Unusual Calixarenes Incorporating Chromene and Benzofuran Moieties Obtained via Propargyl Claisen Rearrangement

Annunziata Soriente,* Mariantonieta D’Acunto, Carmen Talotta, Carmine Gaeta, Paolo Della Sala, Margherita De Rosa, Silvano Geremia, Neal Hickey, Antonio Rescifina,* and Placido Neri*

Cite This: Org. Lett. 2021, 23, 9283−9287

ABSTRACT: Monopropargyloxy-tripropoxy-calix[4]arene 1 was subjected to a propargyl Claisen rearrangement to give unusual calix[3]arene[1]chromene and homocalix[3]arene[1]benzofuran macrocycles. Quantum mechanical density functional theory calculations indicated that an initial [3,3] sigmatropic reaction affords a highly reactive allene intermediate, stabilized by two main diradical pathways leading to six- and five-membered oxygenated rings. In the presence of a n-butylammonium guest, calix[3]arene[1]chromane 6 forms two stereoisomeric complexes stabilized by +N−H···O and cation···π interactions.

A wide variety of calixarene-based supramolecular hosts continue to be obtained even today by innovative chemical modifications of the parent macrocycles.1 In this way, surprising supramolecular properties are continually discovered for appropriately modified calixarene derivatives.1 The most common modification sites are at the lower and upper rims2a (OH groups and para positions,2a respectively),1 as well as the meta positions2b and the methylene bridges3 of the calixarene skeleton. One of the earliest approaches to modifying the calixarene upper rim was the “Claisen rearrangement route” devised by Gutsche,4 in which allyl groups at the lower rim (i.e., allyl ethers) are transferred at the upper rim by thermal rearrangement. An exciting extension of this route could be obtained by using propargyl groups in place of the allyl ones.5 It is well documented7 that six- and five-membered oxygenated rings are obtained in the propargyl Claisen rearrangements when the ortho positions are free. Calix[4]arene derivatives show a peculiar three-dimensional bowl-shaped structure in which the ortho positions are occupied by methylene-bridging groups. Consequently, propargyl Claisen rearrangements starting by calix[4]arene derivatives could give very interesting derivatives with structures that are challenging to predict.

Intrigued by these considerations, we decided to investigate this propargyl Claisen reaction using the monopropargyl ether of tripropylated p-H-calix[4]arene 1 (Supporting Information and Scheme 1) as an appropriate model compound. Thus, 1 was subjected to heating in refluxing diethylaniline (215 °C) for 2 h. Chromatography of the crude product allowed the isolation of 2−4 in 48%, 15%, and 10% yields, respectively (Scheme 1).

Received: October 27, 2021
Published: November 15, 2021
The absence of the typical alkyne methine signal in the $^1$H NMR spectrum of each isolated compound (Supporting Information) was clear evidence that the postulated double sigmatropic migration at the para position did not occur, while the presence of oxygenated rings was at first glance confirmed by signals in the range of 4–6 ppm. One-dimensional (1D) and two-dimensional (2D) NMR data and MS analysis (Supporting Information) agree with the calix[3]arene[1]-chromene structure of 2 in Scheme 1. In particular, 2 showed an entire spin system (Figure 1a) at 4.85 ppm (2H, red signal), 5.81 ppm (1H, blue signal), and 6.50 ppm (1H, green signal) (Supporting Information) and by signals in the range of 3.98 ppm (1H, yellow signal) to each other. Another relevant feature of the $^1$H NMR spectrum of each isolated compound (Supporting Information) is the loss of the symmetry element present in the starting 1, which led to triplicate sets of signals (often accidentally isochronous) corresponding to three non-equivalent (PrO)ArCH$_2$ moieties of 2. It was clear that the propargylated aromatic ring of 1 was rearranged to a chromene moiety by a sigmatropic reaction, which also involved the migration of the adjacent ArCH$_2$ linkage to the original para position. The bridging ArCH$_2$Ar protons of 2 give rise to four AX systems with a $\Delta\delta$ of 0.5–1.1 ppm typical of a cone conformation, indicating that this shape was maintained during the transposition mentioned above.

