Synthesis and structural properties of novel calixarene analogues having Schiff base units

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Novel calixarene analogues having Schiff base units have been synthesised by condensation reaction of the bisaldehyde with *o*-phenylenediamines in the presence of boric acid. The present calixarene analogues form hydrogen bonds between imine nitrogen and phenol hydrogen with 1,2-alternate conformation, confirmed by X-ray crystallography.

Keywords: schiff base condensation reaction, calixarene analogue, hydrogen bond, conformation

Development of conjugated macrocycles is a rapidly growing area of interest because they may form the basis of catalytic,[1] magnetic,[2] liquid crystalline,[3] pharmaceutical,[4] and supramolecular materials.[5] Aldehyde and amine repeat formation and cleavage of Schiff base combination (imino group) reversibly under suitable reaction conditions, finally, reach the thermodynamic most stable state. The library of cyclic compound with various composition ratios is formed when there are some formyl groups and amino groups, respectively, the specific compound obtained selectively. Since the structure of a product depends on the structure of the materials to be used, the correlation with the structure of a spacer and the starting materials which connect a formyl group or an amino group is greatly interesting. For example, the reaction of the bis(hydroxybenzaldehyde) derivatives with diamines in which have various spacer gave 1 : 1 or 2:2 macrocycles.[6] In the synthesis of macrocycles which has Schiff base unit, many researches on correlation with the structure of a spacer[7] and a product are clarified by the construction of various libraries and calculation of molecular orbital.[8] However, there are only few reports about the structural characteristics. We now report on the synthesis of novel calixarene analogues and structural studies in solution and in the solid state as well as their complexation properties with transition metals.

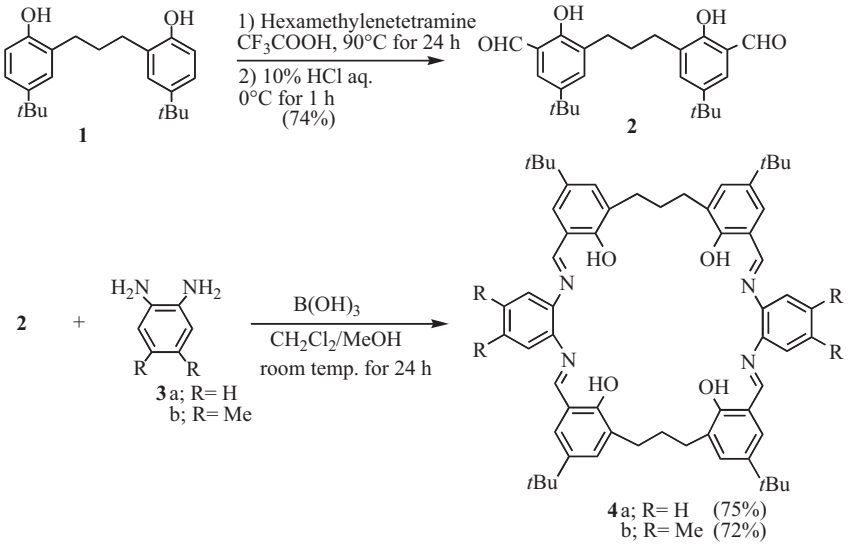
Results and discussion

Synthesis

Novel calixarene analogues having Schiff base units have been synthesised by Schiff base condensation reaction as shown in Scheme 1. Thus, 1,3-bis(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)propane **2** was prepared by formylation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)popane **1**[9] with hexamethylentetramine in trifluoroacetic acid followed by hydrolysis[10] in 74% yield. The attempted codensation reaction of **2** with *o*-phenylenediamine (**3a**) under benzene reflux failed. Only intractable mixture of products was obtained. No formation of the cyclised products was observed. Recently, Hisaeda and coworkers have succeeded in preparation 2 : 2 macrocycle by the using a boric acid template effect.[11] In fact, the condensation reaction of **2** with *o*-phenylenendiamine (**3a**) using the boric ion template method in CH_2Cl_2/methanol at room temperature afforded the desired calixarene analogue **4a** as a 2 : 2 macrocycle in 75% yield. Similar result was obtained in the condensation reaction of **2** with 1,2-diamino-4,5-dimethylbenzene (**3b**) under the reaction conditions described above afforded **4b** in 72% yield.

