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The Synthesis and Conformational Studies of Chiral Calix[6]arene Derivatives Bearing Amino Acid Ester Residues

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Abstract—Chiral calix[6]arene derivatives were synthesized by the reactions of *N*-chloroacetyl amino acid ester and 1,3,5-trimethoxy-*p*-*tert*-butylcalix[6]arene in the presence of K_2CO_3. The self-inclusion of the anisole methoxy groups into the calix-cavity stabilizes the compounds in the major flattened cone conformer as shown by their ^{1}H NMR spectra. The larger substituents on the 2,4,6-positions have larger contributions to the stabilities of the compounds. The theoretical calculations by Molecular Force Field Method furthermore indicate that they are prone to exist in a flattened cone conformation.

Introduction

Calixarenes have attracted widespread attention because of their potential for forming host-guest complexes and serving as useful building blocks in supramolecular chemistry.[1] To take advantage of the macrocyclic cavity for guest inclusion, calix[6]arenes are more promising building blocks due to their large cavity size.[2] In the past few years, chemists have attempted to functionalize the platform of calix[6]arene at the lower rim and upper rim.[3] The high degree of functionality and conformational flexibility, however, complicate the synthesis and often make isolation and characterization of the products an difficult task. As a matter of fact, only limited examples of regioselective modification at the lower rim[2d,4] and upper rim[3a,c,e] are known.

Calix[4]arene gives rise to four typical conformers which are isolable as discrete chemical entities after appropriate *O*-alkylation of the parent tetrahydroxy compound.[1] In contrast, calix[6]arene has a comparatively more complex behavior due to its high degree of conformational flexibility. Even the introduction of substituents as large as cholesterol groups can not immobilize the ring inversion,[5] since the macrocycle inversion not only occurs by the *oxygen-through-the-annulus* pathway, but also by the passage of *para-substituent-through-annulus-rotation*.[6] For this reason, considerable efforts have been devoted to the synthesis of immobilized calix[6]arenes by means of an intramolecular union of two or more phenolic hydroxyls with appropriate bridging or capping sub-units.[2c,7] Some of these compounds indeed were shown the effectiveness of rigidifying the rotational freedom of the phenyl rings. In addition, some calix[6]arene derivatives (capped or uncapped) are capable of complexation to quaternary ammonium,[2c] guanidinium,[2d,4c,7k] and more sophisticated chlorine derivatives[8] with moderate efficiency. It seems imperative for calix[6]arenes to have rigidified preorganised cavity structure for guest recognition, and structure elucidation. However, in some cases, the conformational freedom affords the possibility of formation of a rotaxane between calix[6]arene hexasulfonate and a dimeric bipyridinium guest,[9] and of enzymic models for monocopper site complexes.[10] Therefore, it is still a primary task for chemists to enlarge the family member of calix[6]arene derivatives with functional varieties and to find out the common characters of their chemistry and inclusion properties.

Many approaches have been developed for the chiral modification of calix[4]arenes.[11] Especially the recent results presented by M. Žinić and his coworkers gave clear evidence for the intra- and intermolecular hydrogen-bonded organization of the calix[4]arene amino acid derivatives.[12] If we introduce amino acid ester groups onto the platform of calix[6]arene, noncovalent interactions will probably contribute to the conformational stability of calix[6]arene derivatives. In addition, the chiral centers will provide an asymmetric environment for their guests. As far as we know, very few examples of chiral calix[6]arenes have been reported.[13] The present work shows our efforts on

Keywords: chiral calix[6]arene; amino acid ester; cone conformation.

