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Article *in* The Chemical Educator · January 2013

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US-Africa Collaboration in Guided Inquiry Synthesis and Characterization of the "Frustrated" Amino Acid-Based Calixarene Molecules

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Received August 6, 2010. Accepted September 23, 2010.

Abstract: The Department of Chemistry at Missouri State University-West Plains (MSU-WP) is internationalizing the existing research activities by initiating a collaborative Kenya-U.S. Chiral Science (chiroscience) project. The overarching goal of the project is three-fold: 1) reinvigorate undergraduate research; 2) augment MSU-WP's new Green Nanoscience Research and Mentoring Program; and 3) establish synergistic relationships between different research groups and academic institutions in Kenya and MSU-WP. To stimulate students' interests in the collaborative chiroscience project, we have chosen projects that are not only aligned with NSF's high priority areas but are also relevant to today's society (e.g., cancer, tuberculosis, heart disease, HIV, and host-guest chemistry). For several years, our research groups have been working on two important supramolecular hosts, calixarenes and cyclodextrins (CDs). Calixarenes are macrocyclic structures with defined cavities, having host-guest complexation properties similar to CDs. One of the advantages that calixarenes have over naturally occurring host molecules, such as CDs, is that the size of the internal cavity of the macrocycle is more flexible, i.e., the number of constituent rings range from four to eight. This paper illustrates our ongoing efforts in the area of synthesis and complexation properties of calixarenes. Herein, we report the synthesis of new amino acid-based acylcalixarenes and characterization by means of ^{1}H- and ^{13}C-NMR spectroscopy. The calix[4]arenes possess L-alanine, L-valine, L-leucine, and L-isoleucine moeties at the lower rim. 1D and 2D NMR showed that the new calixarenes adopt the standard "cone" conformations in solution.

Introduction

Our new Kenya-U.S. educational research focuses on our continued efforts to understand chiral recognition mechanisms for improved separation of enantiomeric mixtures [1–9]. Over the past 50 years, the topic of chiral separation [10–15] has become one of the most important frontiers in exploratory analytical and organic chemistry research. Although remarkable advances have been made, relatively few enantiomeric mixtures have been separated. We have successfully utilized various hosts (e.g., cyclodextrins, calixarenes, excitatory amino acid-based chiral surfactants, and nanoparticles) in the separation of enantiomeric mixtures of persistent organic pollutants including polychlorinated biphenyls (PCBs) [12] and polycyclic aromatic hydrocarbons (PAHs) [16]. Optimization of chiral separations has been achieved through collaborative hypothesis-driven modifications of amino-acid based calixarenes [17].

Calixarenes are cyclic oligomers originating from the base-catalyzed condensation of *p*-substituted phenol with formaldehyde. Their characteristic architectural patterns, i.e., phenolic moieties linked by methylene bridges to form hydrophobic cavities, make them capable of host-guest interactions with molecules [17–20]. The earliest examples of calixarene complex formation appeared in the mid 1980s involving nonaqueous systems with calixarenes and amines,[2] and aqueous systems with water-soluble *p*-sulfonatocalixarenes [21–24]. Interest in our laboratory is primarily centered on water-soluble calixarenes and their effectiveness as buffer additives for capillary electrophoresis (CE) [17, 20]. Since most calixarenes are not water-soluble and do not have chiral recognition ability, the functionalization of the upper and lower rims is necessary to fully exploit their properties [22]. Recently, the syntheses and utility of water-soluble *p-t*-butylcalixarenes with L-alanine and L-valine amino acid groups as CE buffer additives has been demonstrated [19].

The focus of the present article is to report the synthesis of (*N*-L-leucinoacyl)calixarene (CX4-L-Leu) and (*N*-L-isoleucinoacyl)calixarene (CX4-L-Ile) and the characterization

