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mPW1PW91 study for conformational isomers of methylene bridge-monosubstituted tetramethoxycalix[4]arenes

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ABSTRACT

Structures of ten conformational isomers of methylene bridge-monosubstituted tetramethoxycalix[4]-arenes, 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-2-ethylcalix[4]arene (1), and methyl 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylate (2) were optimized by quantum mechanical mPW1PW91/6-31G(d,p) (hybrid Hartree–Fock density functional) calculations. The total electronic and Gibbs free energies of the various conformations (cone, partial cone, 1,2-alternate, and 1,3-alternate) of 1 and 2 were analyzed. The cone (equatorial) and partial cone (equatorial) conformers were disclosed to be the most stable among all the isomers of 1 and 2. The calculated structures agreed well with the experimental results. The IR spectra were calculated at the mPW1PW91/6-31G(d,p) level for the most stable conformer of each methylene bridge-monosubstituted tetramethoxycalix[4]arene.

1. Introduction

Calix[4]arenes are macrocyclic molecules consisting of four phenolic rings interconnected by methylene groups [1–4]. The derivatization reactions of calix[4]arenes usually involve the phenolic hydroxyl groups, *p*-positions, or phenolic units as a whole. Homocalixarenes [5] and thiacalixarenes [6], in which the bridging methylene units of the conventional calixarene framework are completely replaced by organic groups or heteroatoms, represent well-known structural modifications of the calixarene family [7,8]. In contrast, calixarenes with monosubstituted methylene bridges (meso positions) are rare [9–12]. The laterally monosubstituted calixarenes may open interesting aspects of calixarene chemistry such as the preparation of oligotopic receptors [13–17] as well as calixarenes attached to a specific target or support [18–21].

The methylene bridge-monosubstituted calixarenes are important [22–28], because in the cone conformation, for example, the methylene protons of the derivative are not equivalent [29]. Thus, there is a possibility of (at least partial) locking the conformation of the monosubstituted calixarenes because of the energy differences between the equatorial and axial orientations of the substituent. In the simplest instance of the monosubstitution on one of the four methylene bridges of the calix[4]arene, an equatorial disposition of the lateral substituent appears to be strongly preferred, even though this does not necessarily inhibit the associated conformational changes; e.g., rotation of the phenolic units through the annulus. The relative stabilities of their conformations have been both experimentally and theoretically studied [22–27]. In general, the conformations of calix[4]arenes are analyzed in terms of four basic arrangements resulting from the "up" or "down" orientation of the phenol rings relative to the average macrocyclic plane passing through the four methylene carbons. These arrangements are usually designated as "cone," "partial cone (PC)," "1,3-alternate (1,3-A)," and "1,2-alternate (1,2-A)" [1] (Scheme 1). In the cone conformation, the four methylene groups are equivalent; however, the two protons of a given methylene group are diastereotopic. By analogy with the chair conformation of cyclohexane derivatives, these protons are usually labeled as "equatorial" and "axial" [30].

Several conformations are possible for a calix[4]arene derivative with a single monosubstituted methylene bridge or two opposite, each monosubstituted, methylene bridges [31,32]. These conformations result from the possible up–down orientations of the aryl groups and the axial/equatorial/isoclinal disposition of the substituent(s). The ideal conformers for each substitution pattern are shown in Scheme 2.

The conformational effects of the formal introduction of substituents on the methylene bridges have not been studied well, most probably because of the lack of synthetic methods for

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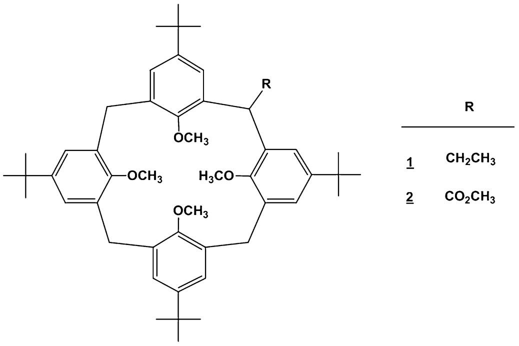


Scheme 1. Methylene bridge-monosubstituted tetramethoxycalix[4]arenes **1**, (5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2-ethylcalix[4]arene), and **2** (methyl 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylate).

the preparation of such compounds. The cone, PC, 1,2-A, and 1,3-A conformers of methylene bridge-monosubstituted calix[4]arenes **1** and **2** (Scheme 1) were optimized by means of mPW1PW91 calculations, and their relative stabilities were compared. The IR spectra for the most stable conformers of **1** and **2** were also generated from mPW1PW91/6-31G(d,p) calculations.

