Nonetheless, the ^{1}H NMR spectrum of **7** showed a singlet signal for the ethylene protons at 2.17 ppm, indicating flexibility of the bridging chain part in solution.

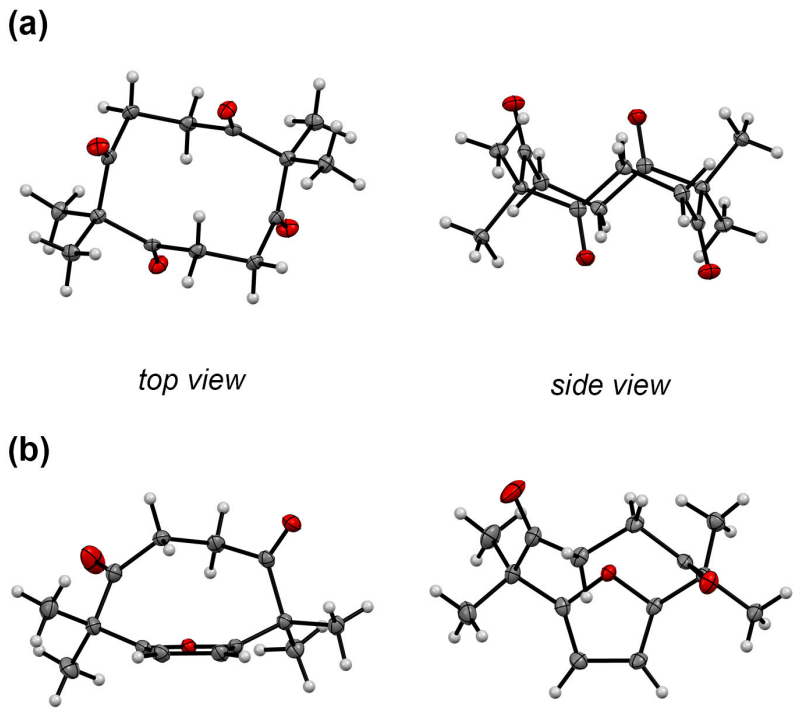
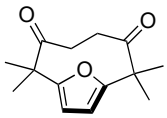
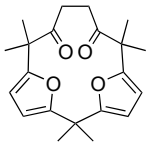
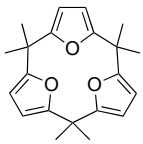
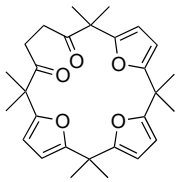
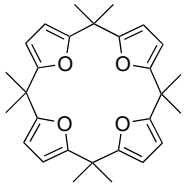


Fig. 1. Crystal structures of compounds (a) **9** and (b) **7**. Thermal ellipsoids are drawn at the 50% probability level.

Table 1. Deformation angles of furan-embedded macrocycles.

Compound	 **7**	 **10**	 **11**	 **12**	 **13**
Deformation angle α (º)	3.69	0.72	1.95	0.33	0.32
Deformation angle β (º)	16.00	2.37	6.53	1.81[a]	0.68

Conformation and torsion angle θ (º) of the ethylene bridge	eclipsed 127.6	anti 165.3	–	anti[a] 176.2[a]	–

[a] As the diketone part of **12** was disordered in the crystal structure, angles and conformation were calculated from the major disorder part.

Changes in the deformation angles for furan-embedded related macrocycles **7** and **10**–**13** determined from the crystal structures are summarized in Table 1. Macrocycle **12** was newly synthesized from a linear trifuran precursor as a reference compound [13] (see Supporting Information). While the deformation angles were decreased upon formation of the furan rings upon the synthesis of calix[4]furan (**13**) from diketone precursor **12**, the formation of calix[3]furan (**11**) caused a remarkable increase of β compared with **10**. It should be emphasized that calix[3]furan (**11**) is known to undergo acid-catalyzed hydrolysis of the furan ring yielding macrocycle **10** to reduce macrocyclic ring strain [8]. Nevertheless, the deformation angle β of **11** is still 9.47º smaller than furanophane **7**, suggesting an unusually large strain energy for **7** and conceivable calix[2]furan.

Estimation of destabilization energy upon aromatic ring formation

Destabilization energies derived from increasing ring strain upon furan/pyrrole ring formation were estimated using theoretical calculations (Fig. 2). Destabilization energy ΔE upon furan ring formation from tetraketone **9** to give furanophane **7** was calculated to be 22.57 kcal/mol, which was larger than that between hexaketone **14** and **15**, and yet comparable to that between octaketone **16** and **17**. Although the first furan ring formation was still realistic for tetraketone **9**, the second furan ring formation process to give calix[2]furan had remarkably large ΔE of 106.52 kcal/mol, which indicated that the second furan formation is an unlikely process. A similar trend was observed for pyrrole ring formation on cyclic tetraketone **9**; while the ΔE of the first ring formation was 18.90 kcal/mol, it significantly increased to be 103.16 kcal/mol for the second pyrrole formation. These calculations supported experimental results that Paal–Knorr reaction using **9** did not give calix[2]pyrrole. While the final pyrrole/furan ring formation is an unrealistic process, it would be possible for **9** to undergo other side reactions between neighboring carbonyl groups, *e.g.* aldol type reactions through enamine. Therefore, many signals due to aliphatic byproducts were observed in the reaction between **9** and ammonium acetate.