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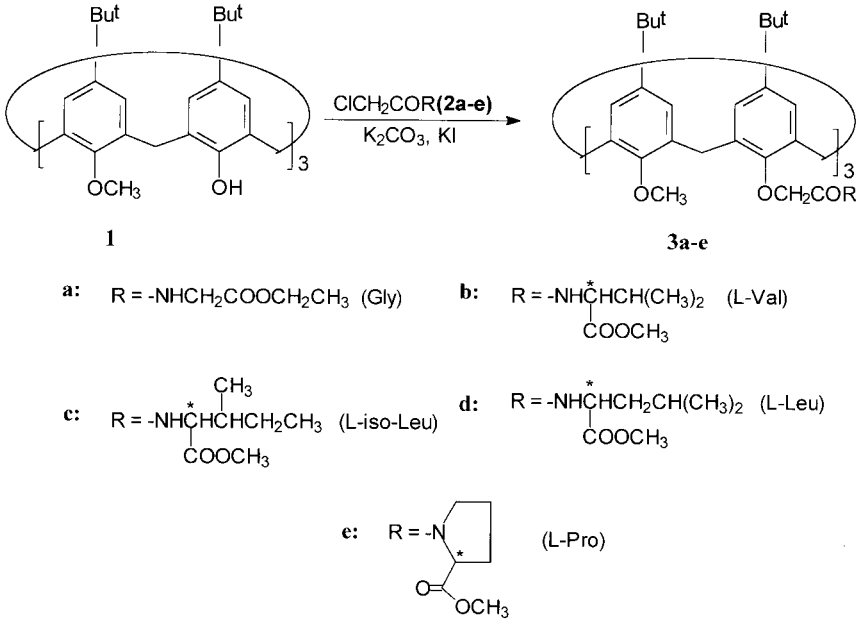

Scheme 1.

the chiral modification of the skeleton of 1,3,5-trimethoxy-*p-tert*-butylcalix[6]arene **1** by amino acid ester residues and a study of their conformational behavior.

Results and Discussion

Synthesis and temperature dependent ^{1}H NMR spectra

The amino acid ester residues were connected to the backbone of 1,3,5-trimethoxy-*p-tert*-butylcalix[6]arene by the reaction of **1** and **2** in the presence of K_2CO_3 in a mixture of anhydrous DMF and THF in the yields of 16–57% (Scheme 1). From the yields of the reaction, it appears that the structure of amino acid ester has considerable influence on the reaction.

The structures of **3a**–**e** were determined by their ^{1}H NMR, ^{13}C NMR, IR, and MS spectra, and confirmed by microanalysis. In the ^{1}H NMR of **3a** (Fig. 1A), the *tert*-butyl groups and aromatic protons show two singlet signals respectively which indicates the two types of *O*-substitution.

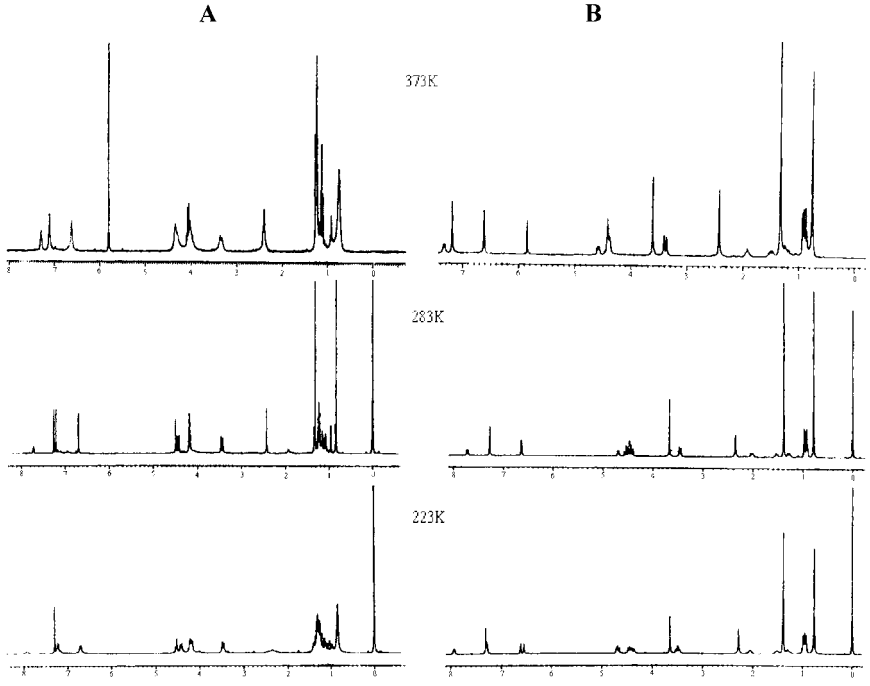

Figure 1. The temperature dependent ^{1}H NMR spectra of **3a** (A) and **3c** (B). The spectra at 223 and 283 K are recorded in $CDCl_3$, whereas the spectra at 373 K are recorded in $CDCl_2CDCl_2$.