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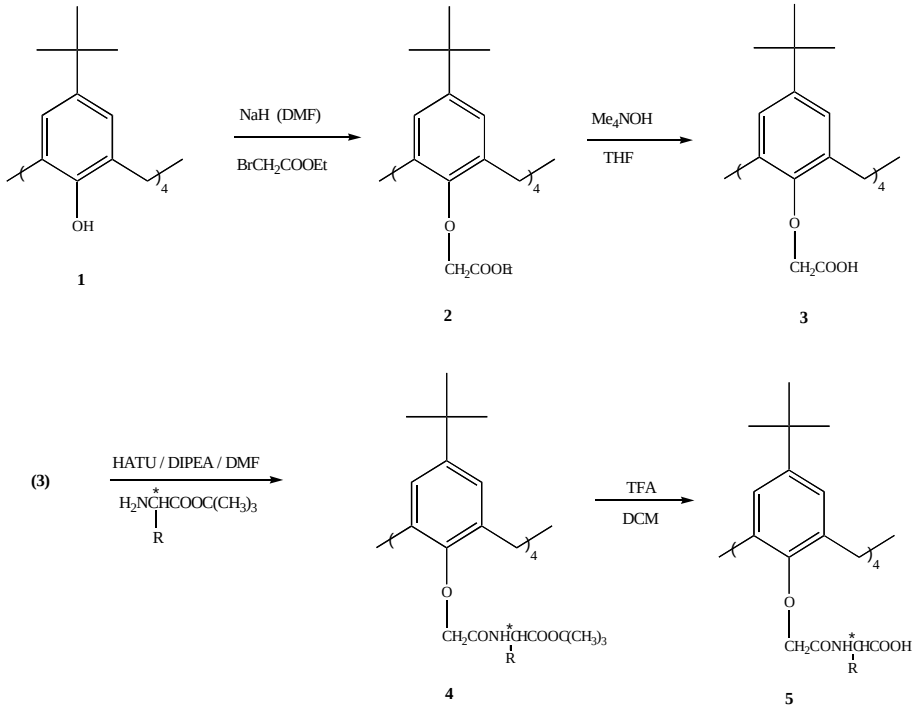


Figure 1. Synthetic scheme of (*N*-L-aminoacyl)calixarenes.

of all four amino acid functionalized calixarenes by nuclear magnetic resonance spectroscopy (NMR) [6, 18]. These molecules are considered "frustrated" in regard to the process of going from a solvated to desolvated "cone-shaped" conformation [25, 26]. The motivation for the research emanated from our ongoing chiroscience project involving the development of novel supramolecular calixpyrrole architectures with ion-binding sites [27–31].

NMR spectroscopy is an important analytical tool which aids in determining the structure of calixarenes [22]. Two-dimensional techniques such as homonuclear (H,H)-correlation (H,H-COSY), nuclear Overhauser enhancement (NOESY), heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple bond correlation (HMBC) spectroscopies were employed to determine proton-proton connectivity through bonds ($^1J_{H\text{-}H}$-$^3J_{H\text{-}H}$), proton interactions through space (distance < 5 Å), short-range proton-carbon connectivities ($^1J_{H\text{-}C}$), and long-range proton-carbon connectivities ($^2J_{H\text{-}C}$-$^4J_{H\text{-}C}$) respectively [1, 6].

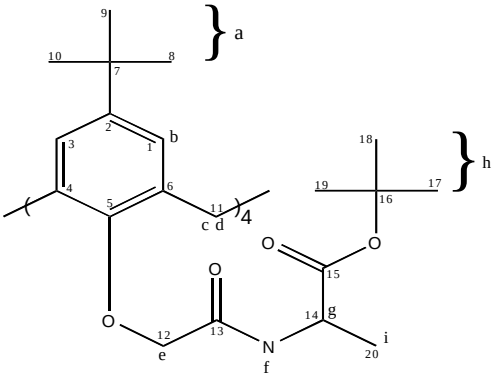
Experimental

To enhance both teaching and learning in undergraduate institutions (such as ours), we chose calixarenes as mascot molecules for guided inquiry lab [32–36]. Students worked four teams consisting of six members each. Each team synthesized a specific calixarene molecule and compared their NMR data with those published in the peer-reviewed journals [17, 22–24]. We were particularly interested in piquing students' interest in chemistry by engaging them in the cutting-edge and interesting educational research projects such as those described by Professor Isiah Warner's group at Louisiana State University [17, 37–39]. Undoubtedly, Professor Warner has enviable qualities in mentoring several women and the traditionally underrepresented groups from US and Africa. He is one of the fathers of research involving cyclodextrins (CDs) and calixarenes. In the present study, the NMR spectral data obtained are almost identical to those already reported in the literature [19, 20, 22]. We decided to include the data in this manuscript as a way of disseminating knowledge especially to scientists in Africa who might have limited access to NMR spectrometers. In the present study, students in the collaborating institutions synthesized amino acid-based chiral acylcalixarenes following the literature procedures (Figure 1) [1, 2, 17, 22, 23]. The structure of each (*N*-L-aminoacyl)calixarene derivative is shown in Figure 2. NMR experiments were carried out in 5-mm NMR tubes on Bruker AMX-400 spectrometer without sample spinning. Literature pulse sequences [1, 5, 6] were used for 1D and 2D experiments (^{1}H-^{1}H COSY: 256 × 256 data matrix size; time domain (td) 256 in F1 and 512 in F2; relaxation delay (rd) = 1.5 s; number of scans (ns) = 16. HMQC: 512 × 512 data matrix size; td 512 in F1 and 1024 in F2; rd = 2 s; ns = 48; dummy scans (ds) = 4. HMBC: 512 × 512 data matrix size; td 512 in F1 and 1024 in F2; rd = 2 s; ds = 16; ns = 84; delay for evolution of long range couplings = 0.06 s). The ^{1}H–^{1}H NOE connectivity maps were obtained with 2D nuclear Overhauser enhancement spectroscopy (NOESY), using pulse sequence $(90o\text{-}t_1\text{-}90o\text{-}J_m\text{-}t_2)_n$, where J_m is the so-called mixing time. The mixing time was 800 ms. In order to suppress contributions from coherent magnetization transfer to the cross peak intensities, the mixing time was stochastically modulated with a modulation amplitude of 5% of the mixing time. The free induction decays for COSY and NOESY were collected with 2048 points in the F2 direction. In addition, the time domain data matrix was expanded by zero filling which resulted in 2048 points in F1 and 4096 points in F2 for both experiments. This was Fourier-transformed to yield a 1024 × 1024 point frequency domain data matrix.