Structural properties

Since calixarene analogues **4a** and **4b** has phenolic hydroxyl groups and imine nitrogens in a molecule, the formation of intramolecular hydrogen bond is expected. First, in order



Scheme 1

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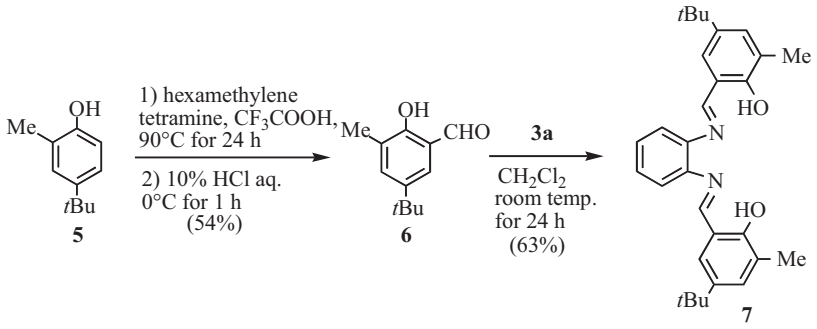

Scheme 2

to check the formation of intramolecular hydrogen bond, ^{1}H NMR spectrum of **4a** and **4b** were measured by two kinds of solvents, $CDCl_3$ and DMSO-d_6. When $CDCl_3$ was used as solvent, the signals for the phenolic hydroxyl group protons were observed at δ 13.32 and 13.30 ppm, respectively. In order to investigate the intramolecular hydrogen bond between the neighbouring phenolic hydroxyl groups and imine nitrogens of **4** in detail, a reference compound **7** was synthesised from 4-*tert*-butyl-2-methylphenol **5** following the similar method in the preparation of **4**.

The intramolecular hydrogen bond was formed between neighbouring OH and imine nitrogen which induced a large downfield shift for OH proton (δ13.32 ppm, Δδ = + 0.26 ppm) and CH=N proton (δ 8.68 ppm, Δδ = + 0.09 ppm) in **4a** compared to compound **7** (OH proton, δ 13.06 ppm; CH=N proton, δ 8.59 ppm). Similar findings were observed for **4b** (δ 13.30 ppm, Δδ = + 0.24 ppm for OH proton). These observations are attributable to the macrocyclic structure of **4**, which might enhance the present intramolecular hydrogen bond.

Interestingly, the chemical shift of the OH protons in **4a** was shifted to upper field to δ 8.92 ppm in DMSO-d_6 than that in $CDCl_3$ (δ 13.32 ppm, Δδ = –4.40 ppm) for **4a**. Similar finding was observed for **4b** (δ 8.99 ppm in DMSO-d_6 and δ13.30 ppm in $CDCl_3$, Δδ = –4.31 ppm). These phenomena were attributed to the intermolecular hydrogen bonding formed between the OH proton and solvent DMSO-d_6. The intramolecular hydrogen bonding formed in compounds **4** was broken and the new intermolecular hydrogen bonding was formed. Therefore, it can be surmised that calixarene analogues **4** form the intramolecular hydrogen bond between phenolic hydroxyl group proton and nitrogen of imino group different from that for calixarenes.[12] The ^{1}H NMR spectrum (in $CDCl_3$) of **4a** indicates the cyclophane ring to be extremely flexible from the observation of no changes of methylene signals at δ = 2.17 and 2.77 ppm for propane bridge (*$CH_2CH_2CH_2$*) even at the lower temperature (–60°C in CD_2Cl_2). Interestingly, decreasing the temperature the chemical shift of OH proton shifted to downfield from at δ 13.30 ppm at 27°C to 14.00 ppm at –40°C in $CDCl_3$. This phenomenon seems to be attributed to the increased intramolecular hydrogen bonding by the much favourable conformation between phenolic hydroxyl group proton and nitrogen of imino group.

The structure of **4a** has been assigned by ^{1}H NMR spectroscopy and confirmed by X-ray crystallography. The ^{1}H NMR spectrum of **4a** shows a singlet for the *tert*-butyl protons at δ 1.30 ppm and a set of doublets for the aromatic protons at δ 7.20, 7.30 ppm (J = 2.4 Hz). Other signals in the ^{1}H NMR spectrum may correspond to both the cone, 1,2-alternate or 1,4-alternate conformer like those for dihomocalix[4]arenes.[13] Fortunately, recrystallisation from MeOH and CH_2Cl_2 produces X-ray quality colourless crystals of **4a**. The crystals include the two molecules of dichloromethane. The ball-and-stick diagram of the structure of **4a** from the single crystal X-ray diffraction analysis, excluding the two CH_2Cl_2 molecules, is shown in Fig. 1. In the solid state, it is clear that compound **4a** adopts a 1,2-alternate conformation.

