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Contraction Process of an Electroactive Actuator Based on a One Microsecond Atomistic Molecular Dynamics Simulation

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Abstract: The contraction process of an electroactive actuator constituted by calix[4]arene units and quaterthiophene segments has been investigated at the microscopic level by using atomistic molecular dynamics simulations in dichloromethane solution using explicit solvent molecules. Results derived from a 1 μs trajectory of the oxidized and deprotonated actuator indicate that the contraction occurs through a non-concerted mechanism in which each actuating units present in the system behave independently. The efficiency of the contraction process can be reduced by the presence of secondary conformational transitions in the calix[4]arene scaffolds. Accordingly, the drastic reduction of the molecular length expected during the contraction process can be limited by such transitions, which involve the rotational isomerism of a phenolate ring. However, such type of conformational transitions does not compromise the actuator power due to its intrinsic capacity to adopt compact molecular arrangements. On the other hand, the rate of the contraction process is influenced by the presence of solvent molecules, which have been found to reduce it by a factor of about 1000.

Keywords: ab initio calculations · calixarenes · polymers · redox chemistry · thiophenes

Introduction

The manufacture of artificial muscles able to mimic the performance and function of natural muscles has attracted great interest in fields such as chemistry, materials science, biophysics, chemical and mechanical engineering and, most recently, nanotechnology. In this context, conducting conjugated polymers (e.g. polypyrrole, polythiophene, polyaniline) have been successfully used to develop molecular actuators able to generate work upon consumption of energy. Thus, these materials undergo large alterations of their volume in response to electrically induced changes in oxidation state. The changes of volume can be due to the diffusion and intercalation of ionic species in the polymer bulk film,[1–3] which maintain the electro-neutrality during the oxidation process, or due to drastic conformational changes that are induced by electrical activation.[4–7]

Recently, a molecular actuator constituted by small thiophene oligomers (quaterthiophene) separated by calix[4]arene scaffolds (25,27-dihydroxy-26,28-dimethoxy calix[4]arene) was developed.[7] This promising material, hereafter denoted as poly(calix[4]arene bis-bithiophene), behaves as an "accordion-like" structure formed by rigid rods interconnected by hinge units, which is able to switch between an extended and a tightly contracted molecular conformation upon electrochemical activation (Figure 1).

The reversible actuation mechanism of this impressive artificial muscle was recently examined at the molecular level using quantum mechanical calculations and atomistic molecular dynamics (MD) simulations.[8] The conformational rearrangements that take place upon the electronic structure changes were explained by separating the oxidation of poly(calix[4]arene bis-bithiophene) in two different steps: oxidation of the quaterthiophene segments and deprotonation of the hydroxyl groups of the calix[4]arene units. Results allowed to conclude that the calix[4]arene scaffolds are the most active elements in the molecular actuation mechanism, where the electrostatic repulsions between their deprotonated oxygen atoms are responsible for the drastic length reduction of the oxidized polymer chains. However, the most important dynamical aspects of this muscle-like actuator remain still unknown, even though the understanding of its conformational dynamics would enable advances in fields

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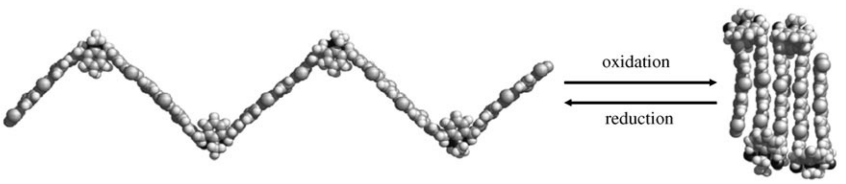

Figure 1. Reversible electrochemical molecular actuation mechanism of poly(calix[4]arene bis-bithiophene), which is constituted by rigid quaterthiophene oligomers separated by calix[4]arene flexible hinges. The extended and contracted arrangements characteristic of the reduced and oxidized states, respectively, are displayed in the left and right sides.

such as robotics, micro and nanotechnology and biomechanics. Unfortunately, experimental techniques are not able to provide detailed information about both the mechanism and dynamics of electromechanical molecular actuators. Therefore, the application of computer simulation techniques is essential to describe at the microscopic level the intrinsic actuation characteristics of poly(calix[4]arene bis-bithiophene).