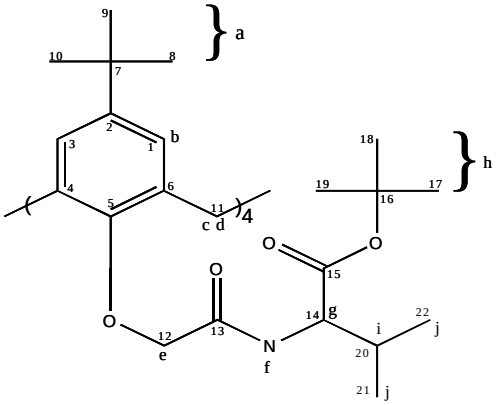
Results and Discussion

Guided Inquiry Teaching and Learning. The need for guided inquiry learning activities was recognized by the National Research Council more than a decade ago [40] and recently by the National Academy of Sciences in 2005.

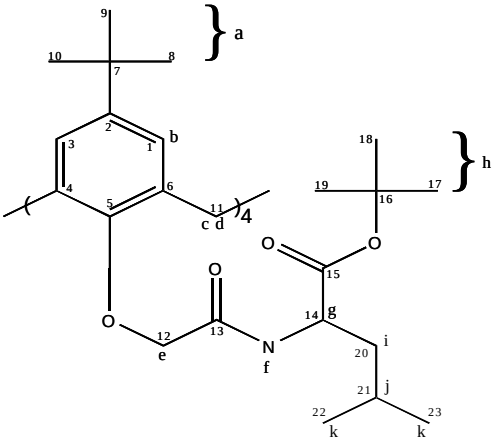
Inquiry proceeds through cycles of instigation [41] guided by specific questions (e.g., How does light interact with mirrors?). Recent developments in cognitive learning theory suggest that effective learning is enhanced when students are actively engaged in the classroom and when they construct their own knowledge following a learning cycle paradigm. The



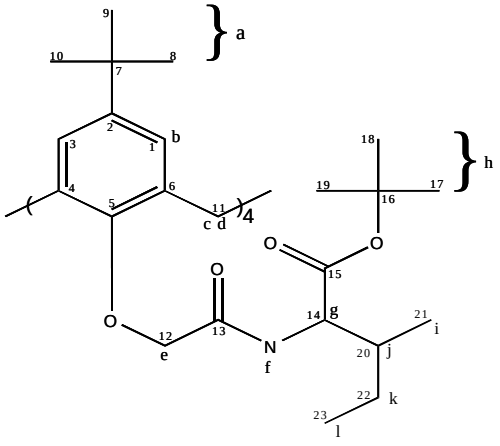
(*N*-L-alaninoacyl)calix[4]arene *t*-butyl ester



(*N*-L-valinoacyl)calix[4]arene *t*-butyl ester



(*N*-L-leucinoacyl)calix[4]arene *t*-butyl ester



(*N*-L-isoleucinoacyl)calix[4]arene *t*-butyl ester

Figure 2. Structures of (*N*-L-aminoacyl)calixarenes.

