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Graphical Abstract

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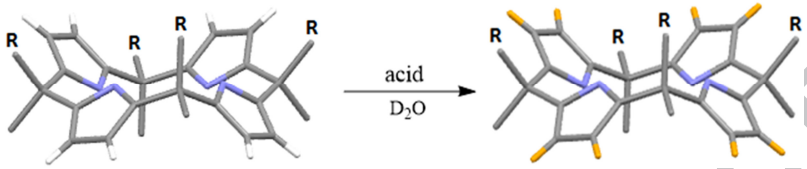

Acid-catalyzed hydrogen-deuterium exchange in β-pyrrolic positions of calix[4]pyrrole at room temperature

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ABSTRACT

Calix[4]pyrrole in D_2O/CH_3CN-$D_2O/CHCl_3$-D_2O using the 98 % sulphuric acid as catalyst was found to high deuterium incorporation and easy-to-make hydrogen-deuterium exchange in β-pyrrolic positions. Compounds **2a**-**d** were obtained by acid-catalyzed hydrogen-deuterium exchange in β-pyrrolic positions of calix[4]pyrroles **1a**-**d**, respectively. Deuterium labelling at the pyrrole-β-position for compounds **1b** and **1c** can be achieved with nearly 100 % incorporation in D_2O-H_2SO_4 and CH_3CN-D_2O-H_2SO_4 systems, and deuterium labelling at the pyrrole-β-position for **1a** and **1d** is more than 90 % in $CHCl_3$-D_2O-H_2SO_4.

1. Introduction

Calix[4]pyrroles are macrocyclic species having an array of four NHs that act as a binding site for anionic and electron-rich neutral guests in organic solvents. In nonpolar organic solvents, the 1,3-alternate conformer is demonstrated to be the most stable for calix[4]pyrrole. Upon the addition of bound neutral substrates, anions, or perturbing substituents to the solution, the calix[4]pyrrole core undergoes a conformational change adopting the cone conformation. In this manner all four pyrrole N–H groups of the calix[4]pyrrole core can participate in hydrogen bonding interactions with the bound guest.[1] In order to qualify the binding affinity and also to develop versatile applications, a large number of the functionalized calix[4]pyrrole derivatives have been designed.[2] Recently, calix[4]pyrroles with potential application as medicaments were reported.[3] In addition, tritiated compounds are of increasing importance for radiolabeling of bioactive compounds in medicinal chemistry applications.[4] Hence, facile, fast, and efficient protocols for the deuteration and tritiation of calix[4]pyrroles are of great value. More recently, as the result of our work with meso-piperidine calix[4]pyrrole,[5] it has occurred to us that the water-soluble calix[4]pyrrole **1b** might serve as such easy-to-make hydrogen-deuterium exchange in β-pyrrolic positions in D_2O at room temperature. Simultaneously, we have found that other calix[4]pyrroles, taking **1a**, **1d** (insoluble in water) and **1c** (slightly soluble in water) as examples, could also make hydrogen-deuterium exchange in β-pyrrolic positions in the appropriate system.

In fact, it was found that pyrrole and N-methylpyrrole could make acid (deuterioacetic acid)-catalysed proton exchange in a dioxan-D_2O solution via the A-S_E2 mechanism in which there is general acid catalysis in 1971 by Gerritt P. Bean.[6] And David M. Muir and co-workers measured the rate of exchange on both the carbon and nitrogen atoms of the pyrrole and indole in the D_2O-acetonitrile-$HClO_4$ system. In contrast to early work by Koizumi and Titan, they found that in mixtures of D_2O and aprotic solvents, N-H exchange was much slower than C-H exchange. [7] Subsequently, a number of tritiated compounds made by the deuteriopyrrole and corresponding material were reported.[8] Interestingly, our preparation method for deuterated calix[4]pyrroles avoided protiodedeuteriation of deuterated pyrrole as starting material in the reaction and purification, and found that 98 % sulphuric acid is a good catalyst of high deuterium incorporation and easy-to-make hydrogen-deuterium exchange. According to the mechanism of the pyrrole, [6] we proposed the mechanism of this reaction (Scheme 1).

Herein, we now report acid-catalyzed hydrogen-deuterium exchange of high deuterium incorporation in β-pyrrolic positions of calix[4]pyrroles **1a**-**d**.