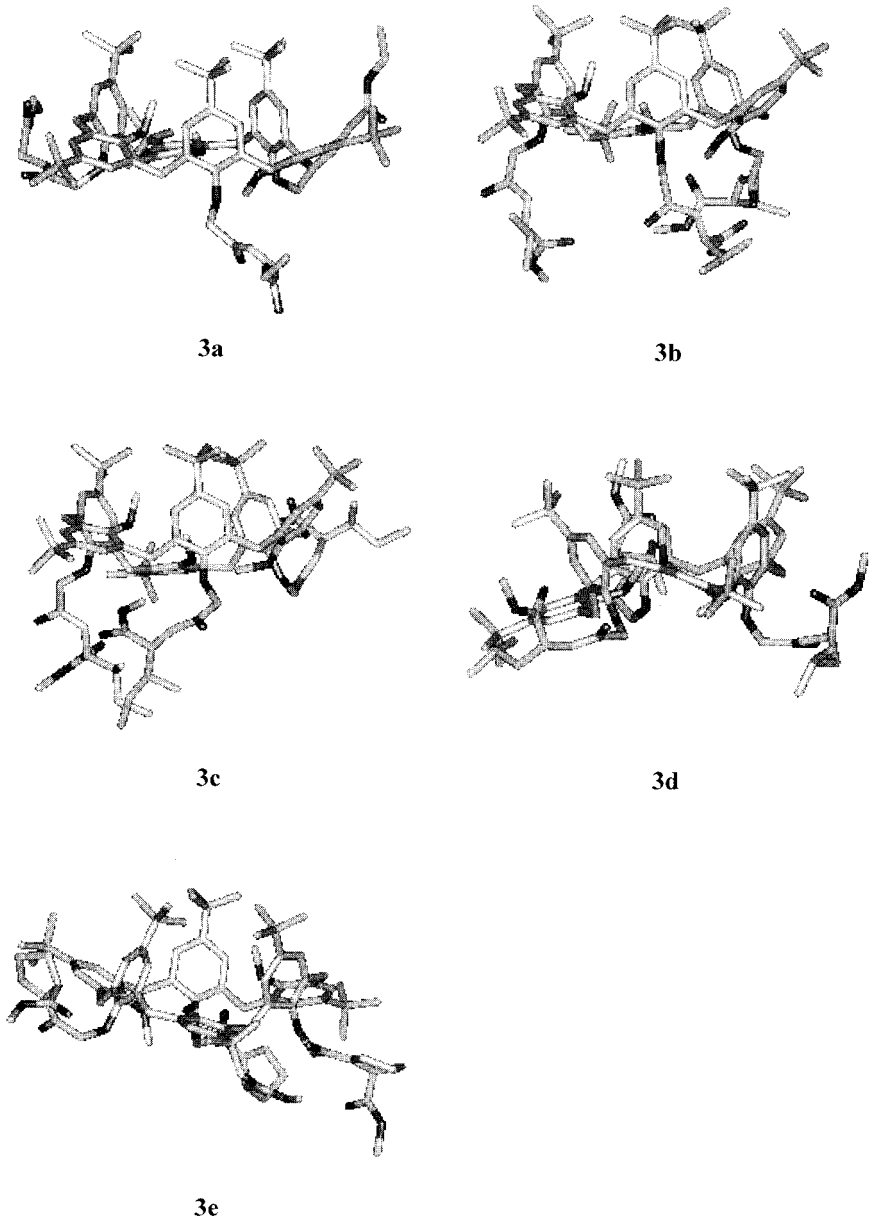

Figure 2. Drawing of the three-dimensional structures of C_{3v} stable conformers of **3a–e**. H atoms are omitted for clarity.

The protons of the methylenes between the phenol rings appear as one pair of doublets at 3.46 and 4.45 ppm. This clearly shows that **3a** mainly exists in a flattened cone conformation with C_{3v} symmetry. As for previous results,[14] self-inclusion of methyl groups into the calix-cavity is also observed since the chemical shift of protons of anisole methoxy groups appears at high field (2.44 ppm). A singlet at 4.50 ppm is assigned to the signal of protons of methylene attached to phenol oxygen and the triplet at 7.74 ppm is attributed to the protons of NH (Fig. 1A). The ^{1}H NMR spectra of **3b–e** not only indicate that they possess the major flattened cone conformation, but also provide evidence for asymmetric structural features. All of them have two pairs of AB systems around 3.40 and 4.50 ppm in their ^{1}H NMR spectra, which is due to the non-equivalency of the protons of methylenes attached to the same aromatic ring (Fig. 1B). As a consequence of the chirality of the stereogenic centers, two singlets appear on the ^{1}H NMR spectra for the two *meta*-protons of every phenol ring (Fig. 1B) and twelve carbon signals for the aromatic carbons in their ^{13}C NMR spectra.

