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## Controlled Isomerization of a Light-Driven Molecular Motor: A Theoretical Study

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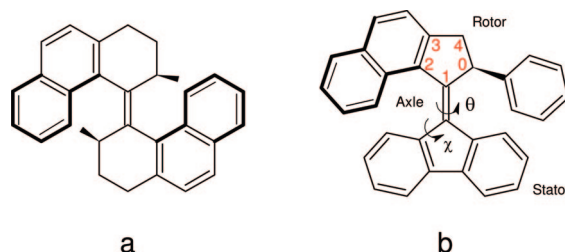
The rotational profiles of 9-(2,3-dihydro-2-phenyl-1*H*-benz[*e*]inden-1-ylidene)-9*H*-fluorene, a recently developed light-driven molecular motor, have been determined in the gas phase and chloroform solution for both the singlet and the triplet electronic states. Calculations in the gas phase were performed at the (U)B3LYP/6-31G(d) and (U)MP2/6-31G(d) levels, while the effects of the solvent were examined considering both implicit and explicit solvation models through self-consistent reaction-field and quantum mechanically/molecular mechanics schemes, respectively. The free energy barriers for the thermal helix inversion obtained in the gas phase (17.0 and 13.6 kcal mol<sup>-1</sup> at the UB3LYP and UMP2 levels, respectively) are in good agreement with the experimental estimation (21 kcal mol<sup>-1</sup>). On the other hand, the implicit solvation model led to a reduction of the barrier, while application of umbrella sampling with explicit chloroform molecules yielded a free energy barrier of 21.3 kcal mol<sup>-1</sup> for the ground state. The geometrical changes produced during the rotation, which are very significant, are discussed in detail.

## Introduction

Molecular machines are widespread in biological systems where a large collection of dedicated protein machines are performing complicated tasks such as cell division or intracellular transport. This kind of machine has inspired both (i) the use of these biological machines in artificial environments outside the cell; and (ii) the design of new synthetic motors at the same scale.<sup>1</sup> The building of artificial molecular motors and machines is essential for the development of bottom-up strategies aimed to construct nanoscale devices, a big challenge at the intersection of chemistry, physics, and biology knowledge. Over the past decade, the construction of new artificial molecular motors as well as the demonstration that energy consumption can produce mechanical work by inducing controlled and unidirectional motions that allow objects to be moved at large scale has been reported.<sup>2,3</sup>

One particular class of artificial molecular motors involves those that are light-driven. There are several advantages as compared to chemical or electrochemical means of stimulation: easy control of energy supply, selectivity, and precise energy application at nanometer resolution.<sup>4</sup> The first reported light-driven molecular motor was based on a symmetric biphenanthrylidene (Scheme 1a).<sup>5</sup> In this motor, the unidirectional rotary motion around the central double bond, which separates the lower and upper halves of the molecule (hereafter denoted the stator and the rotor, respectively), is reached by two olefin photochemical isomerizations, each one followed by a thermal conversion. A dramatic increase of the speed of rotation was achieved when the six-membered ring of the rotor is substituted

## SCHEME 1



by a five-membered ring. This structural modification results in a reduction of the free energy of activation for the two irreversible thermal steps in the rotary process, which is directly correlated with the speed of rotation.<sup>6</sup> To accelerate further the rotational speed, a second generation of light-driven molecular motors was recently introduced by Feringa and co-workers.<sup>6–8</sup> In these new motors, the stator was substituted by a fluorene moiety.<sup>6–8</sup> Interestingly, one of the molecular motors belonging to the second generation (Scheme 1b) was able to move large objects, such as a micrometer-sized glass rod, when it was used dispersed in a liquid crystalline film.<sup>9,10</sup> Specifically, it was found that ultraviolet irradiation at 365 nm induces a photochemical isomerization around the central double bond (motor axle) with inversion of molecular helicity (P→M). Subsequently, a thermal step with another helix-inversion (M→P) at 20 °C completes a 180° rotation. Accordingly, successive steps of irradiation and thermal relaxation induce the movement of the rotor with respect to the stator. Furthermore, in a very recent study, another fluorenyl motor was used to control the preferred helical twist sense of a poly(*n*-hexyl isocyanate), which was covalently attached to the polymer's terminus.<sup>11</sup>

Within a project devoted to controlling the conformational transitions between the folded states of individual peptide molecules by coupling a light-driven molecular motor to the

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main chain and/or side chain of selected residues, we are currently interested in characterizing the rotational profile of 9-(2,3-dihydro-2-phenyl-1*H*-benz[*e*]inden-1-ylidene)-9*H*-fluorene (Scheme 1b), abbreviated NA9PH, using theoretical methods. Thus, both the demonstrated ability to move big objects and the simplicity to induce controlled rotation under ultraviolet irradiation reinforce this molecule as a potential inductor of such conformational transitions. Within this context, Assfeld and co-workers<sup>42</sup> used the QM/MM-SCRF scheme to investigate the conformational changes in a peptide induced by a dye attached as a side chain. The rotational profile of NA9PH has been investigated in detail using two different but complementary approaches. First, quantum mechanical calculations in the gas phase and implicit chloroform solvent have been performed to determine the free energy profiles for the complete rotation cycle. After this, semiempirical QM/MM molecular dynamics simulations<sup>12</sup> have been carried out using the umbrella sampling methodology<sup>13</sup> and considering explicit chloroform molecules to describe the solvent. Results have been compared to available experimental data reported in previous investigations.<sup>7</sup>