Scheme 2-3 provides a summary of the synthesis of calix[4]pyrrole. Briefly, compounds **1a**-**d** are prepared

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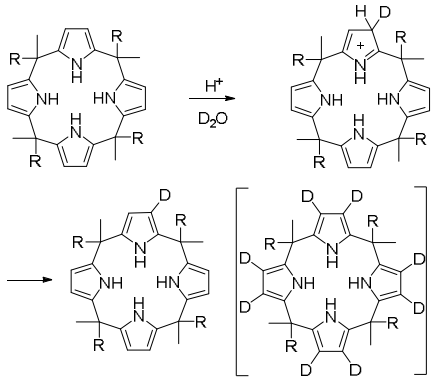
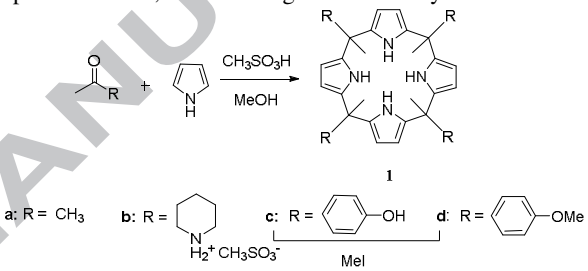


Scheme 1. Proposed mechanism for Hydrogen-Deuterium Exchange in β-pyrrolic positions of calix[4]pyrrole via Lewis acid catalysis.

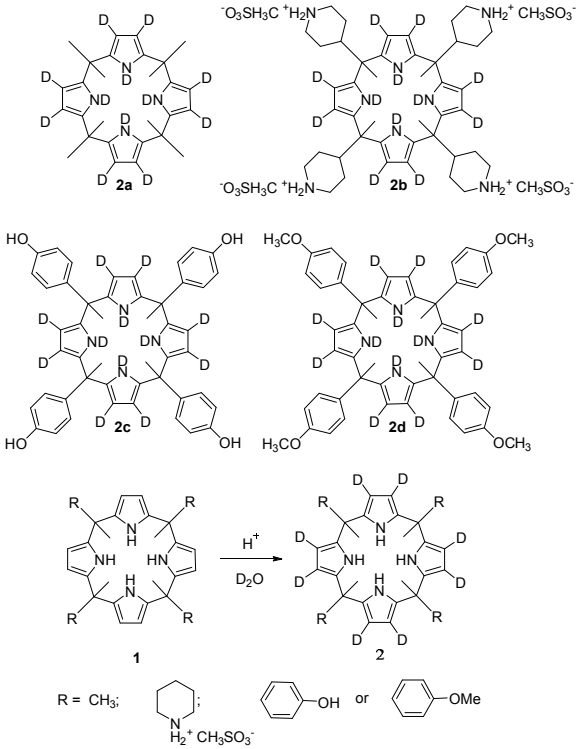
by the corresponding ketone with pyrrole (With condensation reaction of **1b**, Boc is removed simultaneously).[5,9-11] H-D exchange for compounds **1a** and **1d** in $CHCl_3/D_2O$ (10 : 1), compound **1b** in D_2O and compound **1c** in CD_3CN/D_2O (99:1) with 1 % (by D_2O weight) 98 % sulphuric acid, respectively, gave the desired deuterated calix[4]pyrrole **2a**-**d**.

Configurational assignment was performed by a combination of ^1H NMR spectroscopy and single-crystal X-ray crystalographic analysis. The calix[4]pyrroles **1c**-**d** display only one type of β-pyrrole resonance and exhibit, in d_6-DMSO and $CDCl_3$ respectively, a sharp and well-resolved proton spectrum indicative of a time-averaged C4 symmetry, whereas β-pyrrole resonance of the calix[4]pyrrole **1b** displays a doublet. The symmetries of the various isomers were reflected directly in resonances. The αααα isomer has one type of CH group, while the ααββ isomer has two types of pyrrolic CH group.[11] So, we can confirm that calix[4]pyrroles **1c**-**d** are the αααα isomers while calix[4]pyrrole **1b** is the ααββ isomer. The single crystals of **2b** suitable for X-ray diffraction was grown from CH_3CN/D_2O (10/1). The resulting structure revealed that calix[4]pyrrole **2b** adopts the so-called partial cone conformation in the solid state with one $CH_3SO_3^-$ bound to the pyrrolic NH protons. The included $CH_3SO_3^-$ is held within this cleft by a series of N-H•••O hydrogen bonding interactions involving the three N-H groups of the four pyrrole rings (Figure S20), which is consistent with compound **1b**.[5] While the single-crystal X-ray structure of **2c** grown from CH_3CN confirmed that the calixpyrrole core is in a cone conformation, with one solvent molecule included in the aromatic cavity and hydrogen bonded to the four NH groups. The X-ray structure of single crystal obtained by slow evaporation of acetonitrile solutions containing the tetraether **2d** and an excess of N-oxide shows that the receptor adopts a cone conformation with the N-oxide included deep in the cavity (Figure S21 and S22).