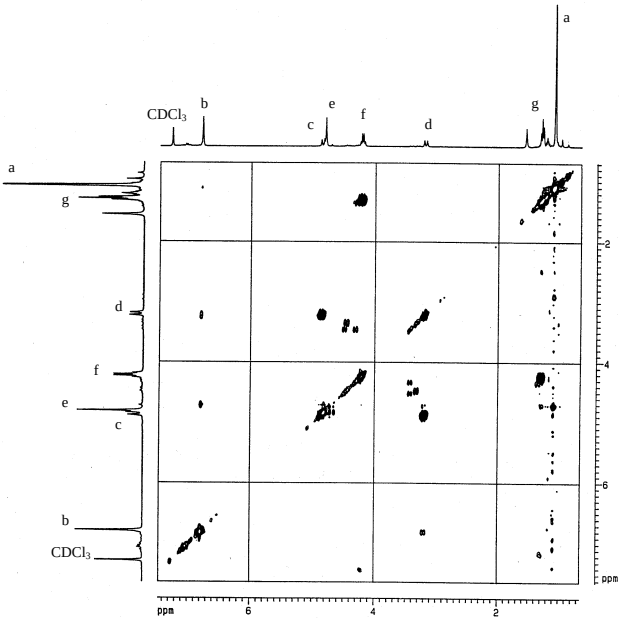


Figure 3. COSY spectrum of calixaryl tetraethyl ester (Compound 2).

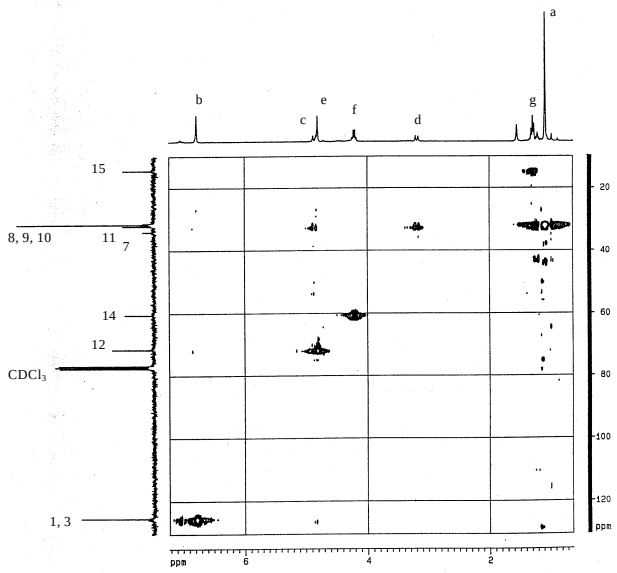


Figure 4. HMQC spectrum of calixaryl ester (Compound 2).

Table 1. ^{1}H and ^{13}C Chemical Shifts (δ) of *p-t*-butylcalixarene-O,O',O", O'"-tetraacetic acid tetraethyl ester (Compound 2)

δ(ppm)	Label	Multiplicity
1.07	a	singlet
1.28	g	triplet
3.19	d	doublet
4.20	f	quartet
4.80	e	singlet
4.85	c	doublet
6.77	b	singlet
17.79	15	—
31.36	8, 9, 10	—
31.89	11	—
33.81	7	—
60.28	14	—
71.32	12	—
125.34	1,3	—
133.44	4,6	—
145.14	2	—
152.98	5	—
170.52	13	—

Table 2. ^{1}H and ^{13}C Chemical Shifts (δ) of (*N*-L-alaninoacyl)calixarene *t*-butyl ester

δ(ppm)	Label	Multiplicity
1.07	a	singlet
1.39	i	doublet
1.44	h	singlet
3.15	d	doublet
4.61	g	octet
4.62	e	singlet
4.63	c	doublet
6.75	b	singlet
7.76	f	doublet
17.82	20	—
27.96	17, 18, 19	—
31.34	8, 9, 10	—
31.84	11	—
32.82	7	—
48.55	14	—
74.47	12	—
81.41	16	—
125.60	1, 3	—
132.82	4, 6	—
145.31	2	—
153.35	5	—
169.69	13	—
172.16	15	—

oldest and best known organized methods of teaching through inquiry are process-oriented guided-inquiry learning (POGIL) [42], problem-based learning (PBL) [43], and peer-led team learning (PLTL) [44]. These methods are effective in engaging students because they focus on the process of learning.

Guided inquiry laboratory instruction has been used successfully in small community colleges as well as in large universities [32, 34, 35]. At MSU-WP, traditional chemistry experiments have been recasted into creative guided inquiry formats. For example, in the Spring of 2012, students enrolled in General Chemistry lab courses engaged in recasting a traditional four-week "Diels-Alder (DA) Synthesis of exo-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Anhydride Monomer" experiment [45] to a guided inquiry experiment. The experiment was designed such that the students collaborated by working in teams. A teaching assistant (TA) and two students enrolled in "Independent Research" courses were embedded into each lab session as mentors. Students had to figure out how to solve a specific puzzle, i.e., in the DA reactions between maleic anhydride and dienes (e.g., furan, pyrrole, and thiophene), which experimental conditions produce the most crystalline monomers? To solve the puzzle, each team wrote a five-page proposal following specific guidelines: 1) perform thorough literature searches and obtain ten most recent lead articles; 2) summarize each article into Introduction, Experiment, Results, Discussion, and Conclusions sections; 3) develop experimental plans, i.e., hypotheses, a list of chemicals and special glassware, schemes (cost, reaction, purification, and identification), timeline, management, and assessment plans; 4) Write a 5-page proposal and seek comments from peers before submitting it to the instructor for approval; 5) Summarize the proposal on five PowerPoint slides then give a 10-minute oral presentation in front of peers and faculty; and 6) after carrying out the experiment, each team prepares a report using the *2010 Journal of Organic Chemistry Guidelines for Authors* and submits it electronically. Buoyed by the success of guided inquiry DA synthesis (above), we employed the same procedure in the synthesis and characterization of Amino Acid-Based Acylcalixarenes, the "Frustrated" molecules [25, 26].