## Computational Methods

**Gas-Phase Calculations.** Starting molecular geometries were obtained from experimental crystallographic data<sup>7</sup> and full geometry optimizations in the gas phase, which were performed at different quantum mechanical levels, for the singlet and triplet states, hereafter denoted NA9PH(S) and NA9PH(T), respectively. Specifically, geometries were initially optimized using the PM3<sup>14,15</sup> semiempirical method and subsequently reoptimized using the density functional theory (DFT) method. All DFT calculations were carried out using the Becke's three-parameter hybrid functional (B3)<sup>16</sup> with the Lee, Yang, and Parr (LYP)<sup>17</sup> expression for the nonlocal correlation, combined with the 6-31G(d) and 6-31+G(d,p) basis sets.<sup>18</sup> The restricted and unrestricted formalism of the semiempirical (PM3 and UPM3) and DFT methods (B3LYP and UB3LYP) was considered for the singlet and triplet states, respectively. Frequency calculations of all of the stationary points were performed to calculate the zero-point vibrational energies (ZPVE) and both the thermal and the entropic corrections. All computed free energies were obtained using the unscaled harmonic vibrational frequencies.

After geometry optimization, the internal rotation of NA9PH(S) and NA9PH(T) was investigated by scanning the rotational dihedral angle  $\theta$  (Scheme 1b) from 0° to 360° in steps of 15° using the flexible rotor approximation. Thus, each point of the path was derived from a constrained geometry optimization, in which the rotational dihedral angle  $\theta$  was fixed. A better description of the rotational energy profiles was achieved by performing single point energy calculations at the second-order Møller–Plesset perturbation level<sup>19</sup> with the 6-31G(d) basis set, that is, MP2/6-31G(d) and UMP2/6-31G(d) levels for single and triplet states, respectively. For the stationary points, free energies were determined by combining the electronic energies computed at the (U)MP2/6-31G(d) level with the thermodynamic corrections derived from the (U)B3LYP/6-31G(d) frequencies.

All quantum mechanical calculations presented in this work were performed using the Gaussian 03 computer program.<sup>20</sup>

**Solvation Models.** The influence of the chloroform solvent on the energy profiles associated with the rotation of the dihedral angle  $\theta$  has been investigated using two different models. The first one is a self-consistent reaction-field (SCRF) model, which describes the solute at the quantum mechanical level, while the

solvent is represented as a dielectric continuum. Specifically, we chose the polarizable continuum model (PCM) developed by Tomasi and co-workers to describe the solvent.<sup>21,22</sup> The PCM represents the polarization of the liquid by a charge density appearing on the surface of the cavity created in the solvent, that is, the solute/solvent interface. PCM calculations were performed in the framework of the (U)B3LYP/6-31G(d) level using the standard protocol, considering the dielectric constant of chloroform ( $\epsilon = 4.9$ ) and the geometries optimized in the gas phase. Thus, previous studies indicated that solute geometry relaxations in solution and single point calculations on the optimized geometries in the gas phase give very similar free energies of solvation.<sup>23–25</sup> In the second model, which was applied in mixed semiempirical quantum mechanics/molecular mechanics (QM/MM) calculations, the solvent was described with explicit chloroform molecules using the model reported by Kollman and co-workers.<sup>26</sup>

**QM/MM Calculations.** QM/MM calculations were performed using the umbrella sampling<sup>27</sup> procedure. For this purpose, a starting configuration of the system under study was prepared for each value of the dihedral angle  $\theta$  scanned in the gas phase. Specifically, the NA9PH was constructed using the LEaP program from the Amber 9 suite,<sup>28</sup> and solvated in a box with enough chloroform molecules to allow  $\sim 30$  Å of buffer region around the solute. The number of chloroform solvent molecules contained in the simulation box ranged between 2530 and 2660 depending on the initial NA9PH geometry. The general Amber force field parameters (GAFF)<sup>29</sup> were used for all classical calculations, the RESP charges (restrained electrostatic potential)<sup>30,31</sup> being explicitly derived for value of the dihedral angle  $\theta$ . The electrostatic potential obtained at the Hartree–Fock level of theory with the 6-31G(d) basis set<sup>18</sup> was used to fit the RESP atomic partial charges.

Initially, each starting configuration was relaxed for 100 ps (2 fs time step). After this, the system was heated from 0 to 300 K during a 200 ps of simulation using the Langevin thermostat with a collision frequency of 1 ps<sup>−1</sup>, and then brought to 1 atm pressure for another 500 ps using a pressure relaxation time of 1 ps. Next, the NA9PH was transformed into a quantum molecule (PDDG/PM3<sup>32</sup> and DFTB/SCC-DFTB<sup>33,34</sup> semiempirical quantum mechanical description) using the QM/MM module available in Amber 9. The system was then equilibrated by running another 50 ps with a NPT ensemble simulation. In all of these simulations, the geometry of the NA9PH molecule was kept restrained using a force constant of 100 kcal/mol. The SHAKE algorithm<sup>35</sup> was used to constrain the covalent bonds involving hydrogen atoms in all classical and QM/MM simulations. The equilibrated systems were used as starting points for the determination of the potential of mean force (PMF).

