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Regio-/stereoselective formation of monosulfoxides from thiacalix[4]arenes in all possible conformations

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ABSTRACT

The partial *S*-oxidation of all four basic conformations of thiacalix[4]arene was carried out using $NaBO_3 \cdot 4H_2O$ as the oxidizing agent. It was found that despite the possible formation of many regio- and stereoisomers, the reactions leading to mono- or disulfoxides were highly regio- and stereoselective depending on the starting conformation. Our results clearly show that the sulfur atoms possessing *syn*-orientation of the appended phenolic units are remarkably more reactive than the sulfur atoms with *anti*-oriented aromatic subunits. Moreover, the most easily formed *syn*-oriented equatorial configuration is highly preferred over the corresponding axial arrangement which was never observed. As demonstrated by the resolution of racemic products, partial *S*-oxidation represents a very interesting tool to access novel inherently chiral building blocks based on thiacalix[4]arenes.

Introduction

For almost two decades thiacalixarenes[1] have attracted considerable attention from the supramolecular community because of their similarity to the much more established calix[*n*]arene family.[2] A unique macrocyclic structure together with easily tuneable 3D shapes of the cavity (*cone*, *partial cone*, *1,2-alternate*, and *1,3-alternate* conformations) make thiacalix[4]arenes good candidates for the role of molecular scaffolds and valuable building blocks in supramolecular chemistry. Moreover, substitution of the CH_2 bridges by sulfur atoms[3] affords these derivatives many novel features virtually unknown and/or impossible in the chemistry of classical (methylene-bridged) calixarenes. Thus, the basic thiacalix[4]arene **1** is a much better complexation agent for transition metals (due to sulfur–metal interactions) than its classical counterpart.[4] The larger cavity size invokes reasonable changes in the conformational preferences and dynamic behavior of thiacalixarenes.[5] Moreover, sulfur atoms can be regio- and/or stereoselectively alkylated to form the corresponding sulfonium salts,[6] or chemoselectively oxidized to yield various sulfoxides and sulfones.[7]

In our previous work[6] we found that the alkylation of thiacalix[4]arenes followed several basic rules, leading to the highly selective formation of only a few regio- and stereoisomers (out of many theoretically possible) depending on the starting conformation used. Thus, as shown in Fig. 1, (i) the equatorial orientation of the *S*-alkyl group was strongly preferred over the axial orientation (in fact, the axial arrangement was never observed); (ii) the proximal sulfur bridges cannot be alkylated and only distally dialkylated compounds can be formed; (iii) the sulfur with *syn*-orientation of neighbouring aromatic units is preferred over the sulfur with the corresponding *anti*-orientation, and (iv) the latter is only alkylated if no *syn* arrangement is available in the molecule. In this context, the stereochemistry of sulfoxides is similar to that of alkylsulfonium salts. Hence, we were curious if the same rules could be applied to the formation of sulfoxides. In this paper, we report the partial oxidation of thiacalix[4]arenes immobilized in all four possible conformations, leading to the corresponding mono- and disulfoxides. Our results indicate that the oxidation can be carried out in a strictly regioselective and/or stereoselective manner depending on the conformation of the starting macrocycle.

Results and discussion

To demonstrate the relationships between the starting conformations and the regio- and/or stereochemistry of the products, previously reported reaction conditions leading mainly to monosulfoxide formation were selected. As previously reported by our group,[8] when stirred with 1.5 equiv. of $NaBO_3 \cdot 4H_2O$ ($CHCl_3$/AcOH, 60 °C, 4 h) compound **1** yielded a mixture of mono- and di-oxidized

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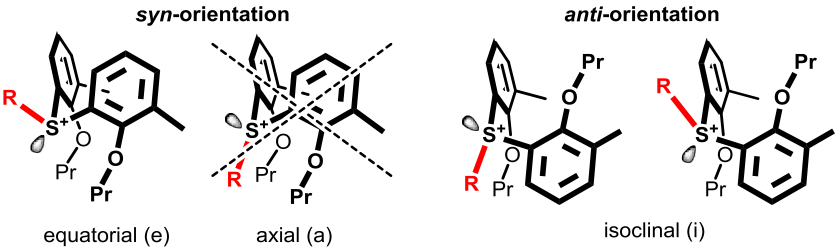