In this study, we investigate the dynamics of oxidized poly(calix[4]arene bis-bithiophene) during the conformational contraction at the atomistic level. This has been performed by monitoring a polymer molecule in solution, which is the experimental environment in which the actuator responses take place, during a long MD simulation with full atomistic representation of both polymer and solvent. The MD trajectory was conducted for a microsecond, which has been estimated to be the lower limit of folding time for biological polymers.[9,10]

Results and Discussion

In a recent study, we reported control simulations of an oxidized polymer chain with deprotonated calix[4]arene units.[11] These simulations, which were conducted for 10 ns at 300 K, started from both extended and contracted arrangements. As expected the contracted arrangement was favored with respect to the extended one by several tenths of kcal mol^{-1}, which was in agreement with the recently reported mechanism.[8] However, no sign about the extended-to-contracted folding process was identified after 10 ns suggesting that higher time-scale simulations are required to cover the entire contraction. Accordingly, in this study a MD trajectory of 1 μs in dichloromethane solution has been carried out for the oxidized and deprotonated system by using the extended arrangement as starting geometry.

The dynamics of the contraction process has been monitored through the time evolution of the shortest distance between pairs of calix[4]arene rings that are not directly linked to the same quaterthiophene segment (computed as centroid-to-centroid distance). As the actuator considered in this work contains six calix[4]arene units, four of such distances have been identified, each distance corresponding to a single actuating unit (Figure 2a). The values expected for such distances in the fully-extended and a fully-contracted arrangements are about 44 and 9 Å, respectively.

As can be seen in Figure 2b, the measured parametric distances evolve without evidencing any correlation among them. This result suggests that the contraction of the actuator takes place through a non-concerted mechanism, in which all the actuating units behave independently. Furthermore, Figure 2b shows that the process of contraction is dif-

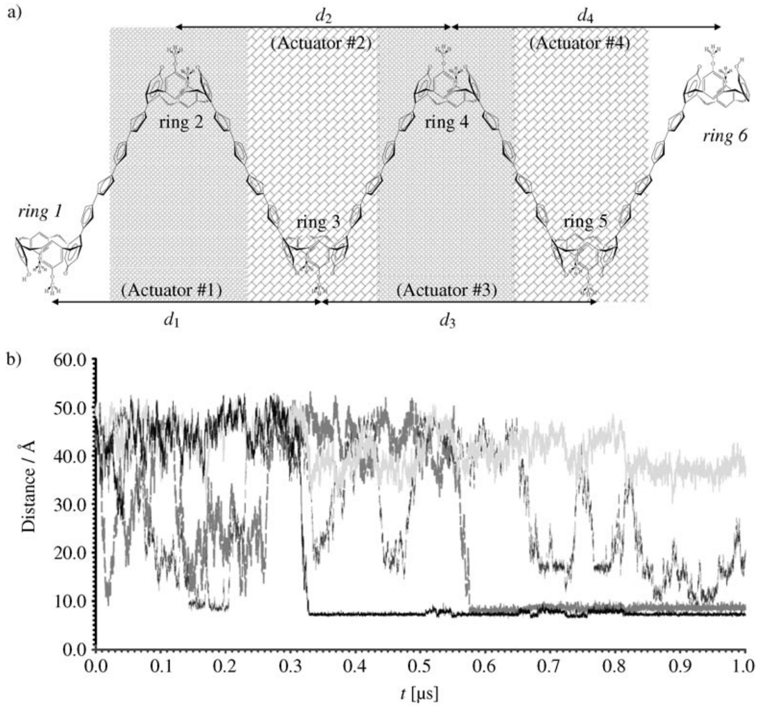

Figure 2. a) Schematic representation of the simulated actuator system. Each of the four central calix[4]arene rings constitutes an actuating unit, each of it is framed by filled background in the scheme. Each actuating unit can be represented by the distances between equivalent calix[4]arene rings that are not linked to the same quaterthiophene segment. Those distances are computed as centroid-to-centroid distance and named as d_n with n ranging from 1 to 4. b) Time dependent evolution of each parametric distance. The actuating units are represented as follows: d_1 (in dashed dark-grey), d_2 (in dashed black), d_3 (light grey) and d_4 (in black), respectively.