Characterization of Amino Acid-Based Acylcalixarenes. A number of interesting points can be raised about the NMR data. First, it is evident from Figure 3 that the calixaryl tetraethyl ester (**2**) adopts a cone conformation as do most of the calixarene esters for which X-ray structures have been obtained [18–20]. In this conformation, the methylene bridge protons are positioned outside the cavity, one axial and the other equatorial with respect to the benzene ring. This results in a splitting pattern, a pair of doublets in the methylene region (3.0–5.0 ppm), with each doublet *J*-coupled at a frequency of approximately 13 Hz. It is important to note that differentconformers of calixarenes exhibit distinctive patterns in the methylene region of the ^{1}H NMR spectra: (1) cone-one pair of doublets; (2) partial cone-two pairs of doublets (ratio 1:1) or one pair of doublets and one singlet (ratio 1:1); (3) 1,2-alternate-one singlet and two doublets (ratio 1:1); and (4) 1,3-alternate-one singlet. Calixarenes most often assume the cone or partial cone conformation [17, 22].

The second point of interest concerns the ^{13}C NMR spectral data summarized in Table 1. Eleven peaks representing different carbon environments were expected. However, only ten peaks were observed. The assignment of each peak was made on the basis of 2D spectra between ^{1}H and ^{13}C [17, 18, 22, 23]. The ^{1}H–^{13}C COSY experiment identified short and long range coupling as a result of through-bond interaction of neighboring protons (Figure 3). Cross peaks were observed between methylene protons (**f**) and terminal methyl protons (**g**) of the ethyl ester, indicating ^{3}J coupling between these neighboring groups. The observed geminal coupling of the methylene protons (**c**, **d**) was an important factor in establishing the nonequivalence of each, and in determining their positions (equatorial or axial) with respect to the benzene ring. A cross peak indicating ^{4}J coupling was also observed between the aromatic protons (**b**) and one of the methylene bridge protons (**c**, **d**), which supports the theory of

Table 3. ^{1}H and ^{13}C Chemical Shifts (δ) of (*N*-L-valinoacyl)calixarene *t*-butyl ester

δ(ppm)	Label	Multiplicity
0.88	j	quartet
1.06	a	singlet
1.44	h	multiplet
1.67	i	doublet
3.15	d	doublet
4.48	g	quartet
4.60	c	doublet
4.77	e	singlet
6.78	b	singlet
7.33	f	doublet
17.85	20	—
19.82	21	—
20.50	22	—
27.06	17, 18, 19	—
31.75	8, 9, 10	—
31.89	11	—
33.93	7	—
53.51	14	—
73.57	4, 6	—
145.31	12	—
78.14	16	—
125.56	1, 3	—
132.78	4, 6	—
145.22	2	—
153.84	5	—
169.66	13	—
172.41	15	—

Table 4. ^{1}H and ^{13}C Chemical Shifts (δ) of (*N*-L-leucinoacyl)calixarene *t*-butyl ester

δ(ppm)	Label	Multiplicity
0.90	k	quartet
1.06	a	singlet
1.44	h	singlet
1.61	j	multiplet
1.66	i	octet
3.16	d	doublet
4.54	e	singlet
4.67	g	sextet
4.77	c	doublet
6.72	b	singlet
7.81	b	doublet
22.23	23	—
23.03	22	—
25.09	21	—
28.23	17, 18, 19	—
31.58	8, 9, 10	—
32.39	11	—
34.00	7	—
41.39	20	—
51.36	14	—
74.70	12	—
81.57	16	—
125.53	1, 3	—
132.66	4, 6	—
145.16	2	—
153.97	5	—
170.38	13	—
173.04	15	—

