# Conformational Isomerism of Electroactive Calix[4]arenes: Influence of the Electronic State in the Flexibility of Thiophene-Containing Calix[4]arene

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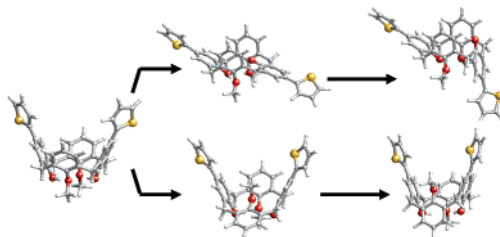
The cone-to-paco conformational isomerism of 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix[4]arene-25,27-diol, a calix[4]arene with thiophene substituents in para position with respect to the hydroxyl groups, has been investigated using ab initio and DFT quantum mechanical methods. This compound models a molecular device constituted by small oligomers of thiophene and calix[4]arene units, whose actuation mechanism is promoted by the conformational flexibility of the latter. To examine the influence of the electronic structure of this electroactive calix[4]arene, three different states have been considered: (i) neutral state; (ii) oxidized state, in which one electron is extracted from each thiophene ring; and (iii) oxidized-deprotonated state, in which the two hydroxyl groups of the oxidized compound are deprotonated. Results are discussed and compared with those obtained for the same molecule but without thiophene substituents, 25,27-dihydroxy-26,28-dimethoxycalix[4]arene. Although the influence of the thiophene substituents is negligible in the neutral state, they play a crucial role in the rotational isomerism of both the oxidized and deprotonated-oxidized states.

Introduction

Calixarenes are synthetic macrocycles used as building blocks in nanotechnology and supramolecular chemistry and as molecular scaffolds for the preparation of novel selective receptors for ions and neutral molecules.[1,2] The most simple and well-studied member of this class of compounds is the calix[4]arene (**1**), a 16-membered macrocyclic ring composed of four phenol rings connected by ortho-methylene bridges. Interestingly, the methylene bridging groups, which allow the rotation of the phenolic rings, provide an unusual conformational flexibility to **1**. The more relevant conformations are the cone and partial-cone (paco), which differ in the orientation of one phenol ring

SCHEME 1. Compounds 1 (R= H) and 2 (R= Me)
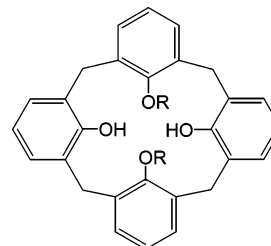
with respect to the other three (Figure 1). The cone-to-paco transition of **1** has been studied using NMR spectroscopy,[3] quantum mechanical calculations,[4,5] and force-field molecular

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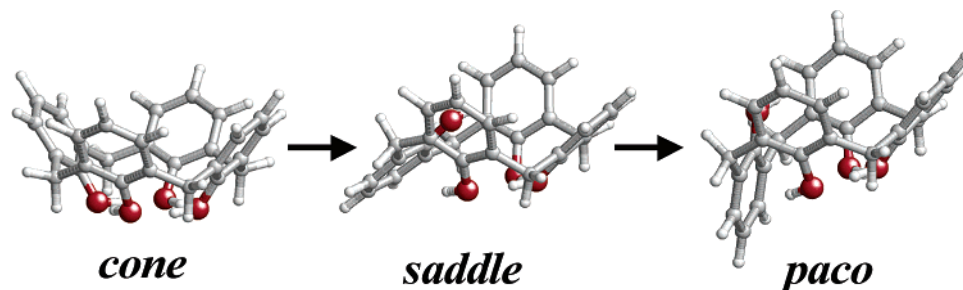
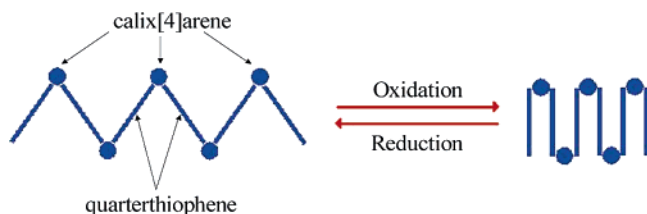**FIGURE 1.** Characteristic conformations of calix[4]arene (**1**).

