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'Double chiral' new members of calixsalen family

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Dedicated to the memory of Dr. Howard Flack

ABSTRACT

Synthesis and X-ray diffraction studies on the first examples of 'double chiral' calixsalens are presented. In these molecules, one can clearly distinguish two chiral zones. The first one is made by the macrocycle base, whereas the second chiral zone is set up of the additional chirality elements in the tail of the molecule. The 'double chiral' calixsalens are formed through cyclocondensation between chiral vicinal diamine of *trans*-1,2-diaminocyclohexane type and chiral C-5 substituted 2-hydroxyisophthalaldehyde derivatives. The absolute configuration of the dialdehyde did not affect the yield of the macrocyclization reaction. The presence of secondary amides in the tail part of the macrocycle leads to formation of hydrogen bonding network in the solid state, while sterical hindrance preserve interdigitation, thus, 'double chiral' calixsalens do not form aggregates typical for other calixsalens.

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1. Introduction

Despite recent progress, a rational and controllable synthesis of macrocyclic compounds still represents a formidable challenge.[1] Among the reactions developed so far, those based on dynamic covalent chemistry have gained more and more popularity. The success of dynamic covalent chemistry-based macrocyclization reactions relies on the reversibility of bond formation and structural predisposition of substrates to form strain-free macrocyclic structures under thermodynamic conditions.[2]

Discovered at the beginning of 21st century thermodynamically controlled, reversible cycloimination reactions between enantiomerically pure vicinal diamine, such as *trans*-1,2-diaminocyclohexane **1** and terepthalaldehyde, provided the triangular hexaimine macrocycle (*trianglimine*) as the sole product.[3] This method soon received wide attention and opened up new possibilities for the synthesis of macrocyclic compounds from relatively simple building blocks. These cyclocondensation reactions are relatively non-sensitive to solvent polarity and substrate concentration, while the shape and stoichiometry of the final product is determined by the structure of the aromatic linker.[4] The use of chiral dialdehydes or diamine substrates with multiple stereogenic centers showed match/mismatch effects that may favor or prevent macrocyclization in the absence of a template.[5–9]

In general, cyclocondensation of **1** with linear 1,4-dialdehydes (such as terepthalaldehyde) provided the [3+3] products, whereas for 1,3-dialdehydes, the primary [3+3] cyclocondensation products sometimes contracted to the [2+2] macrocycles. The introduction of a hydroxyl group at the C-2 position of isophthalaldehyde has a profound effect on the structure and stability of the product. [3+3] Cyclocondensation between enantiomerically pure (*R*,*R*)-**1** and various C5-substituted 2-hydroxyisophthalaldehydes of the general formula **2**, provides calixarene-like chiral macrocyclic ligands, of the general formula **3** (Scheme 1).[10,11] Due to their vase-like structure and the presence of three salen moieties within the macrocycle skeleton, these compound are dubbed '*calixsalens*'. Calixsalens constitute a relatively unexplored class of chiral ligands, capable of forming multimetal complexes of diverse functions and exhibiting catalytic or receptor properties.[12]

Each of the calixsalen structures consist of two parts (rims). The upper rim (head) of the macrocycle comprises of the cyclohexane rings, aromatic carbon atoms with attached imine bonds and hydroxyl substituents. The lower rim (tail) is formed by the rest of the aromatic rings including substituents at the C-5 aromatic carbon atoms. The molecular and supramolecular structures of calixsalens are determined by the size and electronic properties of the substituents at the C-5 positions. Small substituents or polar groups, such as halogens, allow the formation of tail-to-tail dimers that mutually interpenetrate into their corresponding cavities (Fig. 1a). Bulky, hydrophobic substituents reverse the conformation of the macrocycle and prevent tail-to-tail assembly. These macrocycles mostly aggregate in crystals to form head-to-head capsules with internal voids capable of solvent inclusion (see Fig. 1b).[12]

Recently we have shown that the reaction between *rac*-**1** and various C-5 substituted dialdehydes **2** is highly stereoselective

