Lower Rim 1,3-Disubstituted Derivatives of Calix[4]arene Amides Having Amino Acid Ester and Amines as Pendants

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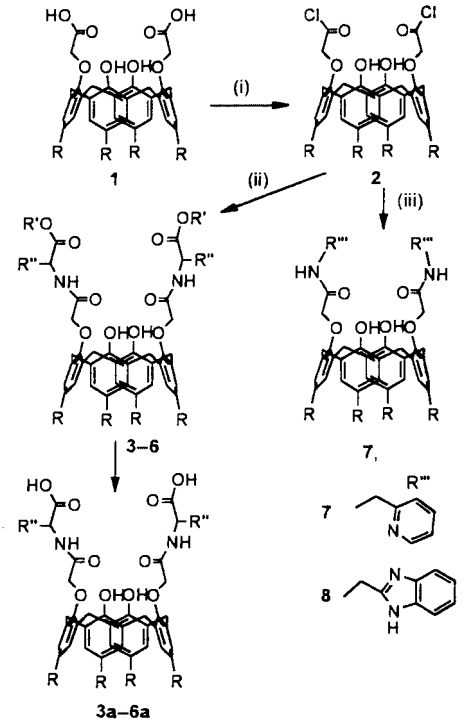
Lower rim modification of calix[4]arene at its 1,3-alternate positions to result in the molecules of potential importance possessing amide bonds and other functional moieties as generated from the reaction between calix[4]arene-1,3-diacid and the amino acids and/or substituted amines was carried out and the structural properties of the products were addressed.

Calixarenes are versatile molecules possessing both hydrophobic and hydrophilic regions.[1] Literature deals with the derivatization of lower and upper rims of calix[4]arenes with ester, acid and amide functions.[2] Upper rim modifications leading to tetra- and 1,3-disubstituted amide derivatives are reported recently in the literature.[3] Also the recent work deals with the syntheses of tetrasubstituted pendants on lower rim with glycine, alanine, valine, leucine, phenylalanine and phenylglycine, as well as 1,3-disubstitued phenylglycine derivatives[4] and these are not expected to have any side chain functional groups. However, 1,3-disubstituted derivatives of calix[4]arene with functional amino acids and/or substituted amines that possess the peptide bond are of potential importance in the field of bioorganic and bioinorganic chemistry as model molecules. Therefore, herein we report the synthesis and structural properties of 1,3-disubstituted amide derivatives of Gly, Ala, Asp and Glu and also two other aromatic amide derivatives possessing pyridyl or benzimidazole moieties.

p-tert-Butylcalix[4]arene-1,3-diacid, **1** was converted to the corresponding 1,3-diacyl chloride, **2** by reacting with $SOCl_2$.[5] When **2** was further treated with the amino acid ester hydrochloride or tosylate, the reactions yielded 1,3-diamide derivatives[6] (**3–6**) with alternate pendants on the lower rim of calix[4]arene in high yields (50–78%) as shown in the Scheme 1. Hydrolysis of **3–6** resulted in the diderivatives with free COOH groups, **3a–6a**.[7] Similarly, 1,3-diamide derivatives **7** and **8** were formed when **2** was treated with 2-(aminomethyl)pyridine or 2-(aminomethly)-benzimidazole, respectively.[8]



Scheme 1. (i) $SOCl_2$, Benzene, reflux. (ii) Amimo acid ester. HCl, NEt_3, THF, RT. (iii) R'''-NH_2, NEt_3, THF, RT. **3**: R'=CH_3; R"=H, **4**: R'=R"=CH_3, **5**:R'=CH_2Ph; R" = $CH_2CO_2CH_2Ph$, **6**: R'=Et; R"=$CH_2CH_2CO_2Et$,**3a**: R"=H, **4a**: R"=CH_3, **5a**: R"=CH_2CO_2H, **6a**: R"=$CH_2CH_2CO_2H$

The structure of **7** is established by single crystal XRD[9] which clearly revealed the calix[4]arene-1,3-diderivative formed through amide bonds on the lower rim exhibiting a distorted cone conformation as shown in Figure 1. There are two intramolecular H-bonds of the type, O–H(phenolic)···O(ether). The amide N-H group of both the pendants exhibited 11-atom H-bond interactions (β-turn) of the type O(phenolic)···H–N(amide) (Figure 1). As a result of this H-bond turn, a 5-atom N–H···O was generated in the pendant. Thus, **7** exhibited two hetero-atom cores, O_4 (four hard oxygen atoms, Figure 1) and the N_4 (four soft nitrogen centers, Figure 1). The bond length data clearly differentiated various COs and CNs present in the molecule.