The $^1$H NMR spectrum of 3 clearly indicated its stereoisomeric nature with respect to 2. In fact, the chromene ring was confirmed by a spin system (Figure 1b) at 4.82 ppm (2H, red signal), 5.77 ppm (1H, blue signal), and 6.42 ppm (1H, green signal) and by two meta-coupled ArH features at 6.13 and 6.69 ppm (Figure 1b).

The most evident difference was a more pronounced differentiation in the chemical shifts of the triplate sets of signals corresponding to the three non-equivalent (OPr)-ArCH$_2$ moieties. This, for example, led the three CH$_3$ signals of OPr$_3$ groups to resonate at 0.49, 0.67, and 0.93 ppm, indicating a strong shielding by aromatic moieties for two of them. Also, a clear diagnostic difference was also detected in the COSY and HSQC spectra of 3. The bridging ArCH$_2$Ar groups of 3 give rise to an AX system at 3.28/4.38 ppm ($\Delta\delta$ = 1.1) that correlates in the HSQC spectrum with a carbon resonance at 30.5 ppm, attributable to a methylene group between syn-oriented aromatic rings. An AB system at 3.92/3.98 ppm ($\Delta\delta$ = 0.06) was detected in the COSY spectrum of 3 that correlates with a methylene carbon at 38.3 ppm between anti-oriented rings, and an AB system at 3.36/3.85 ppm ($\Delta\delta$ = 0.49) that shows a $^3$J with a $^{13}$C signal at 34.7 ppm attributable to a ArCH$_2$Ar group between anti-oriented rings. Finally, an AB system at 3.72/3.81 ppm ($\Delta\delta$ = 0.09) was present that correlates in the HSQC at 28.3 ppm, clearly indicative of a syn relationship between the pertinent rings.

In conclusion, the presence of two anti-oriented and two syn-oriented ArCH$_2$Ar groups is compatible with a calix[4]arene backbone of 3 in a 1,2-alternate conformation (Scheme 1). DFT-optimized structures at the B3LYP/6-31G(d,p) level of theory show an energy difference of 1.02 kcal/mol between cone 2 and 1,2-alternate 3 conformers (Supporting Information). In addition, the DFT-optimized structure of 2 exhibits the chromene ring in the outward orientation almost coplanar with the mean plane of methylene bridges.

Calixchromenes 2 and 3 easily undergo degradation due to the presence of the unsaturated chromene ring. Therefore, we decided to prepare more stable analogues by hydrogenating the double bond (Scheme 1). Thus, the treatment of 2 and 3 with H$_2$ and Pd/C easily afforded the corresponding chromane derivatives 5 and 6 in good yields (Scheme 1; see the Supporting Information). In the solid state, 6 adopts a 1,2-alternate conformation (Figure 2), in which the chromane moiety (A) and an adjacent Ar-OPr ring (B) show an inverted conformation with respect to the other two (C and D) Ar-OPr rings (Figure 2).

The overall conformation of the calixarene can be described by the four dihedral angles between the mean plane of each Ar ring and the mean plane defined by the methylene-bridging groups. The mean planes of the phenyl rings of chromane and its aromatic facing group (A and C) make large outward dihedral angles (161° and −140°, respectively) (Figure 2). Aryl ring B is inclined outward (dihedral angle of 111°), while aryl ring D is inclined slightly inward (dihedral angle of −84°).

The presence of an H atom at the endo position of the chromane moiety allows this very large dihedral angle of 161°, suggesting the possibility of facile inversion of its conformation, from positive to negative angles, and therefore between the 1,2-alternate and partial-cone conformation of the calixarene.

