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Efficient Synthesis of Water-Soluble Calixarenes Using Click Chemistry

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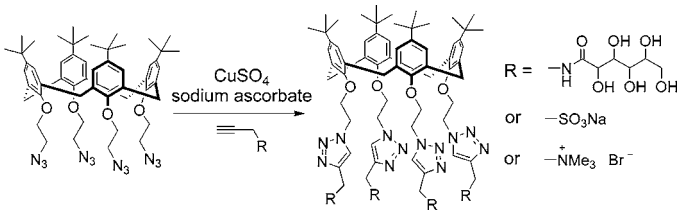
ABSTRACT



Several water-soluble calix[4]arenes were synthesized via Huisgen 1,3-dipolar cycloaddition between azides and alkynes. Cationic, anionic, and nonionic calixarenes were prepared from a common azidocalixarene intermediate. Azidocalixarenes performed better than alkynylcalixarenes as precursors. The aggregation behavior of the water-soluble calixarenes was studied by ^{1}H NMR spectroscopy.

Calixarenes are among the most versatile and useful building blocks in supramolecular chemistry.[1] Water-soluble calixarenes attracted considerable attention very early on because their well-formed hydrophobic cavities make it possible to study molecular recognition in water. Water-soluble groups such as sulfonates,[2] carboxylic acids,[3] amines,[4] and phosphonates[5] have been introduced through various reactions. More recently, calixarenes have become attractive multivalent scaffolds for making amphiphiles useful in both biological[6,7] and chemical applications.[8]

However, synthesis of multivalent water-soluble calixarenes represents a considerable challenge.[9] Certain reaction conditions (e.g., sulfonation) have poor functional group compatibility. If the reaction does not give high conversion, separation of the (highly polar) persubstituted products from incompletely substituted ones is difficult. Because many of the biological and chemical applications mentioned above are influenced by the charge characteristics of water-soluble calixarenes, it is highly desirable to have a modular synthesis that can introduce a variety of water-soluble groups without using protective/deprotective chemistry.

"Click chemistry"[10] seems to be particularly suitable for attaching water-soluble groups. Click reactions are modular, tolerant of a wide range of solvents and functional groups,

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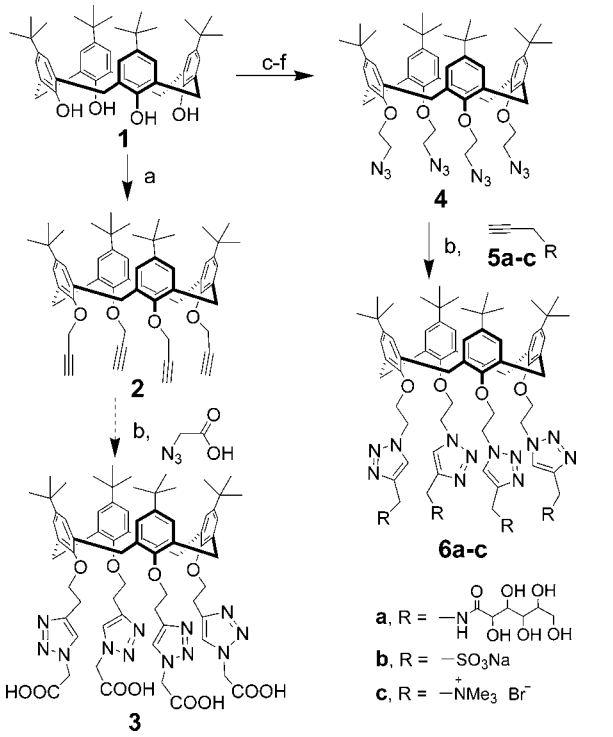
Scheme 1. Preparation of Water-Soluble Calix[4]arenes[a]



[a] Reagents: (a) propargyl bromide, NaH; (b) $CuSO_4$, sodium ascorbate; (c) ethyl bromoacetate, K_2CO_3; (d) $LiAlH_4$; (e) MsCl, Et_3N; (f) NaN_3.

simple to perform, and very high yielding. Click reactions have already been used successfully to prepare enzyme inhibitors in situ,[11] to functionalize surfaces,[12] and to synthesize dendritic polymers.[13] In this communication, we report the preparation of water-soluble calixarenes using the Huisgen 1,3-dipolar cycloaddition of an azide and an alkyne to form a triazole,[14] one of the most efficient click reactions to date.[15]

To attach water-soluble groups via the cycloaddition, we can potentially employ calixarenes functionalized with either alkynes or azido groups (Scheme 1). We first attempted the synthesis of **3** because its precursor **2** could be prepared in one step from commercially available *tert*-butylcalix[4]arene **1**. However, no reaction occurred at room temperature, and complex mixtures formed at 60 °C.[16]

