Molecular Machines

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Unravelling the Shuttling Mechanism in a Photoswitchable Multicomponent Bistable Rotaxane**

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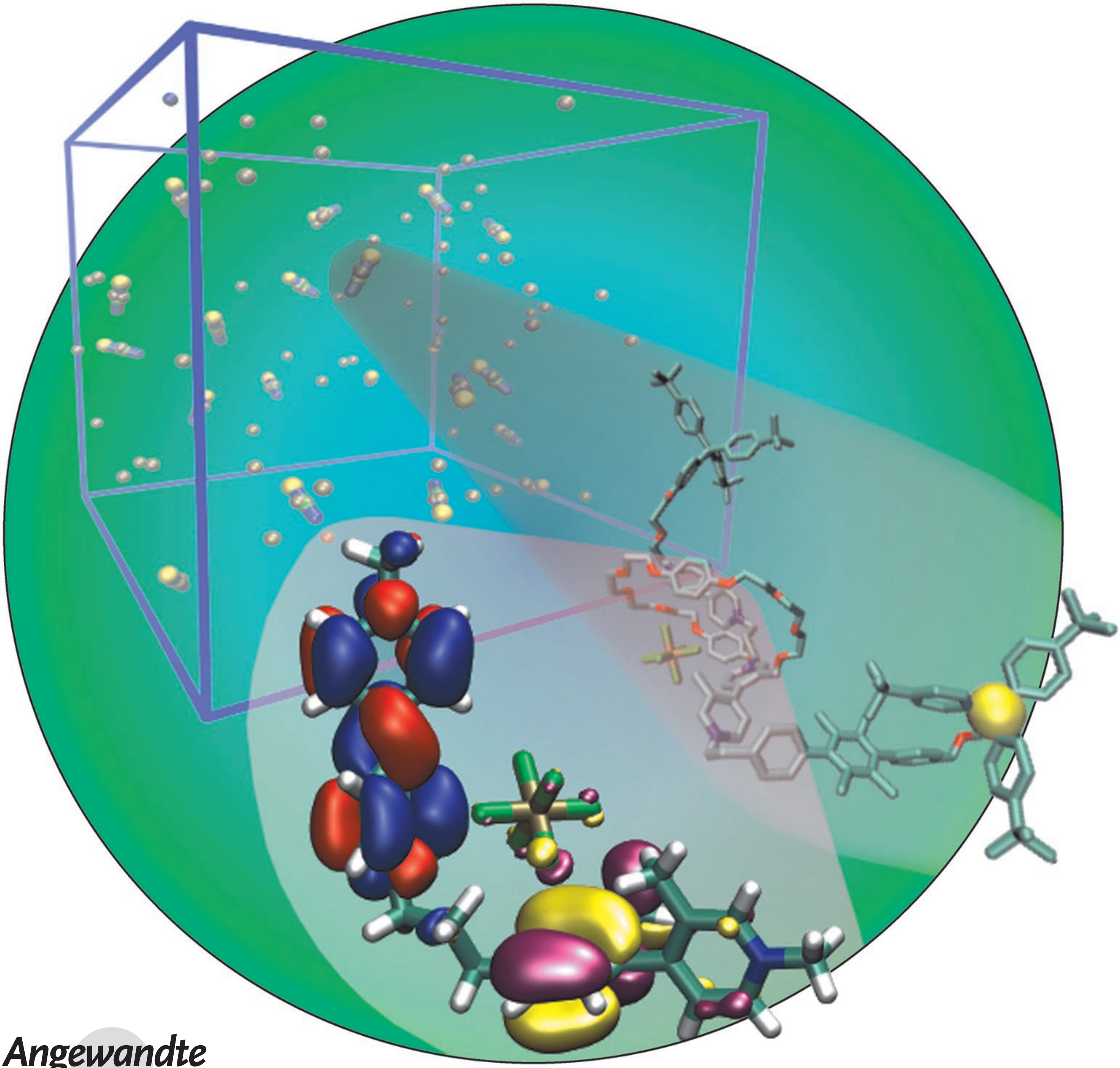
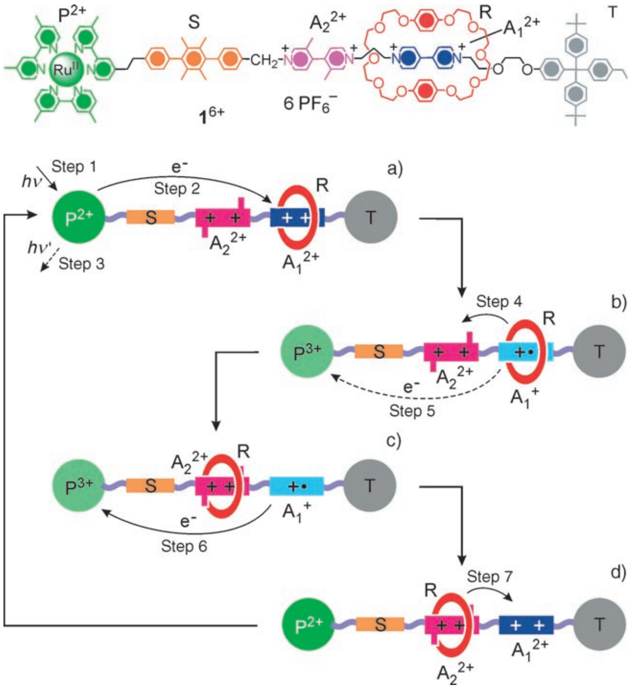