ferent for each actuating unit. Thus, the actuating unit number 4 undergoes a fast contraction after 0.32 μs of simulation, remaining in this state during the last 0.68 μs. The opposite behavior is displayed by the actuating unit 2, which shows several contractions and expansions during the 1 μs simulation. Some of these processes are considerably slow with respect to the contraction mentioned above for the actuating unit 4. For instance, the first contraction, which starts after 0.05 μs of simulation, takes more 0.1 μs. In addition, not only the extended but also the contracted arrangements present a complex dynamics, which is evidenced by the fluctuations of the centroid-to-centroid distance through the whole simulation. The behavior of actuating unit 1 is halfway between those of units 2 and 4. Thus, a complex dynamics involving several contraction and expansion processes are detected during the first 0.55 μs of simulation, while after this period undergoes a fast contraction remaining in this state the rest of the time. Finally, inspection to Figure 2b indicates that the actuating unit 3 remains in an extended arrangement during the whole simulation, no contraction process being detected along 1 μs.

Figure 3, which shows selected snapshots of the simulated actuator along the MD simulation, shows that the contraction of the oxidized and deprotonated actuator leads to a drastic one dimensional change in the direction of the molecular chain after 1 μs, that is, the molecular length is reduced by a factor of three. Furthermore, correlation between the snapshots displayed in Figure 3 and the parametric distances represented in Figure 2 indicates that the molecular conformation showed for 1 μs is very similar to that reached after 0.66 μs of simulation (not shown), while the snapshot displayed at 0.58 μs is similar to that obtained at 0.74 μs (not shown). Indeed, the arrangements displayed at 0.58 μs and 1 μs inter-change several times during the last part of the simulation, this reversible equilibrium being consequence of the dynamics of the actuating unit 3 (Figure 2).

A detailed analysis of the actuating unit 3 indicates that the conformation of the 4th calix[4]arene scaffold changes from "*cone*" to a partial cone, also called "*paco*"; this rotational isomerism was detected after 0.08 μs of MD simulation. In the *cone* conformation the four rings of the calix[4]arene scaffold point in the same direction, while the rotation of one phenolate ring with the two methylene bridges acting as hinges yields the *paco*.[12–14] In order to characterize the energetics of the *cone*-to-*paco* isomerism, quantum mechanical calculations have been applied on the model compound 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix[4]arene-25,27-diol. Figure 4 shows the *cone* and *paco* minimum conformations as well as the transition state (TS) that separates them obtained from ab initio geometry optimizations of the model molecule in the oxidized-deprotonated state. On the other hand, Table 1 lists the relative energies provided by density functional theory calculations of the three conformations considering the model molecule in three different electronic states: the neutral state, oxidized state and oxidized-deprotonated state.

As can be seen, the cone is the most stable conformation independently of the electronic state, while the relative stabilities of both the *paco* and TS decrease when the complex-

Table 1. Relative energies (in kcal mol^{-1}) of the *cone* and *paco* conformations, and the transition state (TS) that separates them, provided by DFT calculations for the different electronic states of 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix[4]arene-25,27-diol.

Electronic state	*cone*	TS	*paco*
neutral	0.0	9.1	2.0
oxidized	0.0	11.3	6.6
oxidized-deprotonated	0.0	34.5	28.1

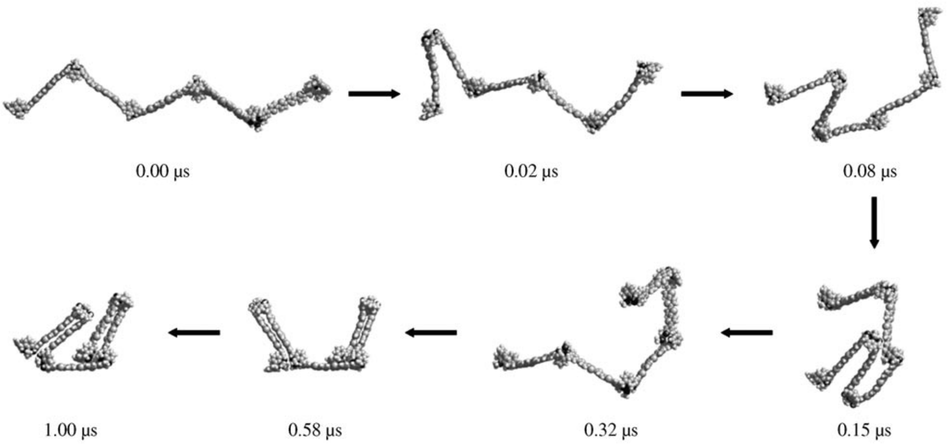

Figure 3. Atomistic representation of selected snapshots to illustrate the contraction of the actuator through the 1 μs MD simulation.