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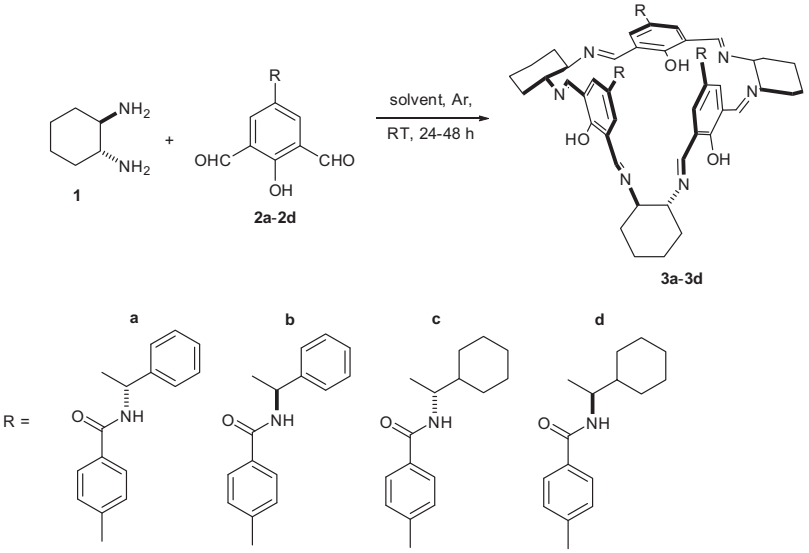

Scheme 1. Synthesis of calixsalens **3** from (*R*,*R*)-**1** and C5-substituted 2-hydroxyisophthalaldehydes **2**.

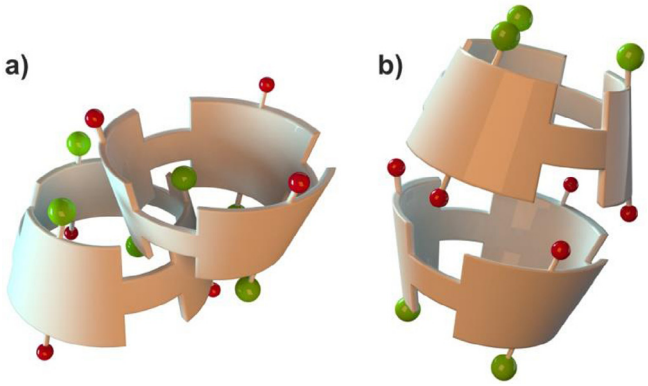

Figure 1. Schematic representation of possible types of host packing in calixsalen crystals: (a) tail-to-tail (host–guest) dimer; (b) head-to-head dimer (capsule). Red balls represent hydroxyl groups; green balls represent substituents at C-5 positions of aromatic rings.

and leads to homochiral *all-R* and *all-S* calixsalens. This chiral self sorting is also visible in the solid state, since macrocycles dimerize in homochiral tail-to-tail dimers and further aggregate in a heterochiral head-to-head manner.[13,14]

In continuation of our interests in template-free synthesis and supramolecular properties of chiral macrocycles and molecular cages, we decided to expand on our studies on calixsalens bearing additional chiral secondary amide substituents at the C-5 position. Two chiral zones can be distinguished in these structures (see Fig. 2). The first one is related to the chirality of the parent diamine and can be treated as a macrocycle base. The second chiral zone will be placed in the 'tail part' of the molecule and associated with the presence of the chiral substituent. Thus, such macrocycles can be named as 'double chiral'. The introduction of an additional chiral fragment in the macrocycle skeleton will not only influence the molecular structure. The use of common supramolecular synthon, namely the N—H···O=C amide···amide hydrogen bonds, may lead to the generation of various structural networks and consequently lead to the formation of a new type of calixsalen associates in the solid state, impossible to achieve with the hitherto known calixsalen molecules.

2. Results and discussion

2.1. Synthesis and structure of 'double chiral' calixsalens

While **1** can be easily obtained in both enantiomeric forms, to date chiral derivatives of **2** are not known. Our initial attempts to

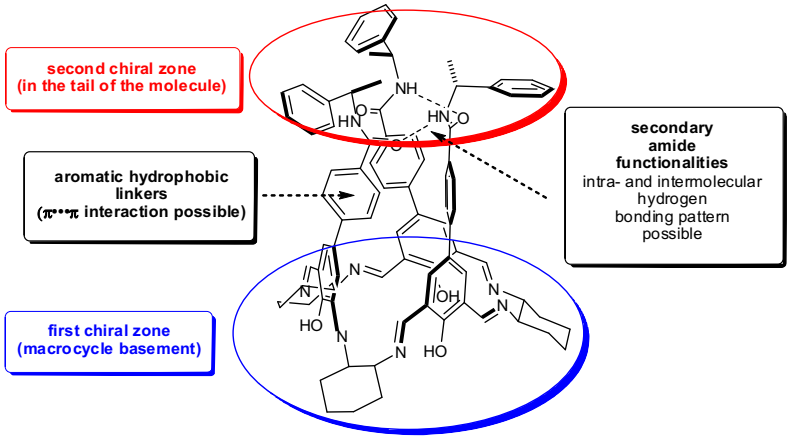

Figure 2. Design concept underlying 'double chiral' calixsalens.

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