Unambiguous assignment of proton/carbon resonances was achieved by carrying out the COSY/HMQC experiments. The amide proton signals were generally shifted downfield to appear in the range 9.32–9.66 ppm ($CDCl_3$) and 8.97–9.20 ppm (DMSO-d_6) for **3–6** (diesters) and 8.88–9.14 ppm for **3a–6a** (diacids, DMSO-d_6). These chemical shifts were comparable with those observed in case of ester derivatives of tetra-substituted amino acid.[3] The data indicated the presence of strong intramolecular hydrogen bonding in **3–6** in $CDCl_3$. However, the shifts observed in DMSO-d_6 indicated the disruption of such interactions without exposing the groups to the solvent. This is supported by non-exchange of the amide protons in D_2O for **3–6** even in the case of DMSO-d_6. However, these protons are exchanged by D_2O in case of **3a–6a** (DMSO-d_6) owing to the changes in the conformation of the pendant groups on going from the diester derivatives to the dicarboxylic acid derivatives. The amide proton appears as a triplet in **7** and **8**. Two phenolic hydroxy groups were observed supporting the formation of 1,3-diderivatives in **3–8** and **3a–6a**. The axial and equatorial calixarene methylene bridged protons (CH_2) showed two pairs of

doublets (**4–6**) due to the chiral nature of the pendant amino acid groups, except in case of **3** (Gly) which showed a pair of doublets due to the absence of a chiral center. The spectra of **3**/**3a** and **4**/**4a** help the assignment in case of **5**/**5a** and **6**/**6a**. The calixarene skeletal bridged methylene group appears as two doublets in **7** and **8** supporting the existence of cone conformation. Carbon-13 NMR spectra also confirms the formation of the amide linkage on calixarene skeleton. The peaks corresponding to the ester, carboxy and amide carbonyls were identified for **3–6** and **3a–6a**. One additional ester/acid carbonyl peak appears from the side chain ester/acid groups in case of **5**/**5a** and **6**/**6a**.

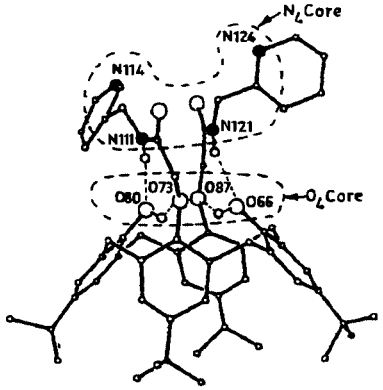


Figure 1. Molecular structure of 7. Dashed lines between two atoms indicate hydrogen bond. Enclosures by dashed lines indicate binding cores.

Molecular weights supporting the 1,3-diderivatives of calix[4]arene (Scheme 1) were obtained from the molecular ion peaks in the FAB mass (**5–8** and **3a–6a**) or EI (**3** and **4**) method. Thus a new set of potentially important molecules based on the lower rim of calix[4]arene were developed through amide bonds to result in 1,3-diderivatives. The 1,3-alternate pendants were grown using amino acids and amines having additional functionalities. All the molecules reported here exist in the cone conformation, exhibiting three different regions for interaction. While the terminal functional groups are suitable for transition metal ion binding (N_4 core, Figure 1), the free phenolic and ether oxygen's are for cation binding (O_4 core, Figure 1) and the arene cavity is for the inclusion of small molecules. The presence of such cores was demonstrated through establishing the crystal structure of **7**. Further studies are currently underway in our laboratory.