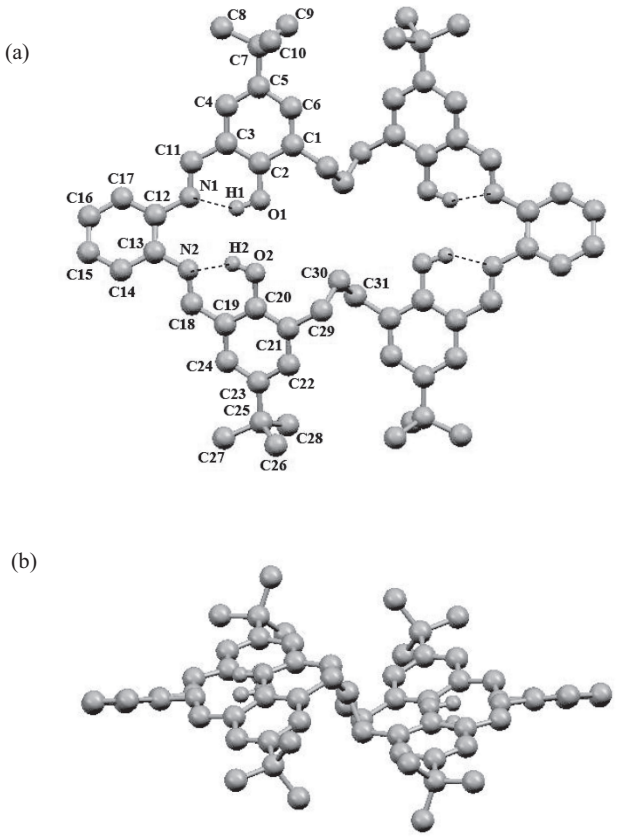

Fig. 1 Ball-and-stick diagram of the X-ray structure of **4a** excluding the two CH_2Cl_2 molecules: (a) top view, hydrogen atoms except phenolic hydrogen atoms are excluded for clarity. Hydrogen bonds are shown as dashed lines; (b) side view.

The structural property of **4a** had been clarified the formation of hydrogen bonds between a phenolic hydroxyl group proton and imino group nitrogen that forms a flat pseudo 6-membered ring structure. In fact, X-ray structure shows the 6-membered ring formed by the hydrogen bond (Fig. 1). Furthermore, **4a** has a symmetrical side centreing on propane bridge and both the 1,2-bisimino benzene rings were orientated outwards with respect to the cavity. The imine unit (C–C=N) and the phenol rings are almost coplanar with interplanar angles of 0.22 and 4.04 (4)°, respectively, whereas on the other side, the imine unit (C–N=C) and the phenylenediamine rings deviate from coplanarity by 27.76 and 36.08°, respectively. The latter non-

planalities from the phenylenediamine ring are much smaller than that of acyclic Schiff base compound (56.2°) reported by Yang *et al.*[14] This finding might be attributable to the cyclic structure of **4**. Schiff base macrocycle **4** contains four intramolecular O–H---N hydrogen bonds between the phenol O atom and the imine N atoms (N---H–O, 1.766 and 1.829 Å). No notable intermolecular interaction between the molecules of **4** or interactions involving the solvent molecules were found.

The complexation experiments of the novel calixarene analogues **4a** and **4b** with transition metals such as $Ni(OAc)_2$ or $Pd(OAc)_2$ were carried out. Unfortunately, although the formation of the desired complexed products were detected by the mass spectroscopy, isolation failed due to its low solubility in organic solvents.

Conclusions

We have synthesised the novel calixarene analogues **4a** and **4b** by a convenient method and characterised their structures. These compounds form the strong intramolecular hydrogen bond between phenolic hydroxyl proton and the imino group nitrogen. However, no notable intramolecular interaction between the neighboring OH groups was found, which might lead strong contribution to the flexibility of these molecules. The complexation studies of the novel calixarene analogues **4a** and **4b** with transition metals are now under investigation in our laboratory.

Experimental

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on a Nippon Denshi JEOL FT-300 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon Denshi JMS-HX110A Ultrahigh performance mass spectrometer at 75 eV using a direct-inlet system. Elemental analyses were performed by Yanaco MT-5 after the samples are dried in vacuum (0.1 torr) at 50°C.