The PMF provided by the umbrella sampling<sup>27</sup> procedure was calculated using a total of 26 windows. A harmonic biasing potential of 30 kcal/mol was applied as umbrella potential with a minimum located at each scanned value of the dihedral angle  $\theta$ . QM/MM production runs of 0.5 ns using both the PDDG-PM3<sup>32</sup> and the SCC-DFTB<sup>33,34</sup> Hamiltonians for the solute were performed to extract 25 000 bins and used to acquire statistics at each window. The total QM/MM simulation time used to determine the whole PMF was 13 ns. The bins obtained from the 26 windows were unbiased and combined using the weighted histogram analysis method (WHAM)<sup>36–38</sup> to generate the PMF.

## Results and Discussion

**Equilibrium Geometries in the Gas Phase.** Complete geometry optimizations of NA9PH(S) and NA9PH(T) were

**TABLE 1: Relevant Geometrical Parameters (See Text) for the Most Stable Structures of NA9PH(S) and NA9PH(T) Obtained in the Gas Phase Using Different Theoretical Procedures**

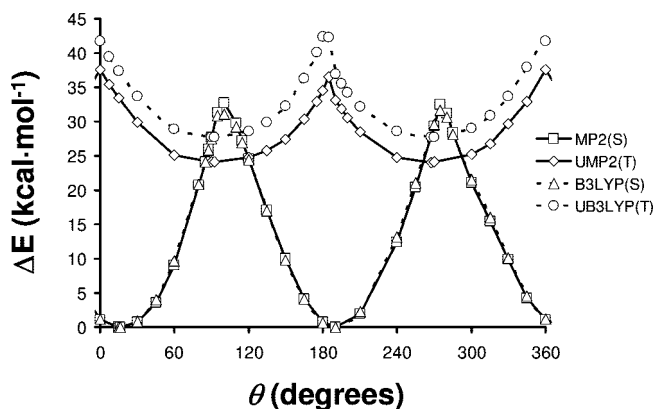
	NA9PH(S)				NA9PH(T)		
	PM3	B3LYP 6-31G(d)	B3LYP 6-31+G(d)	exp. <sup>a</sup>	UPM3	UB3LYP 6-31G(d)	UB3LYP 6-31+G(d)
$\theta^b$	7.9	16.1	16.3	13.4	90.0	92.5	91.5
$d^c$	1.348	1.369	1.370	1.357	1.444	1.466	1.466
$\chi^b$	10.2	3.5	3.6	-1.3	0.4	-3.7	-3.6
$P^{b,d}$	105.4 (T <sub>1</sub> <sup>0</sup> )	94.0 (E <sup>0</sup> )	94.3 (E <sup>0</sup> )	97.8 (E <sup>0</sup> )	144.0 (T <sub>1</sub> <sup>0</sup> )	73.5 (T <sub>1</sub> <sup>0</sup> )	74.2 (T <sub>1</sub> <sup>0</sup> )
$\tau_m^b$	28.5	33.3	33.2	31.7	0.2	7.5	7.5
$\Delta G^e$		0.0	0.0		- <sup>f</sup>	23.5	22.8

<sup>a</sup> From ref 7. <sup>b</sup> In degrees. <sup>c</sup> Bond length (in Å) associated with the molecular axle. <sup>d</sup> The conformation of the five-membered ring belonging to the rotor (Scheme 1b) is indicated in parentheses. Both the phase angle ( $P$ ) and the phase angle ( $\tau_m$ ) have been determined using the model reported in ref 39. <sup>e</sup> In kcal mol<sup>-1</sup>. <sup>f</sup> The PM3 semiempirical method describes poorly the relative stability between the surfaces calculated for the two electronic states (see text).

carried out in the gas phase, with the results summarized in Table 1. Geometry optimization of NA9PH(S) at the B3LYP/6-31G(d) and B3LYP/6-31+G(d) levels yields results close to those determined by X-ray crystallography,<sup>7</sup> the latter being included in Table 1. The optimized geometry values do not show a significant difference when a diffuse function is included in the basis set, especially on the scanned dihedral angle. Thus, the values found for the dihedral angle  $\theta$  (Scheme 1b) differ by only 2.7°, and the phenyl substituent at the stereogenic center was rightly predicted to prefer a pseudoaxial arrangement. Specifically, the isomer with the phenyl substituent and the naphthalene moiety located on the same side with respect to the plane defined by the fluorene ring is the most stable. Hereafter, this isomer will be denoted “Ax”. Furthermore, other important geometrical parameters such as the bond distance associated with the axle that separates the rotor and the stator (see Scheme 1b), the amplitude ( $\tau_m$ ) and phase angle ( $P$ ) that define the pseudorotational preferences of the five-membered ring in the rotor,<sup>39</sup> and the dihedral angle defined by the molecular axle and the fluorene ( $\chi$ , in Scheme 1b) also show good agreement with the values determined experimentally.<sup>7</sup>

On the other hand, the dihedral angles  $\theta$  obtained for NA9PH(T) at the UB3LYP/6-31G(d) and B3LYP/6-31+G(d) levels are 92.5° and 91.5°, respectively. Not much difference is observed with the inclusion of a diffuse function. In this structure, the phenyl substituent at the stereogenic center prefers pseudoequatorial arrangement, with the phenyl and naphthalene moieties lying on opposite sides of the planar fluorine. The bond associated with the molecular axle of this configuration, hereafter identified as “Eq”, is 0.097 Å larger than that of the Ax in NA9PH(S). This increment of the bond length will allow the upper naphthalene moiety of NA9PH(T) to slip over the fluorene more easily during the NA9PH half-rotation. We notice that the bond length reported in Table 1 is larger than that previously calculated by Vicario et al.<sup>7</sup> for a less stable NA9PH(T) structure ( $d_{C-C} = 1.375$  Å). On the other hand, the pseudorotational parameters reported in Table 1 for NA9PH(T) indicate that the five-membered ring of the rotor adopts a twisted conformation (T<sub>1</sub><sup>0</sup>) with a very low amplitude,  $\tau_m = 7.5^\circ$ . Finally, it is worth noting that DFT calculations predict that the free energy difference between the singlet and triplet states is 23.5 kcal mol<sup>-1</sup>, this difference being reduced to 19.9 kcal mol<sup>-1</sup> by applying single point calculations at the (U)MP2/6-31G(d) level.