nonequivalence of the bridge protons (**c**, **d**), and led to the assignment of **d** as the equatorial proton. Although the effectiveness of long-range (H,H)-COSY was reduced after four bonds, coupling through five bonds was also observed in our spectra, with a cross peak between the *t*-butyl (**a**) and the aromatic (**b**) protons, and a cross peak between the acyl methylene (**e**) and the methylene (**f**) protons of the terminal ethyl group. To identify the 3D conformation of **2**, a 2D NOESY experiment was performed. Intramolecular interactions were observed between *t*-butyl (**a**) and aromatic protons (**b**), and between bridging methylene protons (**c**, **d**) as expected. Interestingly, unequal interaction of **c** and **d** with nearby protons was observed. Only one bridging methylene proton (**c**) showed spatial interaction with acyl methylene (**e**) protons, while the other (**d**) interacted with the aromatic protons (**b**). This dramatic difference between the bridging methylene protons' interactions was a strong indication that neither proton was positioned inside the cavity of the calixarene. In order to assign the carbons bearing hydrogens, an HMQC ($^{1}J_{H\text{-}C}$) inverse experiment was performed (Figure 4). It was observed that C-11 (bearing protons **c** and **d**), though directly attached to the benzene ring was located upfield, very close to the *t*-butyl peak, indicating that it is strongly shielded from the applied magnetic field. The arene carbons (C-1, C-3) were located downfield in the aromatic region as expected. Carbons 12 and 14 were unambiguously assigned to protons **e** and **f** respectively, with C-12 being more downfield due to its proximity to electronegative substituents. Because of the high number of quaternary carbons in the calixarene derivatives, structure determination required an extensive long-range ^{1}H-^{13}C correlation experiment, HMBC. The sequence employed was able to connect quaternary carbon atoms to any second, third, or in some cases fourth neighbor. Carbon 13, located most downfield was found to correlate with protons **e** and **f**, exhibiting ^{2}J and ^{3}J coupling respectively. Carbons 4 and 6 correlated with the aromatic (**b**) and bridging methylene (**c**, **d**) protons through two bonds, and with the acyl protons (**e**) through four bonds. Their location in the ^{13}C NMR spectrum (more downfield than C-1 and C-3) is based upon their closer proximity to electronegative oxygen. The disappearance of cross peaks of C-14 and C-15, and their corresponding protons (**f**, **g**) unequivocally showed that the hydrolysis of the calixaryl tetraethyl ester (**2**) to the calixaryl tetraacid (**3**) had been successful.

Tables 2, 3, 5, and V summarize the NMR spectral data for *t*-butyl esters of CX4-L-Ala, CX4-L-Val, CX4-L-Leu, and CX4-L-Ile, respectively. Hydrolysis of each ester (**4**) to its acid form (**5**) was shown by the disappearance of ^{1}H and ^{13}C peaks associated with the *t*-butyl group of the amino acid.

Because the side chain of alanine is a single methyl group, only two cross peaks are noteworthy in its COSY spectrum: one occurring between the amide proton (**f**) and the methine proton (**g**) of the stereogenic carbon; the other occurs between **g** and the terminal methyl protons (**i**) of the side chain. An HMQC correlation between **i** and C-20 confirmed that C-20 is located most upfield in the ^{13}C NMR spectrum of CX4-L-Ala *t*-butyl ester. Another correlation was observed between **g** and C-14, the stereogenic carbon. As expected, a correlation between the *t*-butyl protons of the amino acid (**h**) and C-17, C-18, and C-19 was observed. All other correlations occurred between protons and carbons of the calixarene skeleton. To assign the two quaternary carbons correctly, an HMBC

Table 5. ^{1}H and ^{13}C Chemical shifts (δ) of *N*-L-isoleucinoacyl)calixarene *t*-butyl ester

δ(ppm)	Label	Multiplicity
0.82	i	doublet
0.88	l	triplet
1.06	a	singlet
1.24	k	octet
1.43	h	singlet
1.84	j	multiplet
3.15	d	doublet
4.53	g	quartet
4.53	e	singlet
4.84	c	doublet
6.72	b	singlet
7.37	f	doublet
8.06	h*	singlet
11.89	23	—
15.42	21	—
25.85	22	—
28.28	17, 18, 19	—
31.57	8, 9, 10	—
32.22	11	—
34.02	7	—
38.10	20	—
56.94	14	—
74.54	12	—
81.56	16	—
125.46	1, 3	—
133.09	4, 6	—
145.23	2	—
152.86	5	—
169.76	13	—
171.08	15	—

* The signal is the proton of the carboxylic acid formed by hydrolysis of the *t*-butyl ester.