The conformational characteristics of **3a–e** can be observed from the temperature dependent ^{1}H NMR spectra in detail. In order to investigate the conformational stabilities and variations, the ^{1}H NMR of **3a–e** were recorded in $CDCl_3$ and $CDCl_2CDCl_2$ from 223 –373 K. The self-inclusion of the 1,3,5-trimethoxy groups into the calix-cavity means **3a–e** predominantly exist in flattened cone conformations because the chemical shift of the methoxy group has shifted upfield approximately to 2.4 ppm and no typical signals of other conformations are observed. This is in agreement with the results previously reported.[14]

As the temperature was varied, the ^{1}H NMR spectra of **3b–e** showed no significant changes, and a selected spectrum of

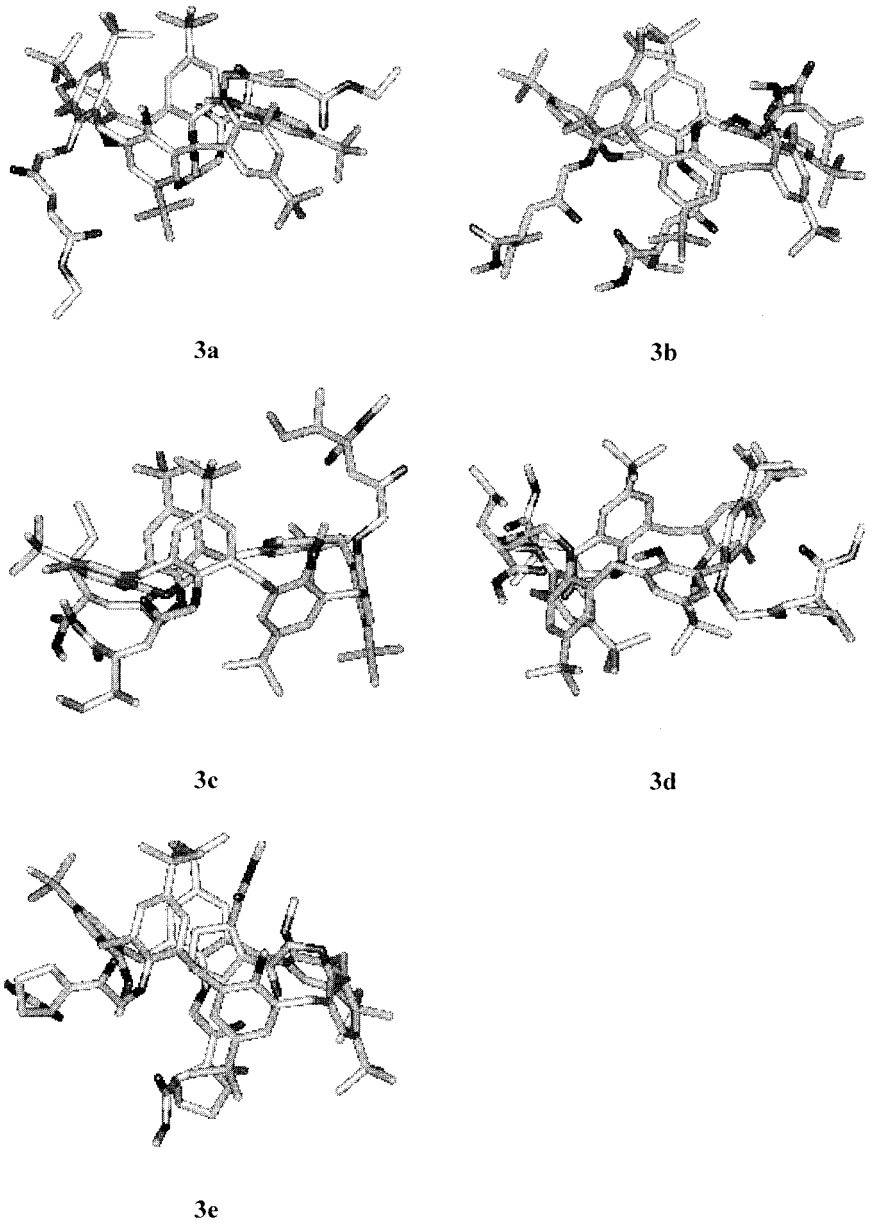

Figure 3. Drawing of the three-dimensional structures of C_s stable conformers of **3a–e**. H atoms are omitted for clarity.