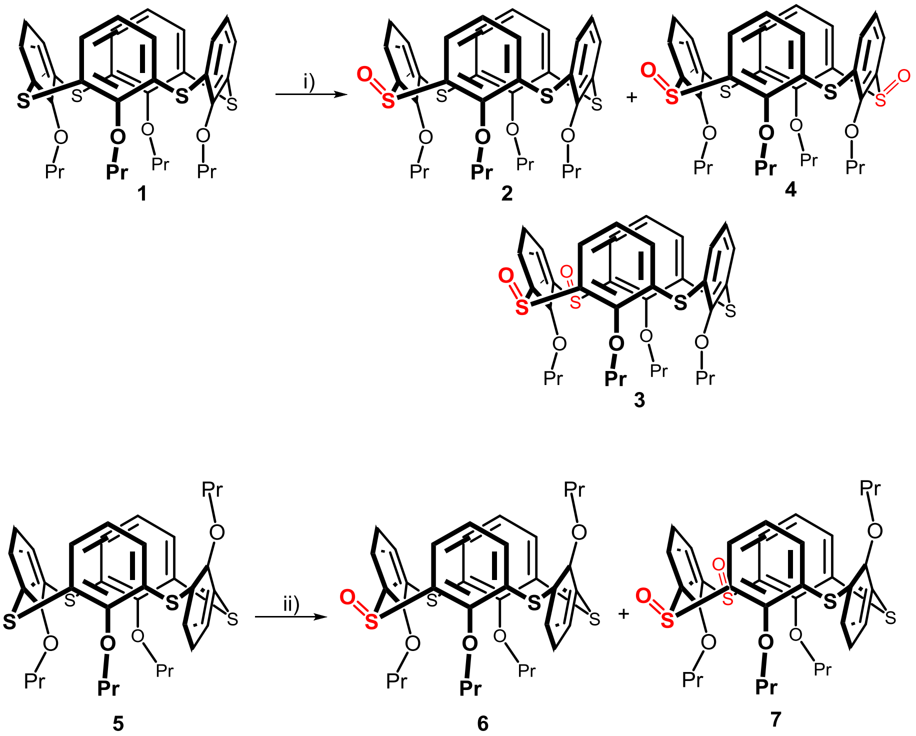
Fig. 1. Mutual orientation of the neighbouring aromatic units in thiacalix[4]arenes and the stereochemical assignment of *S*-alkylated bridges.

products from which isomers **2**, **3** and **4** were isolated in 34%, 22% and 16% yields, respectively. The stereochemistry of sulfoxide **2**, assigned by single crystal X-ray analysis,[8] unequivocally confirmed the equatorial configuration of the sulfoxide group within the *syn* orientation of the phenolic subunits. This indicated that oxidation of the thiacalixarene in the *cone* conformation obeys the same rule as the alkylation of this derivative. On the other hand, contrary to the alkylation reaction, the proximal disulfoxide can be formed without any obvious limitations, as seen by comparing the formation of **3** and **4**.

To check the general applicability of the above mentioned preferences for *S*-oxidation, we extended our previous work by carrying out an oxidation study of the three remaining conformers. Thus, the *partial cone* conformer **5** was oxidized using a slight excess of $NaBO_3·4H_2O$ (1.05 equiv.) to ensure the predominant formation of a monosulfoxide product.[9] Clearly, the *partial cone* conformer can be hypothetically divided into two halves, the first possessing *syn*-orientation of the aromatic subunits (the *cone*-resembling part), and the second exhibiting *anti*-orientation of the phenolic rings (the *1,3-alternate*-resembling part). Unsurprisingly, only the *syn*-oriented part could be oxidized under these conditions to yield sulfoxides **6** and **7** with an equatorial arrangement in 55% and 18% yields, respectively (Scheme 1). These results were in good agreement with oxidation of the *partial cone* conformer bearing benzyl groups on the lower rim, reported in the literature.[7d]

These examples clearly demonstrate the higher reactivity of sulfur atoms with *syn*-orientation of both adjacent phenolic moieties. This fact can be further demonstrated using calixarene **8** in the *1,2-alternate* conformation. As shown in Scheme 2, applying identical reaction conditions as for the *partial cone* conformation ($NaBO_3·4H_2O$, 1.05 equiv., $CHCl_3$/AcOH, 4 h, 60 °C) provided a mixture of isomers **9** and **10** in 51% and 19% yields, respectively (ESI). Again, only derivatives possessing *syn*-orientation of the aromatic units together with equatorial arrangement of the sulfoxide groups were formed. No other disulfoxide isomers were observed in the crude reaction mixture.

In the case of the *1,3-alternate* conformer we were faced with a unique situation as there is no *syn* position which would be strongly preferred. All aromatic subunits in the *1,3-alternate* conformer possess *anti* stereochemistry, which does not allow the preferred equatorial orientation of the sulfoxide groups and yields only the so called isoclinal product.[10] Consequently, the lower reactivity of the *anti* positions could be demonstrated by the fact that a much longer reaction time was needed to achieve sulfoxide formation. Thus, stirring **11** overnight was required, however,



Scheme 1. Reagents and conditions: (i) $NaBO_3·4H_2O$ (1.5 equiv.), $CHCl_3$/AcOH, 60 °C, 4 h (34% **2**, 22% **3**, 18% **4**), (ii) $NaBO_3·4H_2O$ (1.05 equiv.), $CHCl_3$/AcOH, 60 °C, 4 h (55% **6**, 18% **7**).

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