With regard to derivative 4 (Scheme 1), its $^1$H NMR spectrum (Figure 1c) evidenced a different signal pattern with respect to the $^1$H NMR spectra of 2 and 3 (Figure 1a,b). In fact, the chromene signals were absent, while four resonances (1H each) appeared in the range of 2.5–3.5 ppm, pointing to the presence of an ethylene -CH$_2$CH$_2$- bridge moiety. In addition, an aromatic signal was seen at 6.51 ppm (1H, magenta signal), suggesting the formation of a fused furan ring (Figure 1c). The combined use of 2D COSY and HSQC spectra (Supporting Information) allowed joining of the two...
Figure 3. Proposed mechanism of the Claisen rearrangement performed on propargyloxy-tripropoxy-calix[4]arene 1 and its reaction coordinate diagram.

moieties leading to structure 4 in which a benzo[6]furans system is linked to an Ar(OPr) unit through a -CH2CH2- bridge. In detail, three AX systems with a $\Delta G$ of 1.0–1.2 ppm for the bridging ArCH2Ar protons of 4 confirmed the presence of an unaltered cone portion for the remaining three Ar(OPr) units. All of the remaining NMR ($^{13}$C and HSQC) and MS data were in full agreement with the homocalix[3]arene[1]benzofuran structure of 4.9

To understand how the rearranged structures of 2–4 can be formed from 1, we decided to perform a QM DFT study (Figure 3 and Supporting Information) using the Gaussian-16 suite of programs. In the literature, it is proposed that an aryl propargyl Claisen rearrangement usually proceeds through a first [3,3] sigmatropic migration, which leads to an allene intermediate.9 Due to the entity of the system (C40H44O4), all calculated energies involved are reassumed in Table S2 and pictorially shown in Figure 3. The first step is the classic concerted [3,3] Claisen rearrangement, which is even more demanding in terms of Gibbs free energy of activation [32.86 kcal/mol (Table S2, entry 2)]. The successive concerted [3,3] or 1,3 sigmatropic rearrangements to the $\Delta G$ of 34.24 or 64.49 kcal/mol, respectively; on the contrary, the homolytic cleavage of the $\sigma$-benzyl benzylic bond results in a $\Delta G$ of 23.66 kcal/mol (Table S1, entry 4). We were not able to find a concerted diradical TS for the Int1 to Int3b path. This is in accord with a stepwise radical mechanism and the formation of compound 4, which cannot take place through a concerted reaction mechanism. The analysis of Table S2 and Figure 3 shows that the reaction begins with a typical Claisen rearrangement and continues through a radical mechanism that governs the ratio of the product through transition states TS3a and TS3b passing from intermediates Int2a and Int2b, in the triplet state, that are in equilibrium with each other. The optimization of Int2a and Int2b as singlet states was unfruitful. Finally, the inversion of the steps from Int2a to 4 gives an activation energy of 22.66 kcal/mol for the first TS, ruling out this pathway.

At this point, we decided to perform preliminary tests to study the complexation properties of calixchromane 6. The addition of n-butylammonium guest (as barfate salt) to a CD2Cl2 solution of 6 (in equimolar ratio) clearly evidenced significant changes in its $^1$H NMR spectrum at 298 K (Supporting Information) indicative of the formation of complexes.12 1D and 2D NMR analysis of this mixture evidenced the presence of two complexes in a 60/40 ratio (Supporting Information). In detail, three methylene-bridged AX systems and one AB system were present at 3.53/4.63, 3.24/3.43, 3.21/4.25, and 3.56/3.70 ppm that represent the most abundant complex. In addition, AX/AB systems were present at 3.40/4.14, 3.18/4.02, 3.15/3.98, and 3.33/3.75 ppm attributable to the less abundant complex (Supporting Information). Accordingly with the 1,2-alternate structure of 6 (Figure 2), the cationic guest could be nested on one side of macrocycle 6 between the pair of syn-oriented propoxy chains with $\Delta G$ of 32.86 kcal/mol (Figure 4a), as well as on the opposite side between the syn-oriented aromatic rings with $\Delta G$ of 32.86 kcal/mol (Figure 4d). DFT calculations at the B3LYP/6-31G(d,p) level of theory indicated that the syn-OPr stereoisomer [syn-Ar (Figure 4a)] is more stable than the syn-Ar one by 0.18 kcal/mol. Consequently, a Boltzmann
population at 298 K was calculated to be 58% and 42% for the syn-OPr and syn-Ar complexes, respectively. The DFT-optimized structure of the most stable syn-OPr complex (Figure 4a) shows two N−H···O H-bonds with a mean distance of 2.82 Å and a mean N−H···O angle of 160° (Figure 4b); in addition, a cation···π interaction (Figure 4c) was detected between the ammonium group of the guest and an aromatic ring of the host with a N···π centroid distance of 3.37 Å.