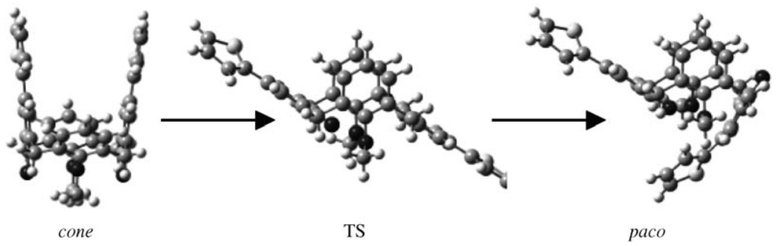

Figure 4. Atomistic representation of the *cone*-to-*paco* rotational isomerism of 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix[4]arene-25,27-diol in the oxidized and deprotonated state.

ity of the electronic state increases. Thus, in the neutral state the barrier of the *cone*-to-*paco* rotational isomerism is comparable to that experimentally determined for calix[4]arenes with different substituents,[15] that is, no special effect is produced by the thiophene substituents. Moreover, the high energy of the TS in the neutral reduced state, which is the rate limiting step of the *cone* inversion, agrees with the slow rate experimentally measured by ^{1}H NMR for this isomerization process in substituted calix[4]arenes.[15,16] Furthermore, oxidation of the two thiophene rings lead to increase the barrier by 2.2 kcal mol^{-1} and to destabilize the *paco* conformation by 4.6 kcal mol^{-1}. However, when the oxidation of the thiophene rings and the deprotonation of the calix[4]arene scaffold occur simultaneously, the stability of both the TS and the *paco* conformation are drastically reduced. Thus, the highest barrier is obtained in the state that produces the contraction of the actuator.

The overall results clearly indicate that the rate of the *cone*-to-*paco* transition becomes slower when the complexity of the electronic state increases. Accordingly, the inversion detected in the 4th calix[4]arene of the actuating unit 3 must be considered as an accidental infrequent event. Thus, there is only a very small chance of the calix[4]arene scaffolds to reach the high energy of the barrier and evolve towards the *paco* conformation. Indeed, the opposite *paco*-to-*cone* isomerization reaction, with a barrier of 6.4 kcal mol^{-1}, is also a slow rate process that, as expected, is not observed during the next 0.92 μs of simulation.

In any case, the features detected in the simulation of the actuator point out that, although the rotational isomerism of the calix[4]arene scaffolds is a slow and infrequent process, when it occurs the efficiency of the contraction is reduced, that is, the actuating unit involved in the isomerization is not allowed to contract (Figure 2b). Nevertheless, the final organization still shows a remarkable degree of contraction, as is evidenced in Figure 5. Comparison of the molecular length for the partially contracted arrangement obtained in this work with that provided for a totally-contracted arrangement illustrates that the former represents up to 80% of the potential maximum contraction. Thus, the conformational flexibility provided by the methylene bridges of the calix[4]arene allows new folding patterns that still permit the formation of compact arrangements. Therefore, the contraction mechanism permits secondary conformational transitions without compromising in excess its actuation mechanical work.

Another point which deserves examination is the influence of the explicit solvent molecules in the contraction of the actuator. For this purpose, additional MD simulations were performed considering an isolated polymer chain, that is, neglecting external forces. Interestingly, the chain, which was initially arranged in an extended conformation, totally contracts after a few nanoseconds of simulation, that is, typically 4.5 ns. These results allow the conclusion that the solvent plays a crucial role in the actuation of poly(calix[4]arene bis-bithiophene) reducing the rate of the contraction process by a factor of about 1000. Analysis of polymer···CH_2Cl_2 and CH_2Cl_2···CH_2Cl_2 contacts revealed that both the viscosity of the solvent and the molecular interactions between the polymer chain and the solvent molecules belonging to the first solvation-shell are responsible of that effect. This is reflected in Figure 6, which shows the partial radial distribution functions of polymer···CH_2Cl_2 contacts, that is, the probability of finding a polymer···solvent contact in terms of distance [$g(r)$], for the initial extended arrangement, the contracted obtained at the end of the 1 μs MD simulation and the totally-contracted structure. As can be seen, the height of the $g(r)$ at distances smaller than 10 Å is considerably smaller for the two contracted arrangements than for the extended one indicating that the amount of polymer···CH_2Cl_2 contacts is higher for the latter organization. On the other hand, the partial radial distribution functions of CH_2Cl_2···CH_2Cl_2 pairs were very similar for the three ar-

