Calix[4]azulene

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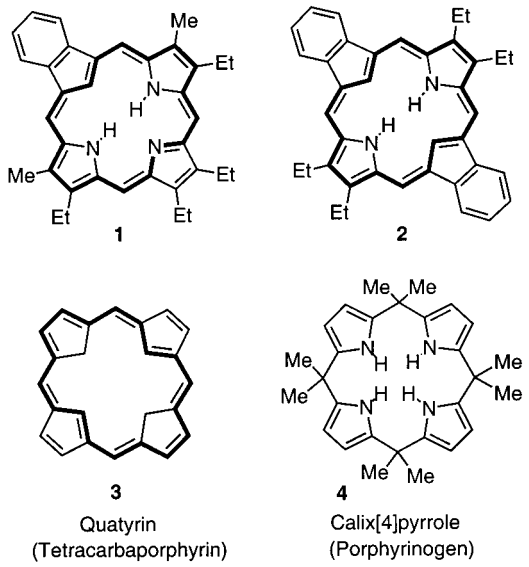
Abstract: Azulene reacts with paraformaldehyde in the presence of florisil to give excellent yields of calix[4]azulene.

Porphyrins represent a class of aromatic heterocycles that can be considered to be Nature's bridged [18]annulenes.[1−3] Porphyrin analogues with furan, thiophene, or related subunits in place of the usual pyrrole rings have been known for many years,[4] but only recently have aromatic systems of this type with carbocyclic rings been discovered.[1,5,6] For instance, carbaporphyrins, such as the indene derivative **1** (Chart 1), have been shown to retain porphyrin-like characteristics and demonstrate substantial diamagnetic ring currents in their proton NMR spectra.[6,7] The synthesis of a dicarbaporphyrin **2** has also been reported, and this system also shows aromatic characteristics by proton NMR and UV-vis spectroscopy.[8,9] Related systems incorporating benzene,[5] cycloheptatriene,[10] and azulene rings,[11] as well as dihydrocarbaporphyrins (carbachlorins),[12] have also been noted. These exciting new systems represent a conceptual bridge[1,2] between porphyrins and Sondheimer's [18]-annulene.[13] The tetracarbaporphyrin system **3** (quatyrin)[2] would be the ultimate link between these classes of aromatic compounds and therefore has great theoretical significance. Indeed quatyrin has been termed the "Holy Grail" in porphyrin analogue chemistry.[8]

The synthesis of porphyrins and related analogues generally depends on the regioselective reactivity of pyrrole toward electrophilic substitution at the α positions,[2] but clearly this consideration is not helpful in contemplating the synthesis of **3**. Calixarenes share many structural similarities to porphyrins in that the aromatic subunits (most commonly phenols) are generally linked by single carbon bridges. Calixarenes have become one of the best studied classes of macrocycles[14] for molecular recognition and binding studies.[15] Recently, hexahydroporphyrins known as porphyrinogens or calix[4]pyrroles (e.g., **4**) have been shown to have many valuable properties as well, including selective anion binding interactions.[16] The resurgence of interest in calixpyrroles, together with our interests in the synthesis of the quatyrin macrocycle, led us to investigate the construction of calixarenes derived from azulene. Azulene favors electrophilic substitution at the 1,3-positions[17] and therefore potentially has the necessary chemical properties to allow the construction of macrocyclic systems.

Chart 1



It was anticipated that azulene would react with formaldehyde in the presence of an acid catalyst to give calixazulenes such as **5** and **6** (Scheme 1). Calixazulene possesses the same carbon skeleton as quatyrin (**3**), although the conversion of **5** into conjugated macrocycles related to **3** would be far from straightforward. In initial experiments, dimethoxymethane was used as a formaldehyde equivalent, and reactions with azulene using a variety of acid catalysts were explored. Extensive polymerization was noted, although in some of the reactions, cyclic oligomers were detected. Reactions using ethanol as a solvent with acid catalysts such as HCl gave no cyclic products, but HBr or HI in acetic acid often afforded low