We then explored the second route using azidocalixarene **4** and water-soluble alkynes (**5a**−**c**). Reactions proceeded very smoothly under similar conditions. One distinctive advantage of this route is that the alkyne-coupling side reaction[16] at most would consume some of **5** but otherwise cause no harm to the calixarene precursor **4**. Another advantage is in the preparation of the water-soluble alkynes **5a**−**c**, which could be synthesized from readily available starting materials in high yields and stored in a freezer indefinitely.[17] High stability is particularly important from the standpoint of safety, because potentially explosive, small organic azides have to be used in the other route involving alkynylcalixarenes.[18]

In general, the coupling reaction between **4** and **5** was complete within 24 h at 60 °C in THF/EtOH/H_2O (1/2/2). Calixarene **6a** was purified by simple precipitation into acetone, and **6b**/**6c** was purified by reverse-phase column chromatography with aqueous methanol as the eluent. The isolated yield in general was about 80%. We also performed the reactions using copper(I) iodide as the catalyst in the presence of organic bases such as diisopropylethylamine, but the reactions were not as clean.

The solubility of the resulting calixarene (**6a**−**c**) varied greatly. The nonionic **6a**, to our surprise, was not soluble at all in water.[19] Anionic calixarene **6b** was soluble in water but insoluble in methanol, acetone, acetonitrile, and tetrahydrofuran. Cationic **6c** had solubility properties quite similar to **6b** in most solvents except methanol, in which it was quite soluble.

Calixarenes **6b** and **6c** were soluble in water probably because of micelle formation. To study their aggregation behavior, we recorded their ^{1}H NMR spectra at different concentrations in D_2O. This method requires a minimal amount of material and has been used previously in the characterization of similar water-soluble calixarenes.[20]

When the concentration of anionic **6b** was increased from 0.2 to 5 mM, the chemical shifts of several hydrogens changed significantly. The largest change in the chemical shift was observed for the *endo* methylene bridge ($ArCH_2$-Ar) hydrogens. Significant changes were observed above 1

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(17) Alkyne **5a** was prepared by ring opening of δ-gluconolactone with propargylamine in 97% yield. Alkynes **5b** and **5c** were prepared in 92 and 80% yields by nucleophilic substitution of propargyl bromide by sodium sulfite and trimethylamine, respectively. See Supporting Information for experimental details.

(18) Azidoacetic acid **3** was synthesized by reacting bromoacetic acid with sodium azide in water and was used directly without further purification; see: Dyke, J. M.; Groves, A. P.; Morris, A.; Ogden, J. S.; Dias, A. A.; Oliveira, A. M. S.; Costa, M. L.; Barros, M. T.; Cabral, M. H.; Moutinho, A. M. C. *J. Am. Chem. Soc.* **1997**, *119*, 6883−6887.

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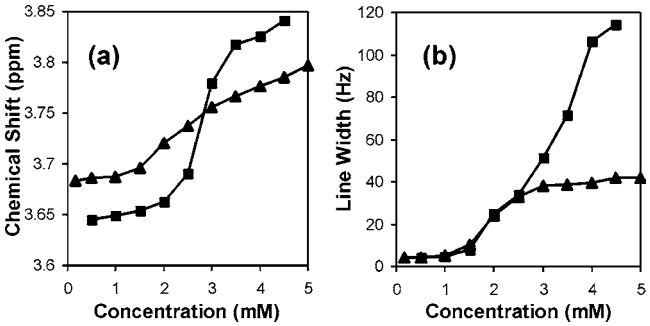

Figure 1. ^{1}H NMR data for **6b** (▲) and **6c** (■) as a function of concentration of the calixarene in D_2O: (a) chemical shift of the *endo* $ArCH_2Ar$ hydrogens and (b) line width of the phenyl hydrogen signal vs concentration.

mM (Figure 1a). The signals also became substantially broader above this concentration. Analysis of the line widths (Figure 1b) gave the same critical micelle concentration (CMC) of 1 mM. The CMC of the cationic calixarene **6c** was also about 1 mM (see Figure 1a and b, data shown in ■). This is not a surprise because, other than carrying opposite charges, the trimethylammonium and sulfonate headgroups are quite similar.

In summary, we have applied click chemistry to the synthesis of water-soluble calixarenes. Because of possible side reactions between the alkynes, couplings between nonpolar azides and water-soluble alkynes gave much better results than those between nonpolar alkynes and water-soluble azides. The highly selective nature of the alkyne−azide cycloaddition should make this click reaction a general method to introduce polar groups without protective/deprotective chemistry.

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Supporting Information Available: Experimental details and NMR spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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