Structural parameters obtained using the PM3 semiempirical method are, in general, in good agreement with those provided using the B3LYP functional (Table 1). Thus, the only remarkable discrepancy appeared on the conformation of the five-membered ring contained in the rotor. For the NA9PH(S), this ring was predicted to adopt the twisted T<sub>1</sub><sup>0</sup> and envelope E<sup>0</sup>



**Figure 1.** Rotational profiles in the gas phase calculated for the singlet (S) and triplet (T) states of NA9PH. Calculations were performed at the (U)B3LYP/6-31G(d) and (U)MP2/6-31G(d) levels (see text).

conformations (see Scheme 1b for atom numbering) at the PM3 and B3LYP/6-31G(d) levels, respectively, the latter puckering being that observed experimentally.<sup>7</sup> Similarly, the two methods differ in the twisted conformation predicted for the NA9PH(T), that is, T<sub>1</sub><sup>0</sup> and T<sub>4</sub><sup>0</sup> at the UPM3 and UB3LYP/6-31G(d) levels, respectively. Furthermore, this semiempirical procedure fails in the relative stability between the triplet and singlet states. Thus, (U)PM3 calculations predict similar energies for the surfaces associated with these two electronic states, while the ab initio and DFT methods used in this work indicate that the potential energy surface of the triplet state is significantly destabilized with respect to that of the singlet state. Despite these limitations, the overall results allow us to conclude that the PM3 Hamiltonian provides a satisfactory qualitative description of the structural properties of NA9PH using very reduced computational resources. This feature is essential for QM/MM calculations, which are very demanding from a computational point of view.

**Rotational Profiles in the Gas Phase.** The rotational profiles obtained in the gas phase by scanning the rotational dihedral angle  $\theta$  at the (U)B3LYP/6-31G(d) level are displayed in Figure 1, while the relative energies and free energies of the minima ( $\Delta E$  and  $\Delta G$ , respectively) and the barriers ( $\Delta E^\ddagger$  and  $\Delta G^\ddagger$ , respectively) are listed in Table 2. The profiles calculated for both NA9PH(S) and NA9PH(T) present two equivalent minima that follow a periodicity of 180°. In the profile calculated for NA9PH(S), the barrier occurs at  $\theta = 100.3^\circ$  with a relative free energy of  $\Delta G^\ddagger_S = 31.4$  kcal mol<sup>-1</sup>. On the other hand, UB3LYP/6-31G(d) calculations on NA9PH(T) provide the barrier at  $\theta = 182.1^\circ$  with  $\Delta G^\ddagger_T = 17.5$  kcal mol<sup>-1</sup>. The latter value shows a difference of  $\sim 5$  kcal mol<sup>-1</sup> with respect to



**TABLE 2:** Energy and Free Energy Barrier ( $\Delta E^\ddagger$  and  $\Delta G^\ddagger$ , respectively; in kcal mol<sup>-1</sup>) for the Rotation of the Dihedral Angle  $\theta^a$ 

	$\Delta E^\ddagger_S$	$\Delta E^\ddagger_T$	$\Delta G^\ddagger_S$	$\Delta G^\ddagger_T$	$\Delta G_{ST}$
Gas Phase					
(U)PM3	28.5	13.0	25.7	15.9	— <sup>b</sup>
(U)B3LYP/6-31G(d)	32.6	14.8	31.4	17.0	23.5
(U)MP2/6-31G(d)	31.4	10.6	33.0 <sup>c</sup>	13.6 <sup>c</sup>	19.9 <sup>c</sup>
Chloroform Solution					
PCM-UB3LYP/6-31G(d)	31.2	14.2	29.5	15.9	23.4
QM/MM PDDG-PM3			22.0		
QM/MM SCC-DFTB			21.3		
$\Delta G^\ddagger$ exp. <sup>d</sup>				21.0	