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6 Spectral data for **3**. mp 182 °C (brown). ^{1}H NMR ($CDCl_3$, ppm): 9.27 (t, 2H, NH, *J* = 4.6, 4.7 Hz); 7.83 (S, 2H, OH); 7.25 (s, 4H, Ar–H); 6.92 (s, 4H, Ar–H); 4.63 (s, 4H, O–CH_2–CO); 4.23 (d, 4H, Ar–CH_2–Ar, *J* = 13.3 Hz); 4.14 (d, 4H, C$^\alpha$H, *J* = 4.95 Hz); 3.72 (s, 6H, OCH_3); 3.43 (d, 4H, Ar–CH_2–Ar, *J* = 13.4 Hz); 1.27 (s, 18H, $C(CH_3)_3$); 1.03 (s, 18H, $C(CH_3)_3$). MS-EI, *m/z* : 906 (M^+). **4**. mp >240 °C (brown). ^{1}H NMR ($CDCl_3$, ppm): 9.42 (d, 2H, N*H*, *J* = 7.43 Hz) , 7.85 (s, 2H, O*H*); 7.08 (d, 4H, Ar–*H*); 6.93 (d, 4H, Ar–H); 4.74–4.69 (m, 2H of C$^\alpha$*H* and 2H of O–CH_2–CO); 4.53 (d, 2H, CH_2–O, *J* = 15.2 Hz); 4.31 (d, 2H, Ar–CH_2– Ar, *J* = 13.5 Hz); 4.18 (d, 2H, Ar–CH_2– Ar, *J* = 13.2 Hz) , 3.46 (d, 2H, Ar–CH_2– Ar, *J* = 13.5 Hz); 3.40 (d, 2H, Ar–CH_2– Ar, 13.3 Hz); 3.69 (s, 6H, OCH_3); 1.47 (d, 6H, CH_3, *J* = 7.21); 1.28, 0.97 (s, 18H each, CMe_3). MS-EI, *m/z* : 934 (M^+). **5**. ^{1}H NMR ($CDCl_3$, ppm): 9.63 (d, 2H, N*H*, *J* = 7.1 Hz); 7.92 (s, 2H, O*H*); 5.03 (m, H, C$^\alpha$*H*–Asp + OCH_2Ph); 4.77 (d, 2H, OCH_2CO, *J* = 12.4 Hz); 4.37 (d, 2H, OCH_2CO, 12.4 Hz); 4.29 (d, 2H, Ar–CH_2–Ar); 4.14 (d, 2H, Ar–CH_2–Ar, *J* = 13.7 Hz); 3.42 (d, 2H, Ar–CH_2–Ar, *J* = 13.7 Hz); 3.24 (d, 2H, Ar–CH_2–Ar, *J* = 13.0 Hz); 2.97 (dd, 4H, C$^\beta$*H*–Asp, *J* = 5.1 Hz); 1.24 (s, 18H, CMe_3); 1.04 (s, 18H, CMe_3). MS-FAB, *m/z*: 1355 (M^++H); 1377 (M+Na^+). Spectral data for **6**. mp 168–170 °C. ^{1}H NMR ($CDCl_3$, ppm): 9.37 (d, 2H, –N*H*–); 7.78 (s, 2H, –O*H*); 6.99 (d, 4H, Ar–*H*); 6.83 (d, 4H, Ar–*H*); 4.85 (d, 2H, O–CH_2–CO, *J* = 15.2 Hz); 4.65 (q, 2H, C$^\alpha$*H*–Glu, *J* = 7.0 Hz); 4.31 (d, 2H, O–CH_2–CO, *J* = 15.2 Hz); 4.24 (d, 2H, Ar–CH_2–Ar, *J* = 12.9 Hz); 4.13 (d, 2H, Ar–CH_2–Ar, *J* = 13.6 Hz); 3.97 (q, 4H, CH_2–CH_2, *J* = 7.1 Hz); 3.40 (d, 2H, Ar–CH_2–Ar, *J* = 13.6 Hz); 3.26 (d, 2H, Ar–CH_2–Ar, 13.0 Hz); 2.29 (m, 4H, CH_2–CH_2); 2.10 (m, 2H, CH_2–CH_2); 1.97 (m, 2H, CH_2–CH_3); 1.19 (s, 18H, CMe_3); 1.18 (t, 6H, CH_2–CH_3, *J* = 7.15 Hz); 1.10 (t, 6H, CH_2–CH_3, *J* = 7.1 Hz); 0.96 (s, 18H, CMe_3). MS FAB 1135 (M^++H); 1157 (M^++Na).