3c is shown in Fig. 1B. This indicates that **3b–e** adopt relatively stable flattened cone conformations. The ^{1}H NMR spectrum of **3a**, however, changes with temperature (Fig. 1A). Both the ^{1}H NMR spectra of **3a** at 223 K and 373 K exhibit signal broadening in different amounts (Fig. 1A). Taking the ^{1}H NMR spectrum of **3a** at 223 K into account, the broadening of the signals at lower temperatures results from the slow interchange of different conformers. As the temperature rises, the coalescence of the signals is apparently exhibited at ambient temperature (Fig. 1A). However, why is the broadening of the signals observed again at even much higher temperature (373 K) (Fig. 1A)? It may be due to the inter-conversions between the C_{3v} flattened cone conformation and higher-energy conformers of **3a**. The major C_{3v} conformation becomes partially disrupted, even though the AB system of the methylenes between phenol rings shows that the C_{3v} conformation is still predominantly maintained at 373 K. Therefore, it is concluded that the conformations of 1,3,5-trimethoxy-2,4,6-tri-*O*-substituted calix[6]arene derivatives are greatly influenced by the 2,4,6-subsitutents. The larger the substituents on the oxygen of 2,4,6-position, the more stable the conformation of the 1,3,5-trimethoxy-2,4,6-trisubstituted calix[6]arenes. The self-inclusion of the anisole methoxy group into the calix-cavity is the main driving force to keep them in the flattened cone conformation.

Molecular mechanics calculations

In order to investigate their conformational behavior in detail, molecular mechanics was adopted in the present study. Because the calix[6]arene derivatives are conformationally flexible, two typical initial conformers were investigated (*flattened cone* with C_{3v} symmetry and 1,2,3-*alternate* with C_s symmetry) that were concluded to be

Table 1. The minimized energy of the C_{3v} conformers of **3a–e** (kcal/mol)

Compound	Total energy	Bonds	Angles	Torsions	Inversions	VDW	Electrostatic	H-bonds
3a	214.107	29.5687	44.7421	64.0336	2.13465	174.051	−100.423	0
3b	264.438	34.3284	47.7354	66.8445	1.90272	182.229	−68.5924	−0.009547
3c	304.767	36.7650	52.0593	63.1283	1.49440	186.934	−35.6138	0
3d	246.989	34.7476	61.7562	55.7529	1.52534	187.265	−94.0579	0
3e	292.728	36.2181	59.7917	82.5033	2.46366	184.484	−72.7326	0

Table 2. The minimized energy of the C_s conformers of **3a–e** (kcal/mol)

Compound	Total energy	Bonds	Angles	Torsions	Inversions	VDW	Electrostatic	H-bonds
3a	224.280	31.0421	44.8130	67.8953	1.89095	165.336	−86.6978	0
3b	279.706	34.1656	46.9486	63.2959	3.20718	182.588	−50.4962	−0.003079
3c	345.185	37.5245	69.6830	73.9371	5.38833	179.868	−21.2159	0
3d	267.317	33.9416	47.0877	74.0687	2.68052	184.574	−75.0351	0
3e	308.006	39.5981	72.7470	98.2849	14.5280	223.620	−140.772	0

stable conformers of 1,3,5-trimethoxy-2,4,6-trisubsituted calix[6]arene by several studies previously.[14a,17]

These initial conformations were constructed by different arrangements of the phenol rings of calix-cavity.[7j] The methoxy groups were pointed into the calix-cavity, and the orientation of CH_2COR were in the same or opposite direction to methoxy groups by setting the C–C–O–CH_2COR dihedral to 90° or −90°, respectively. The most stable conformer was then found by a Molecular Dynamics run followed by Energy Minimization. After analyzing the calculation results, the most stable conformer for every compound was obtained. The optimized molecular structures are depicted in Figs. 2 and 3 and the minimized energies are illustrated in Tables 1 and 2.