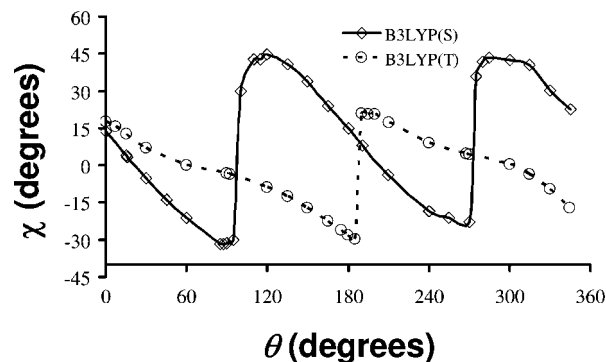
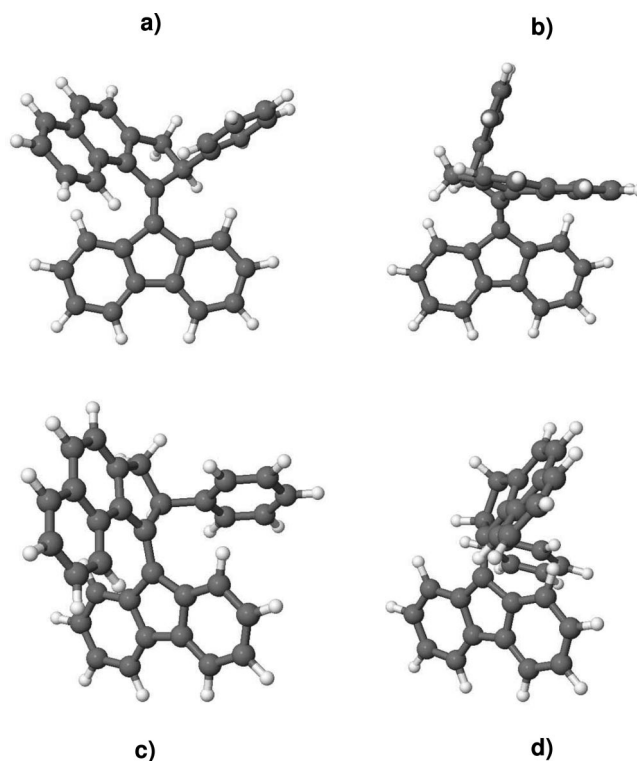
<sup>a</sup> Calculations were performed for the singlet and triplet electronic states of NA9PH. The free energy difference between the minimum energy conformations of the two states ( $\Delta G_{ST}$ ; in kcal mol<sup>-1</sup>) is also displayed. Both gas phase and chloroform solution environments are considered. <sup>b</sup> The PM3 semiempirical method describes poorly the relative stability between the surfaces calculated for the two electronic states (see text). <sup>c</sup> Obtained by adding the (U)B3LYP/6-31G(d) thermodynamic corrections to the electronic energies calculated at the (U)MP2/6-31G(d) level. <sup>d</sup> From ref 7.

estimations previously reported in the literature,<sup>7</sup> which were obtained using similar theoretical methods.

To provide a more accurate estimation of the rotational barrier, single point calculations were developed at the (U)MP2/6-31G(d) level using the (U)B3LYP/6-31G(d) geometries, with the relative free energies between stationary points being obtained by adding to the electronic energy the thermodynamic corrections derived at the latter level of theory. The resulting profiles, which are included in Figure 1, are in good agreement with the DFT ones, especially those obtained for the single state, that is,  $\Delta G^\ddagger_S = 33.0$  and  $31.4$  kcal mol<sup>-1</sup> at the UMP2/6-31G(d) and UB3LYP/6-31G(d) levels (Table 2), respectively. For the triplet state, UMP2/6-31G(d) calculations provide a stabilization of  $\sim 3.5$  kcal mol<sup>-1</sup>. This is reflected not only by the barrier  $\Delta G^\ddagger_T$ , which is  $3.4$  kcal mol<sup>-1</sup> smaller than that derived from the UB3LYP/6-31G(d) calculations (Table 2), but also by the difference between the energies of the minima obtained for the singlet and triplet states ( $\Delta G_{ST}$  in Table 2).

On the other hand, the rotational profiles derived from (U)PM3 semiempirical calculations (not shown) were very similar to those displayed in Figure 1, the free energy of the barrier being  $25.7$  and  $15.9$  kcal mol<sup>-1</sup> for NA9PH(S) and NA9PH(T), respectively. However, this semiempirical procedure fails in the relative stability between the triplet and singlet states. Despite the limitation detected for this semiempirical method, the different theoretical estimations reported in Table 2 are in good agreement with the experimental value of the free energy barrier of activation for the irreversible thermal helix inversion, at the second step of NA9PH half-rotation movement ( $\Delta^\ddagger G^\circ = 21.0$  kcal mol<sup>-1</sup>).<sup>7</sup>

Figure 2 shows the evolution of the dihedral angle  $\chi$  against the scanned dihedral angle  $\theta$  (Scheme 1b) for both NA9PH(S) and NA9PH(T). These profiles provide an approximated template of the flexibility associated with the coupling between the double bond that connects the rotor and the stator and the plane defined by fluorene moiety. Interestingly, there is a bending deformation in the fluorene as well as a deviation from the planarity of the two carbons involved in the double bond with respect to the fluorene plane, these distortions being larger when the rotated dihedral angle is closer to the barriers, that is, the sign of  $\chi$  undergoes a change during the semirotation. Moreover,

**Figure 2.** Evolution of the dihedral angle  $\chi$  as a function of the rotational dihedral angle  $\theta$ , in the gas phase and using the (U)B3LYP/6-31G\* level of calculation.**Figure 3.** Molecular structures of the minima and barriers of the rotational profiles calculated in the gas phase at the (U)B3LYP/6-31G(d) level for NA9PH: (a) minimum of NA9PH(S); (b) barrier of NA9PH(S); (c) minimum of NA9PH(T); and (d) barrier of NA9PH(T).

the two electronic states show a similar behavior, and the largest values reached by  $\chi$  are of  $\sim 45^\circ$  and  $\sim 30^\circ$  for NA9PH(S) and NA9PH(T), respectively. The distortion is smaller for NA9PH(T) than for NA9PH(S) because, as was discussed in the previous section, the bond length that connects the rotor and the stator is larger for the former than for the latter.