Table 6. HMBC Correlations of (*N*-L-valinoacyl)calixarene *t*-butyl ester

Proton	Correlated With	$^{n}J_{C-H}$
a	2	3
a	7	2
b	5	3
b	7	3
c	1, 3	4
c	4, 6	2
c	5	3
d	1, 3	4
d	4, 6	2
d	5	3
e	5	3
e	13	2
g	15	2
h	16	2

experiment was conducted on CX4-L-Ala *t*-butyl ester (Figure 5). Correlations were observed between C-15 and protons **g** and **i**, indicating ^{2}J and ^{3}J coupling, respectively. In addition, a correlation indicating ^{2}J coupling between C-16 and alanine *t*-butyl protons (**h**) was observed. The occurrence of cross peaks signifying ^{2}J coupling between C-13 and protons **e** and **f** was a valuable indicator of successful attachment of the L-alanine *t*-butyl ester to the calixaryl tetraacid (**3**). All other correlations were between carbons and protons of the calixarene cavity.

A double doublet in the aliphatic region of the ^{1}H NMR spectrum of CX4-L-Val *t*-butyl ester led to its assignment as the geminal methyl protons (**j**) of the isopropyl side chain. The COSY spectrum of CX4-L-Val *t*-butyl ester revealed one noteworthy cross peak, occurring between the methine proton (**i**) and the terminal methyl protons (**j**) of the isopropyl side chain. In the HMQC spectrum, strong cross peaks were observed between C-14 and proton **g**, between C-20 and proton **i**, and between C-21 and C-22 and the **j** protons. The most useful information was obtained from the HMBC spectrum (Figure 6). Summarized in Table 6, this spectrum not only shows the correlations between carbons and protons of the calixarene cavity but also shows residual HMQC correlations. For example, the correlation of C-21 and C-22 with protons **g** and **j** is evident in both the HMQC and HMBC spectra. Other correlations were C-13 and C-15 with proton **g** and C-16 with **h** protons, which led to the unambiguous assignment of all carbons in the molecule.

The NMR spectral data for CX4-L-Leu *t*-butyl ester is summarized in Table 4. A pair of doublets indicating the geminal methyl protons (**k**) of the isobutyl side chain, suggests that the protons are nonequivalent. In contrast, the COSY spectrum of the acid form of this derivative shows indistinguishable differences in the interactions of these protons with nearby protons. Therefore, both of these protons are labeled **k** for clarity. Similar to CX4-L-Val, cross peaks between the amide proton (**f**) and protons **e** and **g** in CX4-L-Leu were observed. Strong interactions were observed between **g** and protons **i** and **j**. This may be attributed to the linearity of leucine's isobutyl side chain, by which **g** feels the influence of its neighboring protons more, with no interaction between it and a bulky methyl branch, as is the case with the *sec*-butyl side chain of isoleucine. As expected, there were cross peaks between **i** and **j**, **i** and **k**, and **j** and **k**, indicating strong coupling between these protons. Extraneous cross peaks observed in the ^{1}H NMR spectra may be due to the existence of other conformers of calixarene derivatives. Studies are underway to determine their origin and identity.

Peaks representing the terminal methyl protons (**i**, **l**) of the *sec*-butyl side chain of isoleucine were resolved as a doublet (**i**) and a triplet (**l**) in the ^{1}H NMR spectrum of CX4-L-Ile*t*-butyl ester (summarized in Table 5). However, they were poorly resolved in the ^{1}H NMR spectrum of the acid (Figure 7). In addition to the cross peaks observed for the calixaryl tetraacid (**3**), a cross peak between the amide proton (**f**) and the methine (**g**) proton of the alpha carbon was observed. Also, cross peaks indicating ^{4}J coupling of **f** to **e** and ^{3}J coupling of **g** to **j** were observed. Couplings between **j** and protons **i**, **k**, and **l** were indicated by strong cross peaks observed in the aliphatic region of the spectrum (0.l8–2.0 ppm).

Conclusions

In line with NSF's initiative to include international dimensions in undergraduate programs, MSU-WP is committed to strengthening the ongoing collaboration with African scientists and educators [46, 47]. Since the thalidomide case of the 1960s in the US [48–50], it has been well established that one enantiomer of a racemic mixture may be

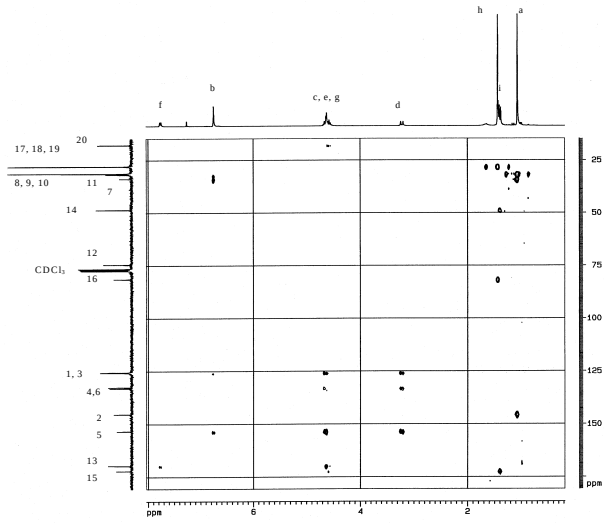


Figure 5. HMBC spectrum of CX4-L-ALA *t*-butyl ester.