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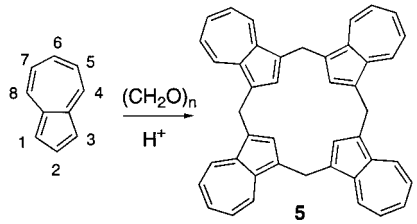
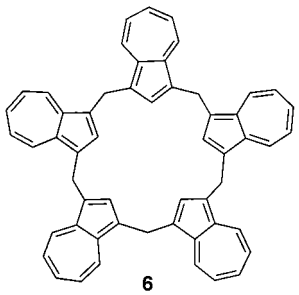
Scheme 1



5
Calix[4]azulene



6
Calix[5]azulene

yields of calixazulenes **5** and **6**. This chemistry was found to be concentration dependent, although high dilutions were not helpful. Using 25 mg of azulene in 100 mL of acetic acid with HBr or HI as the catalyst gave no cyclic products, but in 25 mL of this solvent low yields of **5** and **6** were obtained. These conditions, particularly using HBr as a catalyst at room temperature for 45 min, gave the best yields of calix[5]azulene **6** although <1% of this product could be isolated following purification on Grade II alumina eluting with 75% toluene−hexanes. The proton NMR spectra (e.g., Figure 1A) were helpful in determining the relative proportions of the two major calixazulene products. The tetramer gave a doublet at 8.30 ppm while the pentamer afforded an equivalent resonance slightly upfield at 8.24 ppm. The internal CH gave a singlet at 7.10 ppm for **5** and 7.16 ppm for **6**, while the bridging methylenes appeared at 4.74 and 4.68 ppm, respectively. More concentrated conditions did not give any improvement in the yields. However, when 25 mg of azulene was reacted with dimethoxymethane in 2.5 mL of acetic acid with one drop of HI as the catalyst, 1,3-dimethylazulene was isolated (identified by ^{1}H NMR and EI MS) in low yields. This result indicates that dimethoxymethane can act as a methyl transfer agent in electrophilic substitution chemistry and may therefore interfere with this chemistry. Paraformaldehyde was used as an alternative source of CH_2O in subsequent studies. Slightly improved yields were noted with paraformaldehyde, although the tetramer **5** was always the predominant product. Some improvement in the results was obtained when no strong acid catalyst was used. The best conditions for this solution phase chemistry were obtained when 25 mg of azulene was heated under reflux with $(CH_2O)_n$ (24 mg) in AcOH (25 mL) on a preheated oil bath for 3 min, followed by immediate extraction. Nonetheless, <5% calixazulene products were obtained and difficulties in isolating pure product fractions by column chromatography were encountered. In addition, attempts to produce calixazulenes using acetone as a linking moiety were completely unsuccessful under any of the conditions investigated.

At this stage in the work, we considered the possibility of using solid-phase catalysts for this chemistry as this approach can lead to a higher degree of selectivity. In particular, K10 Montmorillonite clay has been shown be an efficient catalyst in the preparation of dipyrrylmethanes[18] and has also been utilized in the synthesis of tetraarylporphyrins.[19,20] However, reactions between azulene and $(CH_2O)_n$ in the presence of this reagent gave only trace amounts of macrocyclic products. Florisil was also considered as a potential catalyst and surprisingly this produced spectacular results. Reaction of azulene and paraformaldehyde in dichloromethane at room temperature in the presence of Florisil afforded calix[4]-azulene in >70% yield. The product was obtained in pure form as a deep bluish-green colored solid by simply filtering off the catalyst and evaporating the solvent to dryness on a rotary evaporator. Calix[5]azulene was not observed and any open-chain oligomers were apparently retained by the Florisil. The high symmetry of this macrocycle was confirmed by proton NMR (Figure 1B)