The first evidence that acid-catalysed proton exchange occurs on calix[4]pyrrole came from ^1H NMR spectroscopic analyses carried out in D_2O. Compound **1b** displays a doublet peak for the β-CH proton signals at 5.90-5.94 ppm. However, upon the addition of 98 % sulphuric acid, the doublet peak for the β-CH proton signals becomes disappearing after 6 h. When H_2O was added, the doublet peak for the β-CH proton signals appears, which shows the reversibility of proton exchange in the presence of the acid (Figure S18). And the changing of the peak for the β-CH proton signals of compounds **1a**, **1c**-**d** are consistent with **1b** under acid existing. It is worth mentioning that deuterium labelling at the pyrrole-β-position for compounds **1b** and **1c** can be achieved with nearly 100 % incorporation, and deuterium labelling at the pyrrole-β-position for **1a** and **1d** is more than 90 %. Interstingly, early work by Koizumi and Titani showed that N-H exchange was much faster than C-H exchange, but David M. Muir and Mark C. Whiting found that in mixtures of D_2O and aprotic solvents, N-H exchange is sufficiently slow to



Scheme 2. Synthesis of Compounds **1a**-**d.**



Scheme 3. Synthesis of Compounds **2a**-**d**.

be followed using the first overtone of the N-H stretching mode.[7] Now, we unambiguously prove that N-H exchange is much slower than C-H exchange in mixtures of D_2O and aprotic solvents through ^1H NMR spectroscopic analyses with compound **1a** in $CDCl_3$ (Figure 1). Calix[4]pyrrole **1b** was treated with H_2O, and characterized by ^1H NMR spectroscopic analyses, which doesn't show a marked change except for the pyrrole and piperidine NH signals. This suggests that hydrogen-deuterium exchange in β-pyrrolic positions of calix[4]pyrrole is very slow under neutral condition (Figure S19).