Figure 3a and b displays the molecular geometries of the minimum and the maximum found in the rotational profile calculated for NA9PH(S) rotational profile. A close inspection of these geometries suggests a  $sp^2 \rightarrow sp^3$  hybridization transition at the atoms that connect the rotor and the stator, which allows one to minimize the steric repulsion associated with the evolution from the minimum to the maximum. The deviation from planarity calculated for the C<sup>1</sup> atom of the rotor (Scheme 1b for numbering) in the lowest energy structure is  $7.3^\circ$ , which is in excellent agreement with the experimental value ( $5.25^\circ$ ).<sup>7</sup> The biggest deviation,  $24^\circ$ , is located close to the maximum of the gas-phase energy profile, where the sign of the dihedral angle

**TABLE 3: Time-Averaged Geometries Derived from QM/MM Calculations in Chloroform Solution for the Minimum and the Barrier of NA9PH(S)<sup>a</sup>**

	minimum		barrier	
	PDDG-PM3	SCC-DFTB	PDDG-PM3	SCC-DFTB
$\theta^b$	13.3 $\pm$ 0.1	14.3 $\pm$ 0.1	98.4 $\pm$ 0.0	100.1 $\pm$ 0.1
$d^c$	1.351 $\pm$ 0.000	1.383 $\pm$ 0.000	1.371 $\pm$ 0.000	1.415 $\pm$ 0.000
$\chi^b$	5.0 $\pm$ 0.2	5.2 $\pm$ 0.2	17.8 $\pm$ 0.1	16.2 $\pm$ 0.1
$P^{b,d}$	104.3 $\pm$ 0.2 (T <sup>0</sup> )	97.2 $\pm$ 0.2 (E <sup>0</sup> )	-54.0 $\pm$ 1.1 (E <sup>1</sup> )	-75.1 $\pm$ 0.8 (T <sup>0</sup> )
$\tau_m^b$	29.3 $\pm$ 0.1	26.2 $\pm$ 0.1	15.0 $\pm$ 0.1	18.1 $\pm$ 0.1

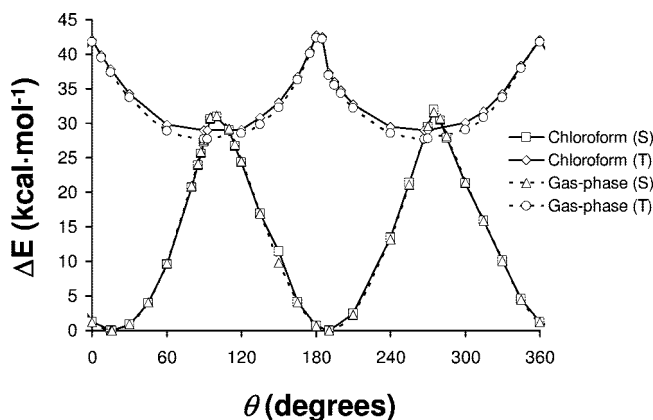
<sup>a</sup> The standard error of the mean is also displayed. <sup>b</sup> In degrees. <sup>c</sup> Bond length (in Å) associated with the molecular axle. <sup>d</sup> The conformation of the five-membered ring belonging to the rotor (Scheme 1b) is indicated in parentheses. Both the phase angle ( $P$ ) and the amplitude ( $\tau_m$ ) have been determined using the model reported in ref 39.

shows that the planarity is inverted, indicating an intermediate conformation. The flexibility in the five-membered ring of the rotor is also detected through the puckering variables used to define the conformation of the cycle. Specifically, a conformational transition  $E^0 \rightarrow T_1^0 \rightarrow E^0$  was predicted for this ring. On the other hand, the structures associated with the minimum and maximum of the rotational profile calculated for NA9PH(T) are depicted in Figure 3c and d, respectively. The dihedral angle  $\chi$  obtained for the triplet state should be mainly attributed to the distortion of the bond that connects the rotor and the stator, the maximum deviation from planarity determined for the C<sup>1</sup> atom being 23°.

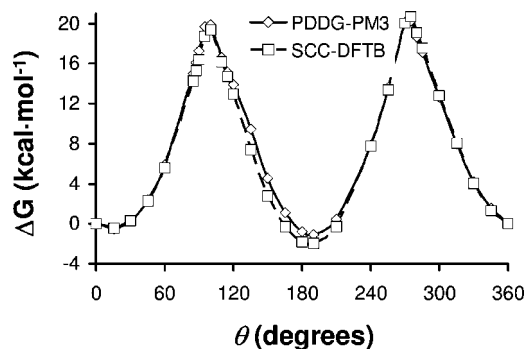
**Equilibrium Geometries in Chloroform Solution.** The influence of the solvent on the geometry of the minimum and the barrier was considered by running 2.5 ns of NPT MD trajectories in explicit chloroform solution under the QM/MM scheme, where NA9PH and chloroform molecules were quantum and classical, respectively. The starting geometries for NA9PH were those derived for the minimum and the barrier from the corresponding rotational profiles (see next section). Simulations of the barrier and the minimum were developed with and without restraints at the dihedral angle  $\theta$ . As was stated in the Computational Methods, QM/MM simulations were run with AMBER 9.0. Unfortunately, this package does not handle unpaired electrons correctly because it does not include the code for UHF calculations; that is, it calculates the energy of the individual electrons but not the difference between having two unpaired versus one paired and an empty orbital.<sup>40</sup> Accordingly, all QM/MM simulations were run on NA9PH(S), the influence of the explicit solvent molecules on the triplet state not being considered. Time-averages of the relevant geometrical parameters obtained for the more representative structures of NA9PH(S) using both PDDG-PM3 and SCC-DFTB Hamiltonians are reported in Table 3.