FIGURE 2. Schematic representation of poly(calix[4]arene bis-bithiophene) molecular actuator.

dynamics simulations.[6,7] The dynamic equilibrium between the cone and paco has been also studied on derivatives of **1**.[1,5,8−15] Results indicated that placement of bulky substituents at the hydroxyl and/or para positions of the rings can be used to alter the preferences of this rotational isomerism.

Among the many applications of calixarenes in nanotechnology, the design of new molecular actuators is one of the more promising. In this context, a conducting polymer actuator constituted by small thiophene oligomers (quarterthiophene) separated by calix[4]arene scaffolds (25,27-dihydroxy-26,28-dimethoxycalix[4]arene) was recently developed.[16,17] The actuation mechanism of this material, which was denoted poly(calix-[4]arene bis-bithiophene), was explained in terms of reversible conformational changes produced by variations in the electronic structure of electrochemically activated polymer molecules (Figure 2). Thus, oxidation produces a drastic contraction, while the corresponding expansion is achieved upon reduction. It should be noted that the impressive performance of this material, which could be envisaged as a potential artificial muscle, is

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based on conformational changes of the molecular chains rather than on ions exchange, as usually occurs with conducting polymer actuators.[18−21]

Recent studies devoted to understand the actuation mechanism of poly(calix[4]arene bis-bithiophene) at the molecular level indicated that, although the conformational changes are induced by the interactions between oxidized quarterthiophene units, the conformational flexibility of the calix[4]arene scaffold is essential for the contraction showed in Figure 2.[22,23] More specifically, an actuating unit was examined considering the neutral form (reduced state), the form with oxidized quarterthiophene segments (oxidized-nondeprotonated state), and the form with oxidized quarterthiophene segments and deprotonated hydroxyl groups at the calix[4]arene scaffold (oxidized-deprotonated state). Results allowed one to conclude that the electrostatic repulsions between the charged atoms of the calix-[4]arene scaffolds are responsible for the length reduction of the poly(calix[4]arene bis-bithiophene) chains.[23] Thus, conjugated quarterthiophene segments should not be considered as the main active elements in the molecular actuation mechanism, although their electrochemical oxidation is essential to promote the calix[4]arene deprotonation and to control the conductivity of the polymer.

A vital step for the complete understanding of the poly(calix-[4]arene bis-bithiophene) actuation mechanism is the determination of how the electroactive thiophene substituent modifies the conformational preferences of the calix[4]arene. In a recent study, we investigated the changes produced in the cone-to-paco conformational transition when the phenolic hydroxyl groups of **1** are partially replaced by methoxy groups.[5] Thus, the rotational isomerism of **1** and 25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**2**) was examined using quantum mechanical calculations. In this work, we incorporate thiophene substituents at the para position of the phenol rings of **2**. The resulting compound, 11,23-bis(thiophen-5-yl)-26,28-dimethoxy-calix[4]arene-25,27-diol (**3**), offers a suitable system to model the hinge of the poly(calix[4]arene bis-bithiophene) actuating unit. The cone-to-paco rotational isomerism of **3** has been examined considering the neutral (reduced) state, the form with oxidized thiophene rings (**3ox**), and the form with both oxidized thiophene rings and deprotonated hydroxyl groups (**3ox−d**).

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SCHEME 2. Compound 3
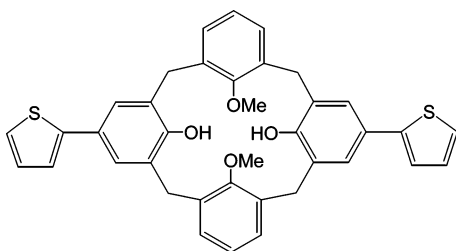
Results allow one elucidate the role of the flexible calix[4]arene scaffold as a structural hinge in the molecular actuator.

Methods

All the ab initio and DFT quantum mechanical calculations were performed using the Gaussian 03 computer program.[24] In all cases, geometry optimizations were carried out at the Hartree–Fock (HF) level using a 6-31G(d)[25] basis set (HF/6-31G(d)). The cone and paco minimum energy conformations were derived from full geometry optimizations, while an appropriate constraint was applied to obtain the saddle conformations (Figure 1). DFT calculations were performed using the following combination: Becke's three-parameter hybrid functional (B3)[26] with the Lee, Yang, and Parr (LYP)[27] expression for the nonlocal correlation (B3LYP). Single-point energy calculations were performed at the B3LYP/6-311++G(d,p)[28] levels using the HF/6-31G(d) geometries. Calculations on 3^{ox} were performed considering the unrestricted quantum-chemical formalism (UHF and UB3LYP) with triplet spin multiplicity, that is, allowing oxidation of the two thiophene substituents. Similarly, calculations on 3^{ox-d} and 2^d were performed within the UHF and UB3LYP frameworks. On the basis of previous works, it is expected that these computational methods will provide reliable results for the compound under study.[5,29]