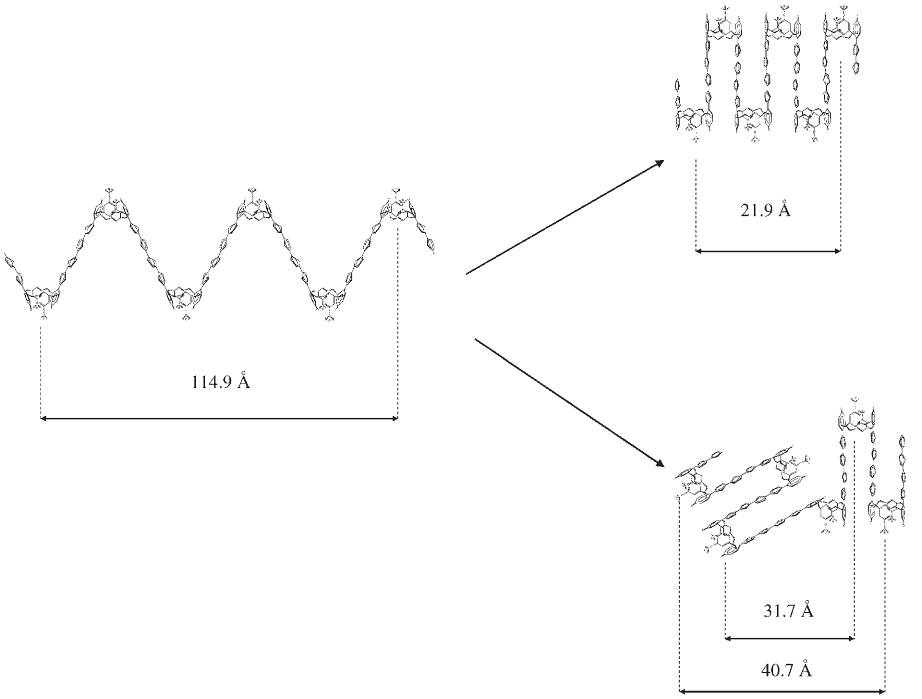

Figure 5. Scheme displaying the extended-to-contracted transition in absence (top) and presence (down) of secondary conformational transitions. The molecular length is provided for each arrangement. As can be seen in the former case the length is reduced by a factor of five, while in the latter one the length diminishes three times.

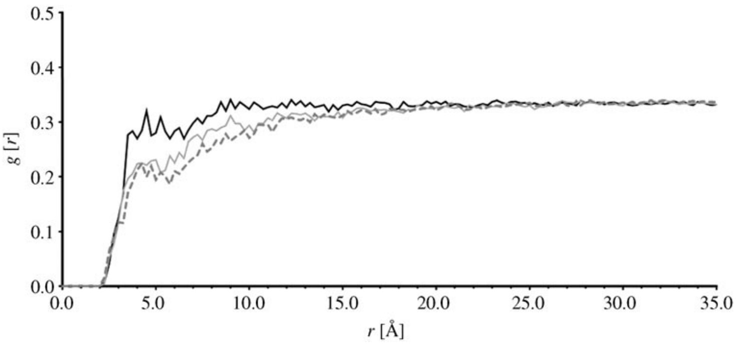

Figure 6. Partial distribution functions of the polymer···CH_2Cl_2 contacts for the extended (black), contracted (light dashed grey) and totally contracted (light grey) arrangements of the polymer chain. The distributions for the extended and contracted arrangements were calculated considering the first and the last 25 snapshots recorded from the 1 μs MD simulation, respectively. The distribution for the totally-contracted arrangement was calculated considering the last 25 snapshots recorded from an additional 10 ns MD simulation performed using such arrangement as starting geometry.

rangements of the polymer chain (data not show) suggesting that the contraction of the actuator does not affect to the structure of the bulk solvent.