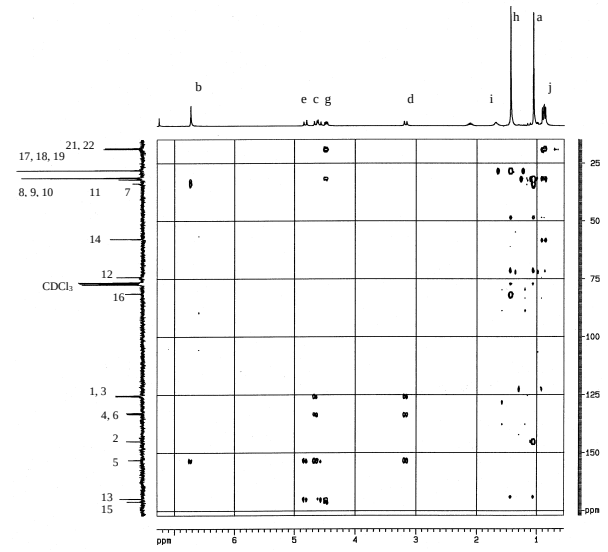


Figure 6. HMBC spectrum of CX4-L-VAL *t*-butyl ester.

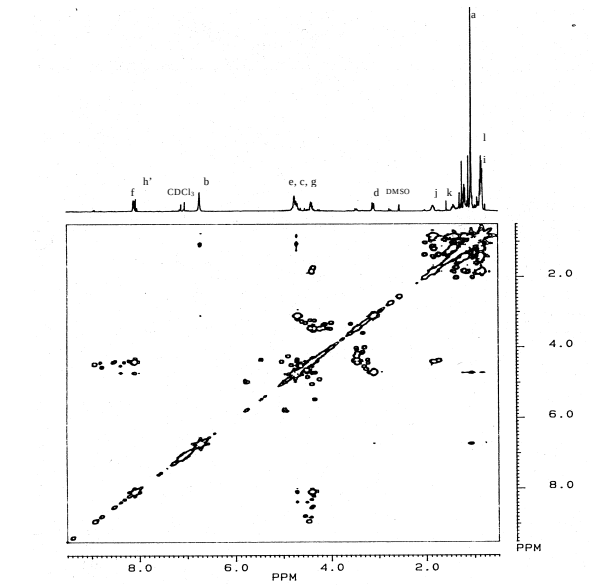


Figure 7. COSY spectrum of CX4-LILE.

beneficial while the other form may be toxic or useless. This tragedy heightened interest in stereochemistry that pervades most branches in chemistry, biochemistry, agriculture, and pharmacology. Therefore suitable methods for ascertaining enantiomeric purity must be developed. Our collaborative Kenya-U.S. educational research project involving the synthesis and characterization of amino acid-based calixarenes and cyclodextrins (CDs) will ultimately promote multicultural STEM workforce.

In conclusion, we have synthesized and characterized *Tert*-butyl esters of (*N*-L-alaninoacyl)calixarene, (*N*-L-valinoacyl)-calixarene, (*N*-L-leucinoacyl)calixarene, (*N*-L-isoleucinoacyl)calixarene, and their corresponding acids. The undergraduate students were the integral part of the collaborative US-Africa guided inquiry synthesis of calixarenes. The participating institutions in the US-Africa consortium include: Kabianga University, Kapkatet University, Kenyatta University, Egerton University, the University of Nairobi, Catholic University of East Africa, Moi University, Kenya Medical Research Institute, Pyrethrum Board of Kenya, St. Patrick's High School Iten, Kapsogut Boys High School, Kericho Teachers College, and Baringo Teachers College. The chiroscience project serves as a cross cultural conduit for spreading the joys of science [9, 51–55]. It was not surprising that the there were several Aha! moments in various research groups. The project was very successful because students were able to do reproduce literature procedures; this made them prepared for graduate school and beyond. Indeed, the NMR spectra of the synthesized calixarenes were in perfect agreement with those reported in the literature. The typical signatures of the splitting patterns of methylene bridge protons and the presence or absence of *t*-butyl singlets were observed. We are currently investigating the effectiveness of our calixarenes as chiral selectors in HPLC and capillary electrophoretic separations of enantiomeric mixtures of EPA's high priority pollutants in Africa [55] and North America [17, 56–58].

Acknowledgments. The senior author (J.K.R.) gratefully acknowledges the National Science Foundation for the CCLI grant (Award # 0837133) and also to Kabianga University for offering him the summer 2012 Visiting Professorship in the School of Science & Technology.

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