Results and Discussion

Two cone conformations have been considered for the three states under study, which differ in the orientation of the thiophene substituents. In the cone-a, the two thiophene rings are arranged antiparallel, while in the cone-p, they are parallel. Three representative paco conformations can be derived from each of such cone arrangements: (i) paco-a^{Thp} and paco-p^{Thp} when the ring that changes the orientation with respect to the other three contains a thiophene as substituent; (ii) paco-a^{OMe-i}

and paco-p^{OMe-i} when the rotation involves an anisole ring and the methoxy group points inward (the methyl fills the calix[4]-arene cavity); and (iii) paco-a^{OMe-o} and paco-p^{OMe-o} when the methoxy group of the rotated anisole ring is arranged outward (the methyl is moved out of calix[4]arene cavity). Figure 3 shows all these conformational states for **3**, including the saddle point conformations, the latter being the transition states of the cone-to-paco rotational isomerism. All these structures were also considered for both 3^{ox} and 3^{ox-d}.

In a recent study, we analyzed the influence of the level of geometry optimization and energy calculation on the rotational isomerism of **1**.[5] For this purpose, calculations were performed at the HF, B3LYP, and B3PW91 levels with the 6-31G(d), 6-311G(d,p), and 6-311++G(d,p) basis sets, the latter being only used for single-point energy calculations. It was found that HF/6-31G(d) geometry optimizations combined with B3LYP/6-311++G(d,p) single-point energy calculations provide results that are in excellent agreement with experimental observations. Accordingly, this level of theory has been used to examine the conformational preferences of **3**, 3^{ox}, and 3^{ox-d}.

Neutral State. Table 1 shows the relative energies calculated for the neutral forms of **3**, the optimized structures being those displayed in Figure 3. For comparison, we list in Table 2 the results obtained for the rotational cone-to-paco rotational isomerism of **2** using the same theoretical methods,[5] where the super-indexes OH, OMe-i, and OMe-o indicate that the rotated ring is the phenol, the anisole with the methyl arranged inward, and the anisole with the methyl arranged outward, respectively.

The cone-p is only 1.0 kcal/mol more stable than the cone-a at the B3LYP/6-311++G(d,p) level, indicating that the interaction between the π-clouds of the thiophene rings is relatively weak. Inspection of the saddle conformations indicates that the TS-p^{OMe-o} and TS-a^{OMe-o} are the lower energy ones, differing between them by only 0.1 kcal/mol. However, the cone-p → TS-p^{OMe-o} barrier is 7.2 kcal/mol, while the barrier cone-a → TS-a^{OMe-o} is only 6.3 kcal/mol. On the other hand, the saddle conformations with the methoxy groups arranged inward, TS-a^{OMe-i} and TS-p^{OMe-i}, are destabilized by about 16 kcal/mol with respect to those with the methoxy group pointing out of the cavity. Obviously, this must be attributed to the steric contacts produced by the methyl of the rotated anisole rings. Regarding the saddle conformations in which the rotated ring contains a thiophene, TS-a^{Thp} and TS-p^{Thp}, they are 0.7 and 1.9 kcal/mol less stable than the TS-a^{OMe-o} and TS-p^{OMe-o}, respectively. Thus, in the former conformations, one of two O–H···O hydrogen bonds characteristic of the cone arrangements (see Figure 3) is lost by the rotation of the ring, which justifies the increase of relative energy.

On the other hand, it should be noted that the paco-a^{Thp} and paco-p^{Thp} conformations are destabilized with respect to the global minimum by only 2.1 and 2.0 kcal/mol, respectively, these values being about 2.5 kcal/mol smaller than those obtained for the paco-a^{OMe-o} and paco-p^{OMe-o}. As expected, the paco conformations with the methyl group pointing inward were the less stable. Amazingly, results obtained for **2** and **3** (Tables 2 and 1, respectively) evidence that the incorporation of thiophene rings as para-substituents does not produce significant changes in the cone-to-paco conformational transition; that is, the relative energies of the saddle and paco conformations are similar for the two compounds.