7 Spectral data for **3a**. mp 210 (brown) °C. ^{1}H NMR (DMSO-d_6, ppm): 8.89 (t, 2H, HN); 8.41 (s, 2H, OH); 7.17 (s, 8H, Ar–H); 4.53 (s, 4H, OCH_2CO); 4.23 (d, 4H, Ar–CH_2–Ar, *J* = 12.8 Hz); 4.03 (m, 4H, C$^\alpha H_2$); 3.47 (d, 4H, Ar–CH_2–Ar, *J* = 13.2 Hz); 1.20 (s, 18H, $C(CH_3)_3$); 1.13 (s, 18H, $C(CH_3)_3$). MS-FAB: 885 (M+Li^+). **4a**. mp 196–198 °C. ^{1}H NMR (DMSO-d_6, ppm): 9.09 (d, 2H, HN, *J* = 7.6 Hz); 8.30 (s, 2H, OH); 7.22–7.17 (m, 8H, Ar–H); 4.77 (d, 2H, OCH_2CO, *J* = 15.1 Hz); 4.41–4.36 (m, 2H each, Ar–CH_2–Ar, + C$^\alpha$H); 4.31 (d, 2H, OCH_2CO, *J* = 15.1 Hz); 4.15 (d, 2H, Ar–CH_2–Ar, *J* = 13.1 Hz); 3.54 (d, 2H, Ar–CH_2–Ar, *J* = 13.1 Hz); 3.45 (d, 2H, Ar–CH_2–Ar, *J* = 12.9 Hz); 1.40 (d, 6H, CH_3–Ala, *J* = 7.27 Hz); 1.20 (s, 18H, $C(CH_3)_3$); 1.12 (s, 18H, $C(CH_3)_3$). MS-FAB *m/z*: 913 (M+Li^+). **5a**. mp 166–168 °C ^{1}H NMR (DMSO-d_6, ppm): 8.88 (d, 2H, NH, *J* = 7.85 Hz); 8.20 (s, 2H, OH); 7.14 (d, 8H, Ar–H, *J* = 6.22 Hz); 4.76 (q, 2H, C$^\alpha$H, *J* = 7.6 Hz); 4.61 (m, 4H, OCH_2CO); 4.26 (t, 4H, Ar–CH_2–Ar); 3.43 (d, 4H, Ar–CH_2–Ar); 2.81–2.78 (m, 4H, C$^\beta H_2$–Ph); 1.20 (s, 18H, $C(CH_3)_3$); 1.17 (s, 18H, $C(CH_3)_3$). MS FAB 1023 ($M+H^+$); 1045 (M+Na^+). **6a**. mp 172 °C. ^{1}H NMR (DMSO-d_6, ppm): 8.87 (d, 2H, NH, *J* = 7.2 Hz); 8.17 (s, 2H, OH); 7.20–7.12 (m, 8H,Ar–H); 4.75 (d, 2H, OCH_2CO, *J* = 14.9 Hz); 4.40–4.33 (m, 6H, 2H each of OCH_2CO, C$^\alpha$H, Ar–CH_2–Ar); 4.21 (d, 2H, Ar–CH_2–Ar, *J* = 13.1 Hz); 3.51 (d, 2H, Ar–CH_2–Ar, *J* = 13.2 Hz); 3.44 (d, 2H, Ar–CH_2–Ar, *J* = 12.9 Hz); 2.36–2.32 (m, 4H, C$^\gamma$H); 2.08–1.99 (m, 4H, C$^\beta$H); 1.20 (s, 18H, CMe_3); 1.11 (s, 18H, CMe_3). MS-FAB *m/z* : 1023 (M^++H); 1045 (M+Na^+).

8 Spectral data for **7**. mp > 240 ºC. ^{1}H NMR ($CDCl_3$, ppm): 0.99, 1.27 (s, 18H each, –CH_3); 3.34, 4.02 (d, 4H each, –CH_2–); 4.52 (s, 4H, CH_2–CONH–); 4.64 (d, 4H, –CONH–CH_2–); 6.83, 7.03 (s, 4H each, aromatic). 7.06–7.11 (m, 2H, Py–H); 7.17 (s, 2H, Py–H); 7.30 (d, 2H, Py–H); 7.54–7.60 (m, 2H, Py–H); 8.36 (dd, 2H, OH); 9.11 (t, 2H, –CO–NH). MS FAB *m/z*: 945 ($M+H^+$). **8**. mp > 240 ºC; ^{1}H NMR ($CDCl_3$, ppm): 0.96 (s, 18H, CH_3); 1.25 (s, 18H, CH_3); 3.28, 3.96 (d, 4H each, –CH_2–); 4.40 (s, 4H, –CH_2–CONH–); 4.85 (d, 4H, –CONH–CH_2–); 6.81, 7.02 (s, 4H each, aromatic protons of Calix); 7.20, 7.50 (m, 4H each, benzimidazole), 8.91 (t, 2H, NH). MS FAB *m/z*: 1023 ($M+H^+$).

9 X-ray data for **7**: Formula wt. 945.22; Space group: *Cc*; *a*/Å: 30.404(7); *b*/Å: 20.926(4) *c*/Å: 22.768(8); β/deg: 133.29(4); *V*/Å^3: 10545(5); *Z*: 8; D_c/g cm^{-3} 1.191; *R* 0.0897; R_w 0.2368.