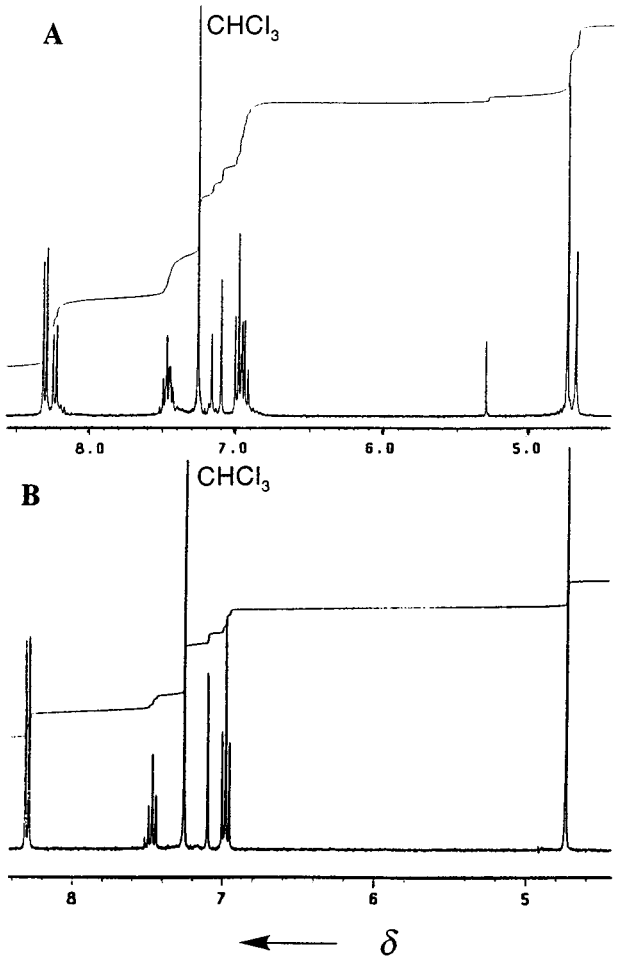


Figure 1. A. 400 MHz proton NMR spectrum of a column fraction from a typical reaction of azulene with paraformaldehyde in refluxing acetic acid showing the presence of calix[4]azulene (major) and calix[5]azulene (minor) products. B. 400 MHz proton NMR spectrum of pure calix[4]azulene (**5**) in $CDCl_3$.

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and carbon-13 NMR spectroscopy, and the structure was further supported by high-resolution mass spectrometry and combustion analysis.

The origin of Florisil's remarkable specificity in this chemistry is not understood, but these conditions provide an extraordinarily convenient method for producing this new calixarene system. Unfortunately, the chemistry fails with other carbonyl compounds. Attempts to react azulene with acetone, hexachloroacetone, 1,3-dichloroacetone, cyclopentanone, or propionaldehyde in the presence of Florisil failed to give any calixazulene products.

The development of a high-yielding route to calix[4]-azulene will make this system readily available for future studies. This novel calixarene is a potentially valuable platform for constructing highly ordered cavities for molecular recognition studies. The ring system also contains the carbon skeleton found in quatyrin, the hypothetical hydrocarbon analogue of the porphyrins, and it may be possible to prepare novel conjugated systems from this precursor.[21]

Experimental Section

Azulene was prepared by a modification of the procedure described by Hafner and Meinhardt,[22] substituting pyrrolidine for dimethylamine in the first step. Florisil (100−200 mesh) was purchased from Aldrich Chemical Co. Mass spectral determinations were made at the Mass Spectral Laboratory, School of Chemical Sciences, University of Illinois at Urbana-Champaign, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029). Elemental analyses were obtained from the School of Chemical Sciences Microanalysis Laboratory at the University of Illinois.

Calix[4]azulene (**5**): A solution of azulene (0.500 g) and paraformaldehyde (0.480 g) in dichloromethane (100 mL) was vigorously stirred with Florisil (20.0 g) for 90 min at room temperature. The mixture was diluted to approximately 1 L with chloroform and suction filtered to remove the Florisil. Evaporation of the solvent under reduced pressure gave the pure calixazulene (0.401 g; 74%) as a bluish-green solid. A sample was recrystallized from benzene−hexanes to give fluffy blue-green crystals, mp 265−268 °C, dec UV/vis ($CHCl_3$): λ_{max} ($\log_{10}$ ϵ) 230 (4.32), 244 (4.31), 292 (3.31), 502 (3.14), 538 nm (3.15); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.74 (8H, s), 6.98 (8H, t, J = 10 Hz), 7.10 (4H, s), 7.47 (4H, t, J = 9.6 Hz), 8.30 (8H, d, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 121.2, 129.1, 133.0, 136.3, 137.6, 139.2; HRMS (EI): calcd for $C_{44}H_{32}$: m/z 560.2504; found: 560.2493. Anal. Calcd for $C_{44}H_{32}$: calcd C, 94.25; H, 5.75. Found C, 94.37; H, 5.69.

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Supporting Information Available: Selected proton and carbon-13 NMR and mass spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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