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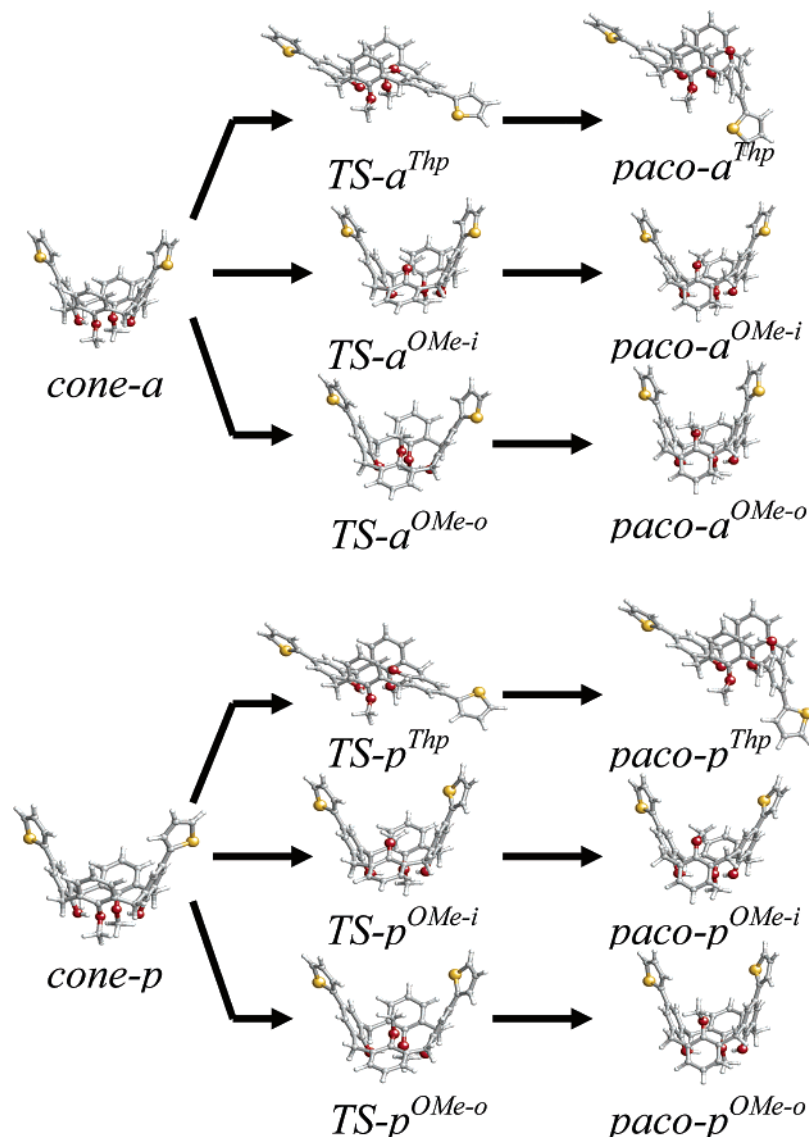(25) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *16*, 217.
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FIGURE 3. Characteristic conformations of **3**.

TABLE 1. Relative Energies (in kcal/mol) of the Cone, Paco, and Saddle Conformations of 3 Predicted at the B3LYP/6-311++G(d,p) Level

cone		TS		paco	
cone-a	1.0	TS-a^{Thp}	8.0	paco-a^{Thp}	2.1
		TS-a^{OMe-i}	23.4	paco-a^{OMe-i}	7.2
		TS-a^{OMe-o}	7.3	paco-a^{OMe-o}	4.7
cone-p	0.0	TS-p^{Thp}	9.1	paco-p^{Thp}	2.0
		TS-p^{OMe-i}	22.9	paco-p^{OMe-i}	7.0
		TS-p^{OMe-o}	7.2	paco-p^{OMe-o}	4.5

TABLE 2. Energies (in kcal/mol) of the Paco and Saddle Conformations Relative to the Cone Minimum of 2 and 2^{d} Predicted at the B3LYP/6-311++G(d,p) Level

|	TS^{OH}	TS^{OMe-i}	TS^{OMe-o}	paco^{OH}	paco^{OMe-i}	paco^{OMe-o}
2	8.1	22.8	7.2	1.7	6.8	4.5
2^{d}	19.7	8.7	14.4	4.5	−2.1	−0.2