Materials

Synthesis of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane **1** was carried out according to the reported procedure.[9]

Preparation of 1,3-bis(5-tert-butyl-3-formyl-2-hydroxyphenyl) propane (**2**): To a solution of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl) propane **1** (1.0 g, 2.94 mmol) in CF_3COOH (10 cm^3) was added a hexamethylenetetramine (1.03 g, 7.34 mmol) and stirred for 24 h at 90°C. Then a reaction mixture was cooled and poured into 10% HCl aqueous solution. After 1 h, the mixture was extracted with CH_2Cl_2. The extracts were washed with 10% HCl aq. and distilled water, dried with Na_2SO_4, and concentrated *in vacuo* to gave crude as a yellow solid. Recrystallisation from hexane/ethylacetate (10 : 1) afforded 1,3-bis(5-*tert*-butyl-3-formyl-2-hydroxyphenyl)propane **2** (856 mg, 74%) as yellow prisms, m.p. 60–63°C; IR; ν(KBr)/cm^{-1} 1652 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.30 (18H, s, *t*Bu), 1.95 (2H, m, $CH_2CH_2CH_2$), 2.75 (4H, t, J = 8.6 Hz, $CH_2CH_2CH_2$), 7.36 (2H, d, J = 2.1 Hz, Ar*H*), 7.48 (2H, d, J = 2.1 Hz, Ar*H*), 9.90 (2H, s, *OH*) and 11.13 (2H, s, *CHO*); MS: *m*/*z* M^+ 396. Anal. calcd. for $C_{25}H_{32}O_4$ (396.23) C 75.73, H 8.13; found: C 75.68, H 8.17.

Preparation of calixarene analogue (**4a**): To a solution of **2** (100 mg, 0.25 mmol) in CH_2Cl_2 (30 cm^3) and CH_3OH (30 cm^3) was added a boric acid (8.0 mg, 0.126 mmol) and stirred for 1 h at room temperature. Then a mixture was added *o*-phenylenediamine (27.3 mg, 0.25 mmol) and yellow precipitates appeared during stirring for 24 h. The precipitates were collected by filtration, washed by methanol and dried *in vacuo*. Recrystallisation from CH_2Cl_2/methanol (1 : 1) afforded calixarene analogue **4a** (88 mg, 75%) as yellow prisms, m.p. 232–233°C (decomp.); IR; ν(KBr)/cm^{-1} 3609, 3283, 2944, 2906, 1621, 1590, 1465, 1362, 1270, 1207, 1048, 908 and 757; ^{1}H NMR ($CDCl_3$) δ 1.30 (36H, s, *t*Bu), 2.15 (4H, m, $CH_2CH_2CH_2$), 2.77 (8H, t, J = 8.6 Hz, $CH_2CH_2CH_2$), 7.25 (8H, m, Ar*H*), 7.20 (4H, d, J = 2.4 Hz, Ar*H*), 7.30 (4H, d, J = 2.4 Hz, Ar*H*), 8.68 (4H, s, *CH*=*N*) and 13.32 (4H, broad s, *OH*); MS: *m*/*z* M^+ 936.6. Anal. calcd. for $C_{62}H_{72}N_4O_4$ (936.56) C 79.45, H 7.74, N 5.98; found: C 79.40, H 7.69, N 6.02.

Preparation of calixarene analogue (**4b**): To a solution of **2** (200 mg, 0.50 mmol) in CH_2Cl_2 (7 cm^3) and CH_3OH (7 cm^3) was added a boric acid (16 mg, 0.25 mmol) and stirred for 1 h at room temperature. Then a mixture was added 1,2-diamino-4,5-dimethylbenzene (**3b**) (69 mg, 0.50 mmol) and yellow precipitates appeared during stirring for 24 h. The precipitates were collected by filtration, washed by methanol and dried *in vacuo*. Recrystallisation from CH_2Cl_2/methanol (1:2) afforded calixarene analogue **4b** (180 mg, 72%) as yellow prisms, m.p. 243–244°C (decomp.); IR; ν(KBr)/cm^{-1} 3743, 3673, 2921, 2886, 1732, 1622, 1575, 1456, 1393, 1266, 1213, 1057, 1003, 875, 773, 646 and 478; ^{1}H NMR ($CDCl_3$) δ 1.30 (36H, s, *t*Bu), 2.19 (4H, m, $CH_2CH_2CH_2$), 2.30 (12H, s, CH_3), 2.76 (8H, t, J = 8.6 Hz, $CH_2CH_2CH_2$), 7.10 (4H, s, Ar*H*), 7.20 (4H, d, J = 2.4 Hz, Ar*H*), 7.30 (4H, d, J = 2.4 Hz, Ar*H*), 8.60 (4H, s, *CH*=*N*) and 13.30 (4H, s, *OH*); MS: *m*/*z* M^+ 992.6. Anal. calcd. for $C_{66}H_{80}N_4O_4$ (992.62) C 79.80, H 8.12, N 5.64; found: C 79.72, H 8.10, N 5.60.