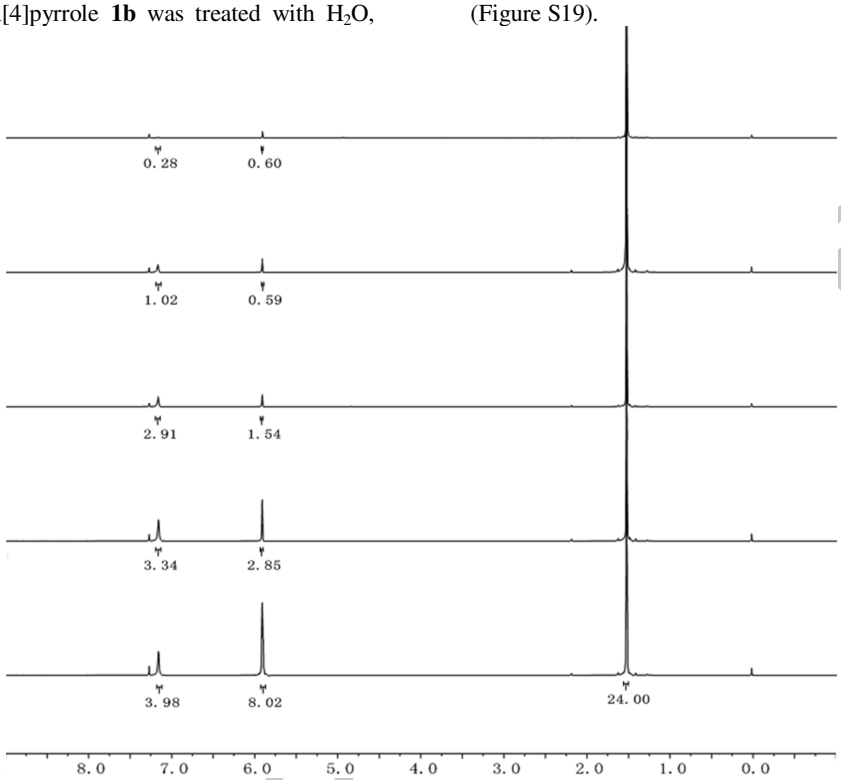


Figure 1. ^1H NMR (600 MHz) spectra of acid-catalyzed hydrogen- deuterium exchange in β-pyrrolic positions of **1a** (1.28 mM) in $CDCl_3$. A) 120 h; B) 72 h; C) 39 h; D) 9 h E) 0 h

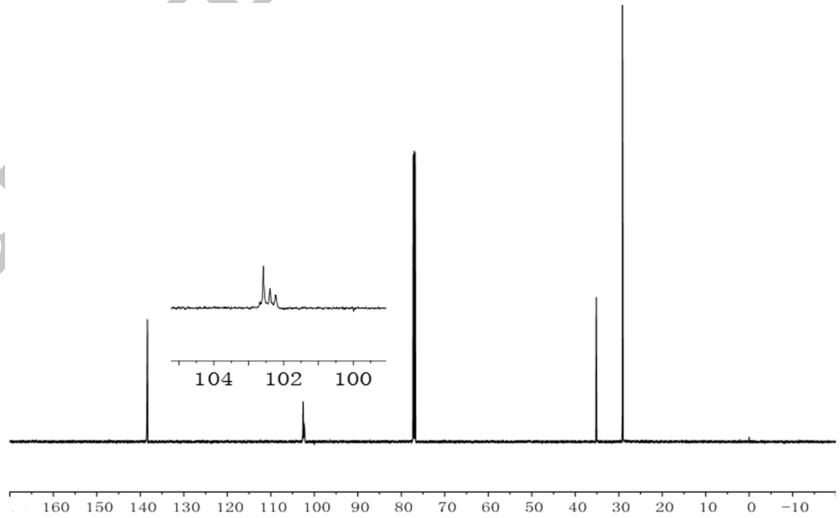


Figure 2. ^{13}C-NMR (150 MHz) spectrum of **2a** recorded in $CDCl_3$.

To gain further understanding of acid-catalysed proton exchange occurs on calix[4]pyrrole, we have measured ^{13}C NMR of **2a**-**d**. Compounds **2a-d** display slipt for the β-C signals at 102.23-102.59 ppm, 103.65-104.10/104.82-105.22 ppm, 104.32-105.00 ppm and 105.91-106.20 ppm, respectively (Figure 2, S7, S12 and S16). That is different from ^{13}C NMR of compounds **2a**-**d**.[5,11-12] Of course, the presence of the D

atom leads to splitting peaks for the β-C signals.

In summary, we have prepared four novel deuterated calix[4]pyrroles **2a-d**, and the structure of compounds **2b-d** unambiguously were characterized by X-ray crystalography. In principal, the present results thus highlight an approach to creat tritiated calix[4]pyrroles and other macrocyclic species with pyrrole, which is important for the synthesis of radiolabeled calix[4]pyrroles for medicinal applications.

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Supplementary data

NMR spectroscopic data and X-ray structural data are available. Single crystal data for compounds **2b** (CCDC 1443139), **2c** (CCDC 1443141) and **2d** (CCDC 1443140) have been deposited in the Cambridge Crystallographic Data Center. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tetlet.2016.03.027.

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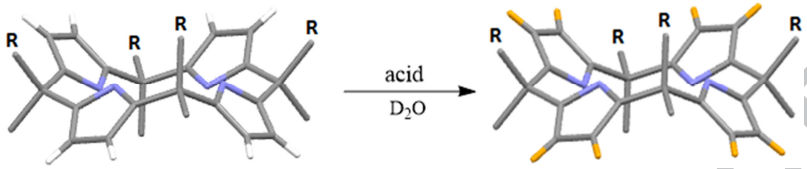

Highlights:

1. Facile, fast, and efficient protocols for the deuteration of calix[4]pyrroles.
2. There are no examples reported the deuteration of calix[4]pyrroles.
3. Highlight an approach to create tritiated macrocyclic species with pyrrole.