The energy data shows that the more stable conformer of **3a–e** is C_{3v}: ΔEa=10.163 kcal/mol, ΔEb=15.268 kcal/mol, ΔEc=40.418 kcal/mol, ΔEd=20.328 kcal/mol, ΔEe=15.278 kcal/mol ($\Delta E=E(C_s)-E(C_{3v})$). It supports the previous conclusion that in **3a–e** the major conformer is the flattened cone. The 1,2,3-alternate conformation can only be a minor contributor. A comparative analysis of the energetic terms in Tables 1 and 2 indicates that various degrees of stability can be interpreted from the energy differences in torsions, van der Waals, electrostatic terms. With different R groups, their total energies appear different. Compound **3b** only possesses intramolecular H-bonds. This is possibly caused by the bent structure of the R groups of **3b**. Since the minimization was performed at 0 K in vacuum, this difference may be explained by solution effects in the NMR experiments.

Conclusions

Chiral calix[6]arene derivatives **3a–e** can be easily prepared by the reaction of 1,3,5-trimethoxy-*p*-*tert*-butyl-calix[6]-arene with *N*-chloroacetyl amino acid esters. They possess flattened cone conformation on the NMR time scale at the temperature range from 223 to 373 K. The temperature dependent ^{1}H NMR spectra indicate that the larger the substituents, the more stable the C_{3v} conformer of the compounds. The molecular dynamics calculations support the observations of ^{1}H NMR experiments.

Experimental

General

Compounds **1** and **2a–e** were synthesized according to the literature procedures.[4a,15] The higher temperature NMR spectra were recorded on a Bruker DMX300 NMR spectrometer and lower temperature were recorded on DPX-400 NMR spectrometer ($CDCl_3$ and $CDCl_2CDCl_2$). The IR spectra (KBr disc) were recorded on a Perkin–Elmer 782 spectrometer. MALDI-TOF MS was recorded on a Bruker BIFLEX III spectrometer using 2-cyano-4′-hydroxy-cinnamic acid (CCA) as the matrix. The specific rotations were measured on an Optical Activity Ltd. AA-10R polarometer. Melting points are uncorrected.

General procedure for the preparation of 3a–e

0.406 g (0.4 mmol) **1**, 1.2 mmol K_2CO_3 and 0.5 g KI were refluxed in a mixture of anhydrous THF (30 mL) and DMF (10 mL) for 0.5 h. Then 5 mL THF solution of **2** (1.2 mmol) was added. The mixture was refluxed for an additional 48 h. After removal of the solvent, $CHCl_3$ (50 mL) was added to the residue, washed with brine three times, and dried over Na_2SO_4. After removal of the solvent and separation by silica gel chromatography ($CHCl_3$–petrolum ether–AcOEt), a white foam solid was obtained.

5,11,17,23,29,35-Hexa-*t*-butyl-37,39,41-trimethoxycalix[6]-arene-38,40,42-trisoxoacetyl-*N*-glycine ethyl ester (3a). Yield 0.175 g (0.12 mmol), 30%, mp 236–237°C (needles in AcOEt) (Found: C, 71.97; H, 8.07; N, 2.92. $C_{87}H_{117}N_3O_{15}$ requires C, 72.32; H, 8.16; N, 2.91%). ν_{max}/cm^{-1} 3430 (NH), 1742, 1680 (CO); δ_H: 7.70 (t, 3H, J=7.2 Hz, N*H*), 7.22 (s, 6H), 6.71 (s, 6H) (Ar*H*), 4.50 (s, 6H, OCH_2CO), 4.45, 3.46 (AB, 12H, J=15.2 Hz, ArCH_2Ar), 4.22–4.15 (m, 12H, NCH_2, OCH_2CH$_3$), 2.44 (s, 9H, OCH_3), 1.34 (s, 27H, *t*-Bu), 1.25 (t, 9H, J=7.1 Hz, OCH$_2$CH_3) and 0.84 (s, 27H, *t*-Bu); δ_C: 169.3, 169.2, 154.2, 150.3, 146.8, 146.2, 133.2, 132.4, 127.9, 124.2, 71.2, 61.4, 60.3, 41.0, 34.2, 34.0, 31.5, 31.1, 29.9 and 14.1; *m*/*z* 1444 (M^+).