Oxidized State. The relative energies of the cone, saddle, and paco conformations of **3^{ox}** are listed in Table 3. This oxidized form was achieved by removing one electron from each thiophene ring of **3**, which was performed imposing a

TABLE 3. Relative Energies (in kcal/mol) of the Cone, Paco, and Saddle Conformations of 3^{ox} Predicted at the UB3LYP/6-311++G(d,p) Level

cone		TS		paco	
cone-a	0.0	TS-a^{Thp}	11.3	paco-a^{Thp}	6.6
		TS-a^{OMe-i}	36.2	paco-a^{OMe-i}	16.1
		TS-a^{OMe-o}	15.3	paco-a^{OMe-o}	10.3
cone-p	0.0	TS-p^{Thp}	11.3	paco-p^{Thp}	6.6
		TS-p^{OMe-i}	35.9	paco-p^{OMe-i}	16.0
		TS-p^{OMe-o}	15.1	paco-p^{OMe-o}	11.1

triplet electronic state rather than a singlet one. Indeed, we found that the latter state is less stable than the former one by about 45 kcal/mol.

Inspection of the optimized conformations reveals some distortions with respect to the structures of **3**, which are due to the repulsion between the two charged substituents. Thus, to minimize this unfavorable interaction, the separation between two thiophene rings increases. This is illustrated in Figure 4, which compares the cone-a conformation of **3^{ox}** and **3**. The distance between the geometric centers of the thiophene rings is about 4 Å larger for the oxidized state than for the neutral one. This result is fully consistent with the actuation mechanism
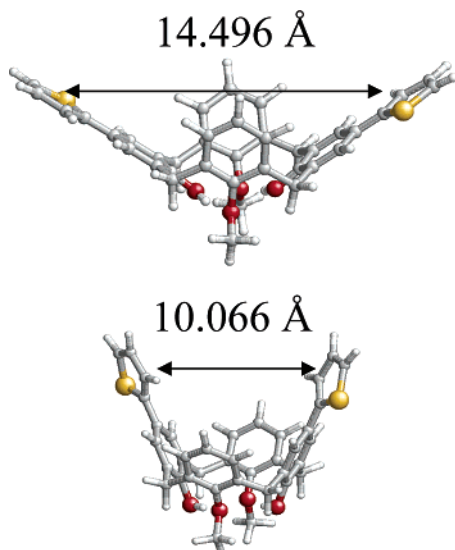
FIGURE 4. Cone-a conformation of 3^{ox} (left) and **3** (right). The distance between the geometric centers of the thiophene rings is indicated.

proposed for poly(calix[4]arene bis-bithiophene).[23] Thus, it was found that, after oxidation, the actuation unit expands to alleviate the repulsion between the charged oligothiophenes.

Comparison between the relative energies obtained for **3** and 3^{ox} reveals that oxidation of thiophene rings induces both an increase of the barriers and, especially, a destabilization of the paco conformations. Furthermore, there are some other specific and interesting differences between the two states that deserve specific comments. The lowest energy saddle conformations are the TS-a^{Thp} and TS-p^{Thp}, which are isoenergetic, rather than the TS-p^{OMe-}o and TS-a^{OMe-}o ones as was found for the neutral state. Thus, the distance between the two positively charged thiophenes increases when the rotated unit is a phenol. As a consequence, the repulsive interaction diminishes, with the resulting saddle conformations becoming more stable than the others by at least 3.8 kcal/mol. Accordingly, in the oxidized state, the cone → TS barrier is governed by the repulsion between the two charged substituents, while in the neutral state, it was controlled by the O−H···O hydrogen bonds. Regarding the saddle conformations with a rotated anisole ring, the relative energy between the structures with the methoxy group arranged inward and outward increases by about 5 kcal/mol with respect to the neutral state.

On the other hand, it should be noted that the paco-a^{Thp} and paco-p^{Thp} conformations are destabilized with respect to the global minimum by 6.6 kcal/mol, while the paco-a^{OMe-}o and paco-p^{OMe-}o are destabilized by more than 10 kcal/mol. Again, the paco conformations with the methyl group pointing inward were the less stable. The overall results clearly indicate that the cone → TS^{Thp} → paco^{Thp}, independent of the parallel or antiparallel arrangement of the thiophene substituents, is the most favored rotational isomerism of 3^{ox}. This fact is in excellent agreement with the conformational expansion proposed for the poly(calix[4]arene bis-bithiophene) actuator after oxidation of the thiophene oligomers;[23] that is, oxidation favors conformational changes in the thiophene-containing rings rather than on the anisole rings.