Preparation of 4-tert-butyl-2-formyl-6-methylphenol (**6**): To a solution of 4-*tert*-butyl-2-methylphenol **5** (2.19 g, 13.3 mmol) in CF_3COOH (22 cm^3) was added a hexamethylenetetramine (9.35 g, 66.7 mmol) and stirred for 24 h at 90°C. Then a reaction mixture was cooled and poured into 10% HCl aqueous solution (150 cm^3). After 1 h, the mixture was extracted with CH_2Cl_2. The extracts were washed with 10% HCl aq. and distilled water, dried with Na_2SO_4, and concentrated *in vacuo* to gave crude as a yellow oil. The residue was treated over colum chromatography (SiO_2) to afford **6** (1.38 g, 54%) from $CHCl_3$ eluent as yellow oil; IR; ν(NaCl)/cm^{-1} 1652 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.32 (9H, s, *t*Bu), 2.27 (3H, s, CH_3), 7.37 (1H, d, J = 2.4 Hz, Ar*H*), 7.44 (1H, d, J = 2.4 Hz, Ar*H*), 9.86 (1H, s, *OH*) and 11.11 (1H, s, *CHO*); MS: *m*/*z* M^+ 192. Anal. calcd. for $C_{12}H_{16}O_2$ (192.12) C 74.97, H 8.39; found: C 74.94, H 8.26.

Preparation of **7**: To a solution of **6** (330 mg, 1.73 mmol) in CH_2Cl_2 (5 cm^3) was added *o*-phenylenediamine (140 mg, 1.29 mmol) and stirred for 24 h at room temperature. The reaction mixture was condensed in vacuum to afford a residue. Although the residue a small amount of hexane (3 cm^3) and a yellow precipitate was collected by filtration, washed by hexane and dried *in vacuo*. Recrystallisation from hexane afforded **7** (248 mg, 63%) as yellow prisms, m.p. 95–96°C. IR; ν(KBr)/cm^{-1} 3514, 3361 (OH), 2956, 1624, 1569, 1466, 1457, 1360, 1305, 1266, 1175, 1149, 1124, 1034, 975, 924, 873, 814, 749, 668, 506 and 429. ^{1}H NMR ($CDCl_3$) δ 1.36 (18H, s, *t*Bu), 2.32 (6H, s, CH_3), 7.04 (4H, m, Ar*H*), 7.22 (2H, d, J = 2.1 Hz, Ar*H*), 7.29 (2H, d, J = 2.1 Hz, Ar*H*), 8.59 (2H, s, *CH*=*N*) and 13.06 (2H, broad s, *OH*). MS: *m*/*z* M^+ 456. Anal. calcd. for $C_{30}H_{36}N_2O_2$ (456.28) C 78.91, H 7.95, N 6.13; found: C 78.76, H 7.91, N 6.16.

Crystallographic data for **4a**: Crystal data for **4a**: $C_{62}H_{74}N_4O_4$, $2(CH_2Cl_2)$ (sum formula: $C_{64}H_{76}Cl_4N_4O_4$), M = 1107.09, triclinic, P–1, a = 9.6084 (12), b = 10.9452 (3), c = 14.349 (2) Å, V = 1435.1 (3) $Å^3$, α = 91.968 (8), β = 101.050 (7), γ = 103.511 (8), Z = 1, D_c = 1.281 g cm^{-3}, μ(Mo-K_α) = 0.258 mm^{-1}, T = 100(2) K, translucent light orange prisms; 20128 reflections measured on a Kappa CCD diffractometer, of which 5072 were independent, data corrected for absorption on the basis of symmetry equivalent and repeated data (min and max transmission factors: 0.946, 0.979) and Lp effects, R_{int} = 0.0648, structure solved by direct methods (Bruker SHELXTL), F^2 refinement, R_1 = 0.0522 for 5072 data with $F^2 > 2\,s(F^2)$, wR_2 = 0.1196 for all data, 3869 parameters. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 651077. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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