5,11,17,23,29,35-Hexa-*t*-butyl-37,39,41-trimethoxycalix[6]-arene-38,40,42-trioxoacetyl-*N*-L-valine methyl ester (3b). Yield 0.35 g (0.23 mmol), 57%; $[\alpha]_D^{20}$=+6.67 (*c*

1.63, $CHCl_3$); mp 139–140°C (Found: C, 72.86; H, 8.53; N, 2.65. $C_{93}H_{129}N_3O_{15}$ requires C, 73.05; H, 8.50; N, 2.75%). ν_{max}/cm^{-1} 3415 (NH), 1740, 1690 (CO); δ_H: 7.66 (d, 3H, J=8.9 Hz, N*H*), 7.27 (s, 3H), 7.25 (s, 3H), 6.64 (s, 3H), 6.63 (s, 3H) (Ar*H*), 4.66 (q, 3H, J=4.0 Hz, NC*H*), 4.55, 4.48 (AB, 6H, J=14.2 Hz, OCH_2CO), 4.45, 4.42, 3.45, 3.44 (2AB, 12H, J=15.2 Hz, $ArCH_2Ar$), 3.67 (s, 9H, $COOCH_3$), 2.36(s, 9H, $ArOCH_3$), 2.36–2.19 (m, 3H, $CH(CH_3)_2$), 1.38 (s, 27H, *t*-Bu), 1.02–0.96 (m, 18H, $CH(CH_3)_2$) and 0.78 (s, 27H, *t*-Bu); δ_C: 171.6, 168.8, 154.4, 150.3, 146.8, 146.2, 133.3, 133.2, 132.7, 132.4, 128.3, 128.2, 124.0, 123.9, 71.3, 60.0, 56.9, 52.1, 34.3, 34.0, 31.6, 31.0, 29.9, 29.8, 19.1 and 17.8; *m/z* 1529 ($[M^+ + 1]^+$).

5,11,17,23,29,35-Hexa-*t*-butyl-37,39,41-trimethoxycalix[6]-arene-38,40,42-trioxoacetyl-*N*-L-*iso*-leucine methyl ester (3c). Yield, 0.1 g (0.064 mmol), 16%; $[\alpha]_D^{20}$=+4.49 (*c* 1.21, $CHCl_3$); mp 114–115°C (Found: C, 73.46; H, 8.61; N, 2.18. $C_{96}H_{135}N_3O_{15}$ requires C, 73.39; H, 8.66; N 2.67%). ν_{max}/cm^{-1} 3418 (NH), 1743, 1693 (CO); δ_H: 7.69 (d, 3H, J=3.3 Hz, N*H*), 7.27 (s, 6H), 6.64 (s, 6H) (Ar*H*), 4.70 (q, 3H, J_1=3.3 Hz, J_2=7.1 Hz, NC*H*), 4.56, 4.47 (AB, 6H, J=14.6 Hz, OCH_2CO), 4.47, 4.42, 3.47, 3.46 (2AB, 12H, J=15.2 Hz, $ArCH_2Ar$), 3.68 (s, 9H, $COOCH_3$), 2.37 (s, 9H, $ArOCH_3$), 2.10–1.95 (m, 3H, $NCHCH(CH_3)CH_2CH_3$), 1.55–1.40, 1.29–1.12 (m, 6H, $CHCH_2CH_3$), 1.39 (s, 27H, *t*-Bu), 1.02–0.81 (m, 18H, $CH(CH_3)CH_2CH_3$) and 0.79 (s, 27H, *t*-Bu); δ_C: 171.6, 168.6, 154.4, 150.4, 146.8, 146.2, 133.2, 133.1, 132.6, 132.4, 128.1, 128.0, 124.0, 123.9, 71.4, 60.0, 56.3, 52.1, 37.8, 34.3, 34.0, 31.6, 31.0, 29.9, 29.8, 25.3, 15.5 and 11.6; *m/z* 1593 ($[M+Na]^+$).