On the contrary, the DFT-optimized structure of the syn-Ar complex in Figure 4d showed a single H-bonding interaction between the ammonium guest and calix-chromane host 6 (Figure 4d) with a N−H···O distance of 2.83 Å and a mean N−H···O angle of 158°. Finally, three cation···π interactions12 (Figure 4e) were detected between the ammonium group of the guest and the aromatic rings of the host with a N···π centroid distance of 3.46 Å.

In conclusion, we have described an example of thermal propargyl Claisen rearrangement starting with monopropargyl-calixarene 1. The reaction affords unusual calix[3]arene[1]-chromene and homocalix[3]arene[1]benzofuran macrocycles due to the molecular rearrangements involving the skeletal ArCH2 moiety in addition to the propargyl group. QM DFT calculations indicated that an initial [3,3] sigmatropic reaction affords a highly reactive allenic intermediate, which is then stabilized by two main diradical stepwise pathways leading to six- and five-membered oxygenated rings. In the presence of a n-butylammonium guest, calix[3]arene[1]chromene 6 forms two stereoisomeric complexes stabilized by N−H···O H-bonding and cation···π interactions. The calix[3]arene[1]-chromene and homocalix[3]arene[1]benzofuran macrocycles described here could pave the way for the synthesis of novel hosts with interesting supramolecular properties.

■ ASSOCIATED CONTENT

* Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03643. Detailed synthetic procedures, 1D and 2D NMR spectra, complexation studies, details of DFT calculations, Cartesian coordinates, X-ray data, and tables of crystal data (PDF)

Accession Codes

CCDC 1979551 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Annunziata Soriente — Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, I-84084 Fisciano, Salerno, Italy; orcid.org/0000-0001-6937-5405; Email: titti@unisa.it

Antonio Rescifina — Dipartimento di Scienze del Farmaco e della Salute, Università di Catania, I-95125 Catania, Italy; orcid.org/0000-0001-5039-2151; Email: arescifina@unic.it

Placido Neri — Dipartimento di Chimica e Biologia "A. Zambelli”, Università di Salerno, I-84084 Fisciano, Salerno, Italy; Email: neri@unisa.it

Authors

Mariantonietta D’Acunto — Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, I-84084 Fisciano, Salerno, Italy

Carmen Talotta — Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, I-84084 Fisciano, Salerno, Italy; orcid.org/0000-0002-2142-6305

Carmine Gaeta — Dipartimento di Chimica e Biologia "A. Zambelli”, Università di Salerno, I-84084 Fisciano, Salerno, Italy; orcid.org/0000-0002-1660-3977

Paolo Della Sala — Dipartimento di Chimica e Biologia "A. Zambelli”, Università di Salerno, I-84084 Fisciano, Salerno, Italy; orcid.org/0000-0002-6379-0332

Margherita De Rosa — Dipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, I-84084 Fisciano, Salerno, Italy; orcid.org/0000-0001-7451-5523

Silvano Geremia — Centro di Eccellenza in Bio cristallografia, Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, I-34127 Trieste, Italy; orcid.org/0000-0002-0711-5113

Neil Hickey — Centro di Eccellenza in Bio cristallografia, Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, I-34127 Trieste, Italy; orcid.org/0000-0003-1271-5719

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c03643

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Neri, P.; Sessler, J. L.; Wang, M.-X. Calixarenes and Beyond, 1st ed.: Springer International Publishing: Cham, Switzerland, 2016.