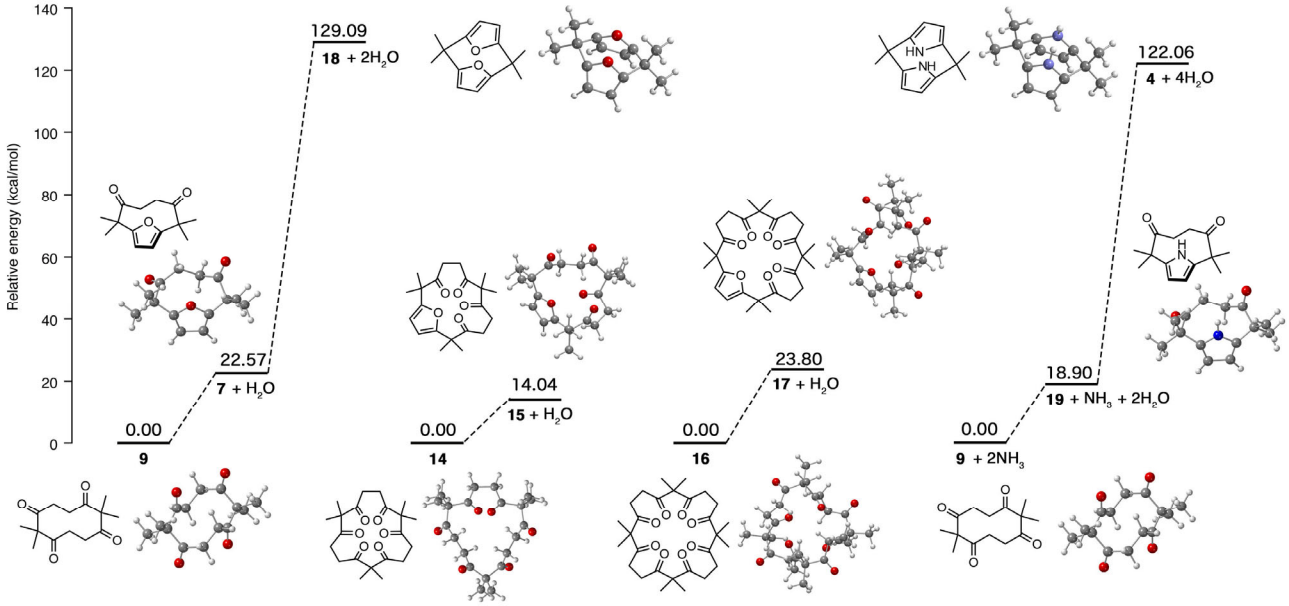


Fig. 2. Destabilization energies *ΔE* diagram upon the furan formation reaction from tetraketone **9** to give calix[2]furan **12** via furanophane **7**, hexaketone **14** to give **15**, and octaketone **16** to give **17**, and *ΔE* upon the pyrrole formation reaction from tetraketone **9** to give calix[2]pyrrole **4** via **18** (from left to right).

CONCLUSION

In conclusion, we synthesized cyclic tetraketone **9** and strained furanophane **7** as plausible precursors for calix[2]pyrrole and calix[2]furan. Paal–Knorr-type reaction using **9** and **7**, however, did not proceed under the conditions that worked for synthesis of calix[3]pyrrole or calix[3]furan. Deformation angle analysis using single crystal X-ray structures revealed that furanophane **7** had the largest α and β among analogous furan-embedded macrocycles. Theoretical calculations revealed that the second aromatic ring formation process had a remarkably large destabilization energy (*ΔE* > 100 kcal/mol) that would be unrealistic to overcome with conventional thermal reactions. Although Paal–Knorr approaches using a cyclic tetraketone were found to be difficult, our attempts showed that synthesis and isolation of calix[2]-type macrocycles are a more challenging task for synthetic chemists than calix[3]pyrrole synthesis. Despite the difficulty, calix[2]-type macrocycles are expected to have attractive reactivities derived from their extremely high strain energy. Furthermore, such synthetic research would be useful for cyclophane chemistry and the development of novel approaches to porphyrinoids. Further investigations are ongoing in our laboratory.

Acknowledgements

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Toward calix[2]-type macrocycles: Synthesis and structural analysis of cyclic tetraketone and highly strained furanophane

Taichi Sano, Yuhua Sun, Taichi Mukai, Yuya Inaba, Tomoki Yoneda Yuki Ide, Jenny Pirillo, Yuh Hijikata and Yasuhide Inokuma

Cyclic tetraketone and diketone-linked furanophane were synthesized from a linear tetraketone to investigate the possibility of synthesizing calix[2]pyrrole and calix[2]furan. The crystal structure of the furanophane exhibited the largest deformation angles among known analogues. Theoretical calculations indicate that the initial ring formation by Paal-Knorr synthesis for cyclic tetraketones is possible; however, the desired calix[2]-type macrocycle will be very difficult to form because of very large destabilization energy upon the second ring formation.