2. Computational methods

The initial conformations of the axial and equatorial isomers of **1** and **2** were constructed by means of molecular mechanics (MM), molecular dynamics (MD), and semi-empirical AM1 calculations of HyperChem [33]. Further optimization performed by conformational searches using simulated annealing has been described elsewhere [34]. The cone, PC, 1,2-A, and 1,3-A conformers of the isomers of **1** and **2** obtained from the MM/MD and AM1 calculations were fully re-optimized by a Hartree–Fock density functional (HF–DF) method to determine the relative energy and structure of each distinct conformer. The modified Perdew–Wang 1-parameter (mPW1) calculations [35,36] such as mPW1PW91 are hybrid HF–DF models that provide good results both for the covalent and non-covalent interactions [37]. The mPW1PW91/6-31G(d),/6-31G(d,p), and/6-311 + G(d,p) optimizations were performed using Gaussian 09 [38] to obtain more accurate total electronic energies, Gibbs free energies, and structures of the conformational stereoisomers of **1** and **2**.

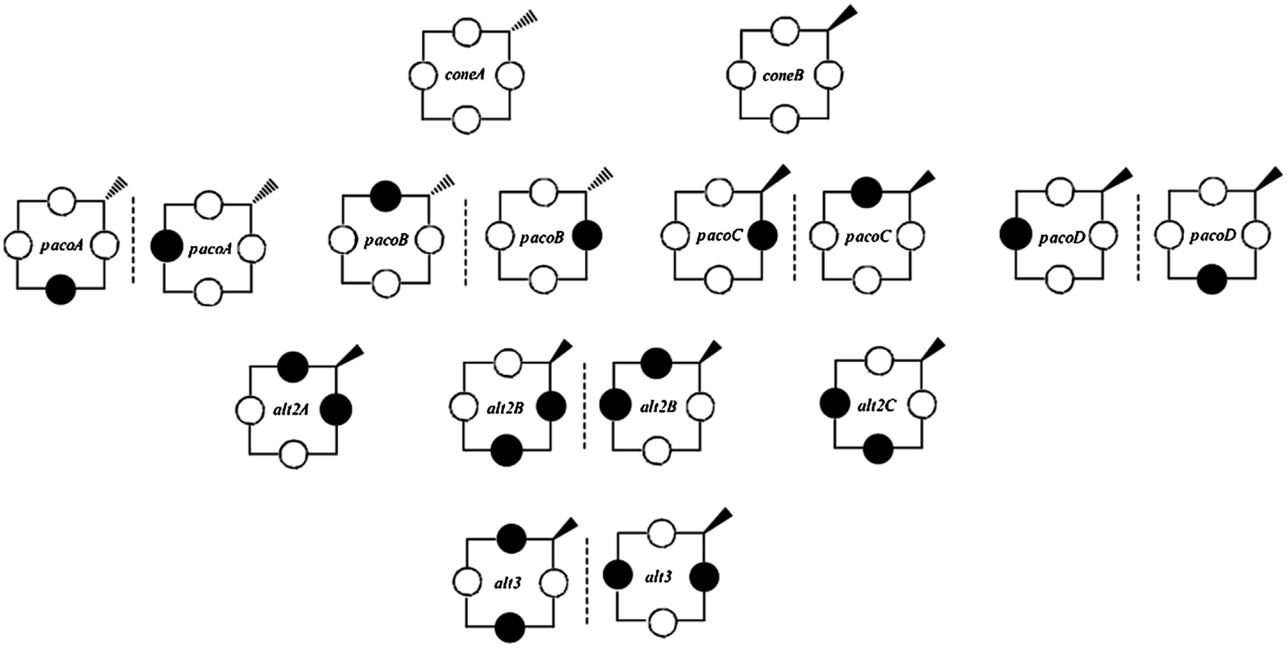
The mPW1PW91 calculations were also used to generate the normal mode frequencies of the final structures. None of the vibrational spectrum showed negative frequency, confirming that the optimized structures exist at the energy minima. For the direct comparison with the experimental data, the calculated vibrational frequencies were scaled by the recommended scale factor (0.893) [39]. The broadened IR spectra were obtained assuming a Lorentzian line width of 10 cm^{-1}.

3. Results and discussion

3.1. Configurational and conformational considerations

Because the derivatives of **1** and **2** possess a monosubstituted methylene bridge, the substituent at the bridge may be located at the axial, equatorial, or isoclinal position. The different possible dispositions of the substituents on the selected conformations of the macrocycles are shown in Scheme 2.

The steric considerations indicate that the equatorial or isoclinal dispositions of the substituents at the monosubstituted methylene bridges would be favored over the more sterically crowded axial dispositions. In some substitution patterns, this may subsequently influence the preferred conformation of the macrocycle resulting from different “up” or “down” orientations of the ring. The major conformations in the solution of **1** and **2** have been experimentally determined to be a mixture of cone and PC forms of the equatorial isomer [22–27]. The crystal conformation of **2** has been experimentally determined to be the PC conformation of the equatorial isomer [26].



Scheme 2. Possible conformers of methylene bridge-monosubstituted tetramethoxycalix[4]arenes (**1** and **2**). Filled and unfilled circles represent the “up” and “down” orientation of the methoxy groups, respectively. Mirror images are separated by a broken line. Notations such as coneA are adopted from reference [23] and listed in Table 1.