(2) (a) Troisi, F.; Pierro, T.; Gaeta, C.; Neri, P. The p-Bromodienone Route to Nucleophilic Functionalization of Calixarene Eox RIm. Org. Lett. 2009, 11, 697–700. (b) De Rosa, M.; Soriente, A.; Concilio, G.; Talotta, C.; Gaeta, C.; Neri, P. Nucleophilic Functionalization of the Calix[6]arene Para- and Meta-Position via p-Bromodienone Route. J. Org. Chem. 2015, 80, 7295–7300.
(3) Shalev, O.; Biali, S. E. The Lithiation/Oxygenation Approach to Calix[6]arenes Selectively Functionalized at a Pair of Opposite Methylene Bridges. *Org. Lett.* 2018, 20, 2324−2327.

(4) (a) Gutsche, C. D.; Levine, J. A. Calixarenes. 6. Synthesis of a functionalizable calix[4]arene in a conformationally rigid cone conformation. *J. Am. Chem. Soc.* 1982, 104, 2652−2653. (b) Gutsche, C. D.; Levine, J. A.; Sujeeth, P. K. Calixarenes. 17. Functionalized Calixarenes - the Claisen Rearrangement Route. *J. Org. Chem.* 1985, 50, 5802−5806.

(5) (a) Anderson, W. K.; LaVoie, E. J.; Whitkop, P. G. Steric and electronic factors which effect the thermal cyclization of metasubstituted aryl propargyl ethers. Synthesis of 5- and 7-substituted 3-chromenes. *J. Org. Chem.* 1974, 39, 881−884. (b) Harfenist, M.; Thom, E. The Influence of Structure on the Rate of Thermal Rearrangement of Aryl Propargyl Ethers to the Chromenes. The gem-Dimethyl Effect. *J. Org. Chem.* 1972, 37, 841−848. (c) Anderson, W. K.; LaVoie, E. J. Thermal Cyclization of Substituted Aryl Propargyl Ethers. The Scope and Regioselectivity of the Reaction in the Synthesis of Substituted 3-Chromenes. *J. Org. Chem.* 1973, 38, 3832−3835.

(6) Bifulco, G.; Riccio, R.; Gaeta, C.; Neri, P. Quantum mechanical calculations of conformationally relevant H-1 and C-13 NMR chemical shifts of N-, O-, and S-substituted calixarene systems. *Chem. - Eur. J.* 2007, 13, 7185−7194.

(7) Jaime, C.; De Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. Carbon-13 NMR chemical shifts. A single rule to determine the conformation of calix[4]arenes. *J. Org. Chem.* 1991, 56, 3372−3376.

(8) The dihedral angle between the mean plane of a phenyl ring and the mean plane defined by the methylene-bridging groups ranges from 180° to −180°. An absolute value of greater (less) than 90° indicates an outward (inward) orientation of the phenyl ring with respect to the center of the calixarene. A negative sign indicates the inversion of the conformation with respect to the chromane moiety taken as a reference.

(9) (a) Roa, U.; Balasubramanian, K. K. Claisen rearrangement of aryl propargyl ethers in poly(ethylene glycol)- a remarkable substituent and solvent effect. *Tetrahedron Lett.* 1983, 24, 5023−5024. (b) Srinivasadesikan, V.; Dai, J. F.; Lee, S. L. Quantum mechanistic insights on aryl propargyl ether Claisen rearrangement. *Org. Biomol. Chem.* 2014, 12, 4163−4171.

(10) Majetich, G.; Hicks, R. Applications of microwave accelerated organic chemistry. *Res. Chem. Intermed.* 1994, 20, 61−77.

(11) Beno, B. R.; Wilsey, S.; Houk, K. N. The C7H10 potential energy landscape: Concerted transition states and diradical intermediates for the retro-Diels-Alder reaction and [1,3] sigmatropic shifts of norbornene. *J. Am. Chem. Soc.* 1999, 121, 4816−4826.

(12) Talotta, C.; Gaeta, C.; Neri, P. Ende-Complexation of Alkylammonium Ions by Calix[4]arene Cavity: Facilitating Cation−π Interactions through the Weakly Coordinating Anion Approach. *J. Org. Chem.* 2014, 79, 9842−9846.