Conclusion

We have performed a 1 μs MD trajectory of the oxidized and deprotonated poly(calix[4]arene bis-bithiophene) in dichloromethane solution, which is the experimental environment where the actuator responses take place, to provide an atomistic description of the contraction process. Results indicate that the actuating units containing in the polymer behave independently, the dynamics associated to the contraction being different in each case. The time required for the whole contraction process is slightly smaller than 1 μs, the molecular length being reduced about three times after this period. The contraction is greatly affected by both the solvent and the presence of secondary conformational transitions as the isomerization of the calix[4]arene, which may lead to reduce the rate of the contraction and to decrease the efficiency of the actuation, respectively. In summary, the deprotonation of the oxidized poly(calix[4]arene bis-bithiophene) produces a drastic molecular contraction that takes about 1 μs and occurs through a non-concerted mechanism in which all the actuating units act as independent entities.

Methods

Molecular dynamics simulations were performed by using the high performance parallel work program NAMD 2.5,[17] intensively using 512 CPUs for a single trajectory at the Barcelona Supercomputing Center (BSC). The bonded and van der Waals parameters for the calix[4]arene units were taken from literature,[18,19] whereas quaterthiophene blocks were kept rigid at the all-*anti* conformation. For the thiophene rings standard van der Waals parameters of AMBER99 libraries were employed.[20] The partial charges distribution were specifically developed for a chemical repetitive unit, that is, four thiophene rings and one calix[4]arene scaffold, in the oxidized and deprotonated state.[8] The solvent was represented with the OPLS3 model of dichloromethane.[21]

Atom pair distance cutoffs were applied at 14 Å to compute van der Waals interactions, that is, if two residues or a residue and a solvent molecule have any atom within 14 Å the interaction between the entire pair is evaluated. In order to avoid artifact discontinuities in the Lennard-Jones potential, a switch function was applied to allow continuum decay of energy when atom pair distances are ≥ 12 Å. The electrostatic interactions were computed using the non-truncated electrostatic potential by means Ewald summations. The real space term was determined by the van der Waals cut-off (14 Å), while the reciprocal term was estimated by interpolation of the effective charge into a charges mesh with a grid thickness five points per volume unit, that is, Particle-Mesh Ewald (PME) method.[22] All the bonds of the quaterthiophene were kept fixed to the distances determined at QM level[8] while bond lengths of the calix[4]arene units were constrained using the SHAKE algorithm.[23] The numerical integration step was 2 fs.

The system studied was built by placing a molecular actuator, constituted by six calix[4]arene rings and five quaterthiophene units, inside a previously equilibrated box with 10842 molecules of dichloromethane. Once the actuator was inserted, the dichloromethane solvent molecules overlapping any atom of the polymer were removed. The final system contained 32526 explicit atoms. Before starting the MD run series, 1×10^4 steps of energy minimization were performed to relax conformational and structural tensions. Different consecutive rounds of short MD runs were performed in order to equilibrate the density, temperature and pressure: 0.5 ns of NVT-MD (thermal relaxation) followed by 1 ns of isobaric relaxation (NPT-MD). Both temperature and pressure were controlled by the weak coupling method, the Berendsen thermobarostat[24] by using a time constant for heat bath coupling and a pressure relaxation time of 1 ps. The NPT-MD production run lasted up to 1 μs long and coordinates were saved every 1000 steps (2 ps intervals) for subsequent analysis.

Ab initio and DFT quantum mechanical calculations on 11,23-bis(thiophen-5-yl)-26,28-dimethoxycalix[4]arene-25,27-diol were performed using the Gaussian 03 computer program.[25] Geometry optimizations were carried out at the ab initio Hartree–Fock (HF) level using a 6–31G(d) basis set.[26] The *cone* and *paco* minimum energy conformations were derived from full geometry optimizations, while an appropriate constraint was applied to obtain the TS conformations. DFT calculations were performed using the following combination: the Becke's three-parameter hybrid functional[27] with the Lee, Yang and Parr[28] expression for the nonlocal correlation (B3LYP). Energies were obtained by performing single point energy calculations with the B3LYP method combined with the 6-311++G(d,p) basis set[29] on the geometries previously optimized at the ab initio HF level. The oxidized and oxidized-deprotonated states were calculated considering the unrestricted quantum-chemical formalism with triplet spin multiplicity, that is, allowing oxidation of the two thiophene substituents.

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