As can be seen, the geometry of the minimum in solution is very similar to that obtained in the gas phase (Table 1). Thus, the dihedral angles  $\theta$  and  $\chi$  predicted by the PDDG-PM3 method differ by only 5.4° and 5.2°, respectively, with respect to those obtained using the PM3 in the gas phase, while the differences between SCC-DFTB and B3LYP methods are 1.8° and 1.7°. On the other hand, the puckering predicted for the minimum in the gas phase was essentially identical to that obtained in chloroform solution; that is, PDDG-PM3 and PM3 predict the T<sub>1</sub><sup>0</sup> conformation, whereas SCC-DFTB and B3LYP prefer the E<sup>0</sup> one.

Table 3 also shows the more relevant structural parameters obtained for the barrier in chloroform solution. In the gas phase, this structure was predicted to be at  $\theta = 95^\circ$  by both the B3LYP and the PM3 methods, in solution the deviation with respect to this value ranging between 3° and 5°. Moreover, comparison between the geometries obtained for the minimum and the



**Figure 4.** Rotational profiles in chloroform solution calculated for the singlet (S) and triplet (T) states of NA9PH using the PCM method in the framework of the (U)B3LYP/6-31G(d) level. Rotational profiles obtained in the gas phase using the same theoretical level have been included for comparison.

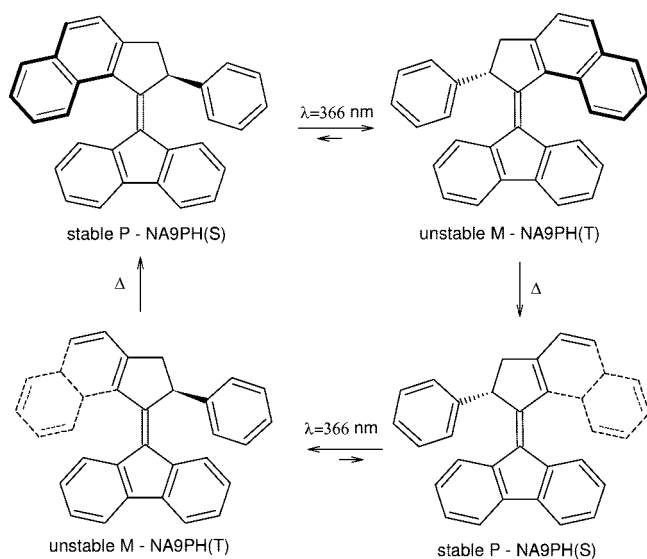


**Figure 5.** Rotational profiles in chloroform solution calculated for the singlet (S) state of NA9PH using QM/MM with umbrella sampling at PDDG-PM3 and SCC-DFTB levels.

barrier in chloroform solution reflects distortions similar to those discussed above for the gas phase. Specifically, the length of the bond that connects the rotor and the stator and the dihedral angle  $\chi$  increase, while the variation of the pseudorotational angle  $P$  evidences a conformational change of the five-membered ring located at the rotor.

**Rotational Profiles in Chloroform Solution.** The effects of the solvent on the rotational profile have been taken into account using implicit (singlet and triplet states) and explicit (singlet state) solvation models. The PMFs calculated using the PCM solvation model within the (U)B3LYP/6-31G(d) framework are displayed in Figure 4, which includes the profiles obtained in the gas phase at the same computational level for comparison, while Figure 5 details the profiles derived from QM/MM trajectories. The free energy barriers in solution obtained using PCM and QM/MM calculations are listed in Table 2.

## SCHEME 2



As can be seen in Figure 4, implicit solvation effects do not introduce significant changes in the rotational profile of NA9PH(S), the maxima and minima predicted in chloroform solution being very close to those in the gas phase. However, a stabilization of 1.9 and 1.1 kcal mol<sup>-1</sup> in the rotation free energy barrier of NA9PH(S) and NA9PH(T), respectively, was detected. Thus, the barriers predicted by the implicit solvation model are  $\Delta^{\ddagger}G_S = 29.5$  kcal mol<sup>-1</sup> and  $\Delta^{\ddagger}G_T = 15.9$  kcal mol<sup>-1</sup>, respectively. On the other hand, inspection of the QM/MM results obtained using the PDDG-PM3 and SCC-DFTB Hamiltonians reveals a free energy barrier of 22.0 and 21.3 kcal mol<sup>-1</sup>, respectively, for NA9PH(S).