Oxidized-Deprotonated State. The 3^{ox-d} state is generated by deprotonating the two hydroxyl groups of 3^{ox}. Consequently,

TABLE 4. Relative Energies (in kcal/mol) of the Cone, Paco, and Saddle Conformations of 3^{ox-d} Predicted at the UB3LYP/6-311++G(d,p) Level

cone		TS		paco	
cone-a	0.0	TS-a^{Thp}	34.8	paco-a^{Thp}	28.3
		TS-a^{OMe-i}	35.8	paco-a^{OMe-i}	34.8
		TS-a^{OMe-o}	33.2	paco-a^{OMe-o}	15.8
cone-p	0.1	TS-p^{Thp}	34.6	paco-p^{Thp}	28.2
		TS-p^{OMe-i}	33.0	paco-p^{OMe-i}	34.2
		TS-p^{OMe-o}	33.2	paco-p^{OMe-o}	15.3
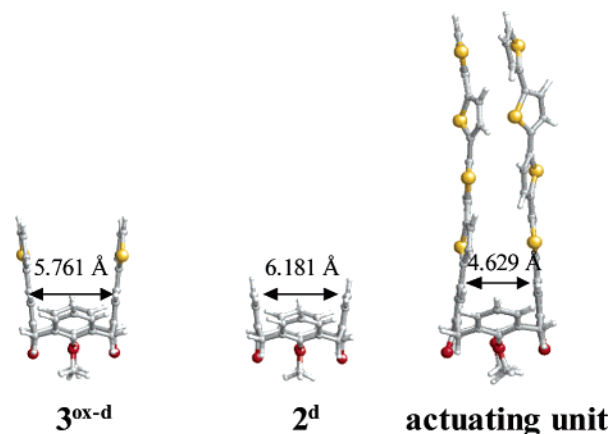
FIGURE 5. Cone conformations of 3^{ox-d} (cone-a), 2^d, and a model actuating unit of poly(calix[4]arene bis-bithiophene) (cone-a). The distance between the ends of the six-membered rings linked to the deprotonated oxygen atoms (C_{Ph}···C_{Ph}) are indicated.

3^{ox-d} is a zwitterion with two negative charges at the calix[4]-arene scaffold and two positive charges distributed between the thiophene substituents, which retain the radical cation structure. The relative energies of 3^{ox-d} are listed in Table 4, while those calculated for compound **2** deprotonated at the hydroxyl groups of the phenol rings (2^d) are displayed in Table 2 for comparison.

Deprotonation introduces significant changes in both the relative stabilities and the structures of the different conformations. A drastic reduction of the distance between the geometric centers of the thiophene rings is expected for the cone-a and cone-p conformations of 3^{ox-d}. This shortening should be a consequence of the repulsive electrostatic interaction between the charged oxygen atoms of the phenolate rings, which tend to separate as much as possible. This structural effect is detected in 2^d (Figure 5). Thus, the O···O distance for the two phenol rings of **2** is 4.357 Å, this distance increasing to 5.575 Å after deprotonation. The shifting away of the charged oxygen atoms induces an approach between the ends of the corresponding six-membered rings. This is shown in Figure 5, which indicates that the distance between such ends (C_{Ph}···C_{Ph}) is 6.181 Å. The same feature, even amplified, was recently detected for one complete actuating unit of poly(calix[4]arene bis-bithiophene) in the oxidized-deprotonated state.[23] This is also reflected in Figure 5, with the O···O and C_{Ph}···C_{Ph} distances being 5.901 and 4.269 Å, respectively. As expected, the structural parameters obtained for 3^{ox-d} (the O···O and C_{Ph}···C_{Ph} distances are 5.382 and 5.761 Å, respectively) are in excellent agreement with those obtained for 2^d and the complete actuating unit; that is, the parameters measured for 3^{ox-d} are halfway between those determined for 2^d and the actuating unit.