5,11,17,23,29,35-Hexa-*t*-butyl-37,39,41-trimethoxycalix[6]-arene-38,40,42-trioxoacetyl-tris-*N*-L-leucine methyl ester (3d). Yield 0.22 g (0.14 mmol), 35%; $[\alpha]_D^{20}$=−15.5 (*c* 0.47, $CHCl_3$); mp 123–124°C (Found: C, 73.18; H, 8.76; N, 2.52. $C_{96}H_{135}N_3O_{15}$ requires C, 73.39; H, 8.66; N, 2.67%). ν_{max}/cm^{-1} 3418 (N*H*), 1744, 1687 (CO); δ_H: 7.64 (d, 3H, J=7.2 Hz, N*H*), 7.26 (s, 6H), 6.64 (s, 6H) (Ar*H*), 4.78–4.66 (m, 3H, NC*H*), 4.56, 4.45 (AB, 6H, J=14.4 Hz, OCH_2CO), 4.46, 4.42, 3.19, 3.20 (2AB, 12H, J=15.3 Hz, $ArCH_2Ar$), 3.68 (s, 9H, $COOCH_3$), 2.37 (s, 9H, $ArOCH_3$), 1.83–1.58 (m, 9H, $CH_2CH(CH_3)_2$), 1.39 (s, 27H, *t*-Bu), 0.96 (d, 9H J=4.5 Hz), 0.92 (d, 9H J=4.5 Hz) ($CH(CH_3)_2$) and 0.79 (s, 27H, *t*-Bu); δ_C: 172.5, 168.6, 154.2, 150.5, 146.7, 146.2, 133.2, 133.1, 132.6, 132.2, 128.0, 127.9, 124.0, 123.8, 71.4, 60.0, 52.2, 50.3, 41.1, 34.1, 33.9, 31.5, 30.9, 29.9, 29.8, 24.6, 22.7 and 21.6. *m/z* 1593 ($[M+Na]^+$).

5,11,17,23,29,35-Hexa-*t*-butyl-37,39,41-trimethoxycalix[6]-arene-38,40,42-trioxoacetyl-*N*-L-proline methyl ester (3e). Yield 0.25 g (0.164 mmol), 41.0%; $[\alpha]_D^{20}$=−38.8 (*c* 1.64, $CHCl_3$); mp 263.5–265°C (white powder in AcOEt)-(Found: C, 73.06; H, 7.90; N, 2.62. $C_{93}H_{123}N_3O_{15}$ requires C, 73.34; H, 8.14; N, 2.76%); ν_{max}/cm^{-1} 1742, 1655 (CO); δ_H: 7.27 (s, 3H), 7.26 (s, 3H) 6.63 (s, 3H), 6.62 (s, 3H) (ArH), 4.80–4.30 (m, 15H, OCH_2O, $ArCH_2Ar$, $NCHCOOCH_3$), 3.89–3.76 (m, 6H, NCH_2), 3.80 (s, 9H, $COOCH_3$), 3.46 (d, 3H, J=12.0 Hz), 3.42 (d, 3H, J=12.0 Hz) ($ArCH_2Ar$), 2.22 (s, 9H, $ArOCH_3$), 2.20–1.99 (m, 12H, NCH_2CH_2), 1.38 (s, 27H, *t*-Bu) and 0.77 (s, 27H, *t*-Bu); δ_C: 172.6, 167.2, 154.4, 151.7, 146.3, 145.9, 133.4, 133.3, 132.9, 132.8, 128.2, 128.1, 123.6, 123.5, 72.5, 60.1, 59.2, 52.8, 46.8, 34.3, 34.0, 31.7, 31.1, 29.8, 29.7, 28.9 and 25.1; *m/z*: 1523 ($[M-1]^+$).

Temperature dependent ^{1}H NMR spectra determination

The temperature dependent ^{1}H NMR spectra of **3a**–**e** were measured from 223–373 K at ten degree intervals. Among them, the spectra of 223–283 K were recorded in $CDCl_3$ on an AVANCE-400 NMR spectrometer and the spectra of 293–373 K were recorded in $CDCl_2CDCl_2$ on a Bruker DMX300 NMR spectrometer.

Molecular modeling

All calculations were done on a Silicon Graphics O2 workstation using Cerius 2 version 3.8 package developed by Molecular Simulations Incorporated (MSI). Dreiding force field 2.21 was used.[16] All the geometrical parameters were optimized without any constraint. The Energy Minimizations were performed until the energy gradient RMS was lower than 0.01 kcal mol^{-1} A^{-1}. In order to obtain a representative low-energy conformers, the following procedure was used: The molecule was heated to 1000 K in 5 ps, 600 K in 5 ps, 400 K in 5 ps, and subsequently 50 ps of molecular dynamics calculation at 300 K were run. Then the structure with the lowest energy during the simulation was taken and energy minimized.

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