A detailed analysis of the geometries recorded from QM/MM trajectories shows structural features similar to those found in the gas phase. Specifically, in the region close to the barrier, the carbon atoms involved in the bond that connects the rotor and the stator transform their hybridization from sp<sup>2</sup> to sp<sup>3</sup>, facilitating the rotation of naphthalene over the fluorene. This is evidenced by the increase of the average values of the bond length that involve such carbon atoms and the dihedral angle  $\chi$ . On the other hand, the average of phase angle  $P$  is completely unmeaning, even though the standard error of the mean shown in Table 3 is low, because the standard deviation obtained from statistical treatment shows a very large value (75° and 56° with the PDDG-PM3 and SCC-DFTB Hamiltonians, respectively). This indicates that in the region of the barrier, a wide set of conformations, very close in energy, are visited by the five-membered ring of the rotor during the restrained QM/MM MD trajectories. It should be noted that, typically, complex systems are dense in saddle points, and, therefore, transition states are not necessarily identified with such saddle points but ensembles of transition states.<sup>41</sup>

**Switching Mechanism.** In a previous work of Vicario et al.,<sup>7</sup> the rotation of the double bond that connects the rotor and the stator in NA9PH was described through a two-step mechanism (see Scheme 2). The first step consists of a photochemical isomerization with inversion of molecular helicity (P  $\rightarrow$  M). In this unstable NA9PH structure, which involves a conformational change of the five-membered ring located at the rotor, the exocyclic phenyl substituent is forced to adopt a strained pseudoequatorial arrangement. In the second step, the strain of the previous unstable structure is released through an irreversible thermal helix-inversion (M  $\rightarrow$  P), which produces a stable

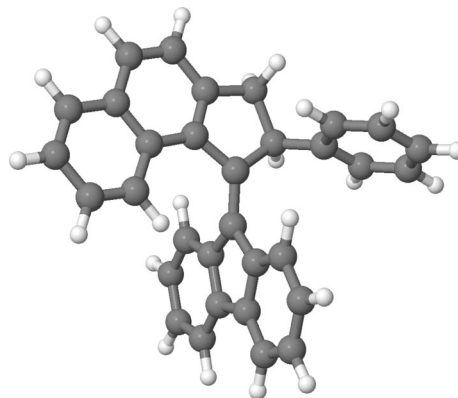


Figure 6. Structure obtained for the conical intersection between the two electronic states of NA9PH.

TABLE 4: Relevant Geometrical Parameters (See Text) for the Most Stable Structures of NA9PH Singlet–Triplet Conical Intersection Optimized in the Gas Phase Using CASSCF(2,4)/STO-3G and CASSCF(4,6)/STO-3G Theoretical Procedures

	CASSCF/STO-3G	
	(2,4)	(4,6)
$\theta^a$	73.0	72.6
$d^b$	1.490	1.491
$\chi^a$	-4.35	-3.87
$P^{a,c}$	-81.7	-80.3
$\tau_m^a$	1.56	1.68

<sup>a</sup> In degrees. <sup>b</sup> Bond length (in Å) associated with the molecular axle. <sup>c</sup> The conformation of the five-membered ring belonging to the rotor (Scheme 1b) is indicated in parentheses. Both the phase angle ( $P$ ) and the amplitude ( $\tau_m$ ) have been determined using the model reported in ref 39.

NA9PH structure. It is worth noting that there is a clear correspondence between this mechanism and the minima obtained in the rotational profiles calculated in this work. Specifically, the minimum of NA9PH(S) corresponds to the stable P structure, while the minimum of NA9PH(T) refers to the unstable M structure. The optimized structures reported in this work evidence that the rotation is facilitated by the elongation of the bond between the rotor and stator, that is, reduction of the double bond character. The barrier determined experimentally, 21 kcal mol<sup>-1</sup>,<sup>7</sup> is in good agreement with the theoretical estimations reported in this work, which unfortunately are limited by the relatively low accuracy of the computational levels used to describe this large molecule.

On the other hand, the switch from NA9PH(T) to NA9PH(S) is expected to occur after crossing the rotational barrier of the former through a conical intersection between the surfaces of the two states. To identify qualitatively the existence of this conical intersection between the ground and excited states, a geometry optimization of NA9PH in the gas phase using CASSCF(2,4)/STO-3G and CASSCF(4,6)/STO-3G has been carried out, with a total of 16 and 225 configurations, respectively. An intermediate structure, which is displayed in Figure 6, was located at about  $\theta \approx 73^\circ$  in both levels of calculation used (see Table 4). In this structure, the naphthalene moiety and the 5-membered ring of the rotor ( $\tau_m = 1.6^\circ$  and  $1.6^\circ$ , respectively) are planar, while the carbon atom of the fluorene involved in the bond connecting the rotor and the stator shows a small but non-negligible degree of bending; that is, it deviates 15.7° and 15.9° from planarity, respectively.



## Conclusions

In this work, we applied different theoretical methods to study the rotational profiles of the NA9PH light-driven nanomachine. The singlet and triplet states of NA9PH have been considered at the quantum mechanical level, while the solvent effect was described using two different procedures: (i) implicitly using the SCRF approach; and (ii) explicitly under the QM/MM scheme. Our (U)B3LYP/6-31G(d) estimate of the free energy barrier in the gas phase for the singlet and triple states was 31.4 and 17.0 kcal mol<sup>-1</sup> (33.0 and 13.6 kcal mol<sup>-1</sup> at the (U)MP2/6-31G(d) level), respectively. These values are in good agreement with the energy barrier experimentally determined for the thermal helix inversion (excited state) of NA9PH, that is, 21.0 kcal mol<sup>-1</sup>. The incorporation of solvent effects through the PCM method produces a reduction in the free energy barriers of few kilocalories, while the umbrella sampling study under the QM/MM SCC-DFTB scheme yields a free energy barrier of 21.3 kcal mol<sup>-1</sup> for the ground state. Analysis of barrier shows that the naphthalene and the five-membered ring of the rotor are planar, even though the bond that connects the rotor and the stator presents a significant deviation from the planarity in the atom belonging to the fluorene. This distortion allows an easy pass of the rotor over the stator.

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