On the other hand, the saddle conformations of 3^{ox-d} are about 33−36 kcal/mol less stable than those of the cone-a and cone-

p, which are almost isoenergetic, independent of the chemical nature of the rotated ring, the orientation of the methyl group of the anisole rings, and the relative arrangements of the two thiophene rings. Accordingly, deprotonation of 3^{ox} induces a significant enhancement of the barriers involving the rotation of the phenol ring and the anisole ring with the methyl group pointing outward, that is, more than 23 and 17 kcal/mol, respectively, while the TS-a^{OMe-i} and TS-p^{OMe-i} remain practically unaltered. Regarding to the paco conformations, the paco-a^{Thp} and paco-p^{Thp} conformations are unfavored with respect to the cone arrangements by about 28 kcal/mol, revealing a destabilization of 22 kcal/mol with respect to 3^{ox}. On the other hand, the destabilization of the paco-a^{OMe-o} and paco-p^{OMe-o} conformations with respect to the corresponding arrangements increases by 4−5 kcal/mol after deprotonation, while that of the paco-a^{OMe-i} and paco-p^{OMe-i} is about 18−19 kcal/mol. The overall results displayed in Table 4 suggest that the presence of cone-to-paco rotational isomerism in 3^{ox-d} is very improbable. It should be noted that this is fully consistent with the actuation mechanism recently proposed for poly(calix[4]arene bis-bithiophene).[23]

The conformational energies obtained for 3^{ox-d} are quite different from those calculated for 2^d. Thus, inspection to Table 2 reveals that the highest energy barrier, 19.7 kcal/mol, corresponds to the TS^{OH} conformation since in this arrangement the negatively charged oxygen atom of the rotated ring is directly confronted with π-electron density of the other phenolate ring. The TS^{OMe-i} barrier also presents a discrepancy with respect to the results displayed in Table 4 for the corresponding saddle conformations of 3^{ox-d}. Thus, in TS^{OMe-i}, the methyl group of the rotated anisole ring interacts favorably with the deprotonated oxygen atoms of the phenolate rings, which stabilize this conformation with respect to the cone one. On the other hand, it should be noted that the paco^{OMe-i} and paco^{OMe-o} conformations are stabilized with respect to the cone arrangement by −2.1 and −0.2 kcal/mol, respectively. The differences found between 2^d and 3^{ox-d} should be mainly attributed to the following two reasons: (i) the zwitterion nature of the latter compound is responsible for the complex equilibrium between attractive and repulsive interactions that are not present in 2^d; and (ii) the delocalization of the charges is higher in 3^{ox-d} than in 2^d since in the former the π-system extends to the thiophene substituent; that is, the interactions induced by such charges are weaker in the former compound.

Conclusions

The conformational flexibility of the thiophene-containing calix[4]arene, 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix-[4]arene-25,27-diol, has been examined through the cone-to-paco rotational isomerism. The effects of the electronic structure on the conformational preferences of this electroactive calix-[4]arene have been considered by studying three different states: neutral (**3**), oxidized (3^{ox}), and oxidized-deprotonated (3^{ox-d}). Furthermore, the influence of the parallel or antiparallel arrangement of the thiophene rings has been analyzed for the three states.

Calculations on **3** indicate that the thiophene rings do not play any active role in the cone-to-paco conformational transition. Thus, the conformational preferences obtained for **3** are similar to those predicted for **2**, with the latter being unsubstituted by thiophene rings. Oxidation of **3** to 3^{ox}, which was performed by extracting one electron from each thiophene ring, increased the barriers and reduced the relative stability of the paco conformations. Furthermore, the interaction between the positively charged substituents produces significant changes in the molecular structure of the calix[4]arene scaffold; that is, the distance between the two thiophene rings is considerably larger in 3^{ox} than in **3**. Finally, 3^{ox-d} was generated by deprotonating the hydroxyl group of the two phenolic units. The conformational properties of 3^{ox-d} are completely different from those obtained for 2^d, indicating that the thiophene rings have a significant influence on this complex state. Thus, deprotonation of 3^{ox} produces a destabilization of both the saddle and paco conformations. These results indicate that the cone-to-paco rotational isomerism is an improbable event in the actuation mechanism of poly(calix[4]arene bis-bithiophene). Accordingly, the conformational transitions associated with the calix[4]arene scaffolds are not expected to alter the contraction movement induced by the oxidation of the actuator.

Supporting Information Available: Optimized coordinates and energies for all the cone, paco, and saddle conformations of the species calculated. This material is available free of charge via the Internet http://pubs.acs.org.

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