The bottom-up construction and operation of multicomponent molecular systems capable of performing specific, directional mechanical movements under the action of a defined energy input—namely, molecular machines—are currently under extensive investigation.[1,2] This research not only constitutes a fascinating challenge in the field of nanoscience, but could also find applications in areas such as material science, diagnostics, and medicine. However, despite the large number of molecular machines that have been constructed,[1–4] only a rather limited number of studies are available that are aimed at elucidating the details of the working mechanism and the factors that influence the molecular motions in this kind of systems.[5] Herein we present the results of a computational investigation on the mechanism of operation of a photoswitchable bistable rotaxane that functions as an autonomous molecular shuttle powered by visible light.[6] By using different computational techniques—ranging from first principles simulations to statistical analysis—we calculated the shuttling free energy, and successfully reproduced the experimental estimations for the relative stability of the different molecular co-conformations. We also calculated the shuttling relaxation time, which allowed the role of the counteranions to be explained. Intriguing properties that have not (yet) been observed are predicted, thereby suggesting directions for future studies.



Scheme 1. Structural formula of rotaxane $\mathbf{1}^{6+}$ and a graphical representation of its working mechanism as a "four-stroke" molecular shuttle powered by visible light: a) destabilization of the stable translational isomer, b) ring displacement, c) electronic reset, and d) ring reset.

The bistable rotaxane $\mathbf{1}^{6+}$ (Scheme 1) was specifically designed[7] to achieve photoinduced ring shuttling in solution. This compound has a modular structure: its ring component R is a π-electron-donating bis-*para*-phenylene[34]crown-10 macrocycle, while its dumbbell component is made of several covalently linked units consisting of a ruthenium(II)–polypyridine complex (P^{2+}) as the photosensitizer and stopper, a *para*-terphenyl-type rigid spacer (S), a 4,4′-bipyridinium (A_1^{2+}) and a 3,3′-dimethyl-4,4′-bipyridinium (A_2^{2+}) π-electron-accepting station, and a tetraarylmethane group as the terminal stopper (T). The Ru-based unit plays the dual role of a light-fueled power station and of a stopper, while the mechanical switch consists of the two electron-accepting stations and the electron-donating ring. Six hexafluorophosphate ions (PF_6^-) are also present as the counteranions to the positively charged rotaxane. The stable translational isomer of $\mathbf{1}^{6+}$ in the ground state is the one in which the R component encircles the A_1^{2+} unit, which is consistent with the fact that this station is a better electron acceptor than the other one.

The strategy devised to obtain the photoinduced shuttling movement of R between the two stations A_1^{2+} and A_2^{2+} is based on a "four-stroke" synchronized sequence of electronic and atomic processes (Scheme 1).[6] Excitation of the photoactive unit P^{2+} by light (step 1) is followed by the transfer of an electron from this unit to A_1^{2+} (step 2), a process which competes with the intrinsic decay of the P^{2+} excited state (step 3). After the reduction of A_1^{2+}, with the consequent "deactivation" of this station, the ring moves (step 4) by 1.3 nm towards A_2^{2+}, a step that is in competition with the back electron transfer from A_1^+ (still encircled by R) to the oxidized unit P^{3+} (step 5). Eventually, a back electron transfer from the "free" reduced station A_1^+ to the oxidized unit P^{3+} (step 6) restores the electron-acceptor ability to this radical cationic station. As a consequence of this electronic reset, a thermally activated back movement of the ring from A_2^{2+} to A_1^{2+} takes place (step 7). Steady-state and time-resolved spectroscopic experiments, together with electrochemical measurements recorded in acetonitrile solution, showed[6] that the absorption of a visible photon by $\mathbf{1}^{6+}$ can cause the occurrence of a forward and backward movement of the ring—that is, a full mechanical cycle, according to Scheme 1.

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From a computational viewpoint, direct simulation of the photoexcitation and electron transfer in such a large molecule are not feasible and, additionally, it would provide limited insight into the mechanism of the molecular motion. It is, therefore, more profitable to start analyzing the system just after the electron transfer has occurred, and focus on the ring displacement. The time scale of the shuttling movement and the complexity of the system require a multiscale approach. The general picture can indeed be obtained only by enlarging our focus progressively from a quantum mechanical (QM) treatment of the charged stations to a molecular mechanical (MM) description of $\mathbf{1}^{6+}$ in acetonitrile, and eventually to a coarse-grained (CG) description of several rotaxane molecules in solution.

Simple steric considerations reveal that the counterions, if bonded to the axle of the dumbbell, may act as a hindrance to the shuttling movement and hence may play an important role in determining the final efficiency of the molecular shuttle. QM calculations performed with GAUSSIAN03[8] by using the B3LYP/6-31g* approach and the polarizable continuum model[9] to include the effects of the solvent indicate a binding energy of 11.7 and 10.3 kcal mol^{-1} between a PF_6^- ion and the charged fragments of the dumbbell in the oxidized (ground) state (Figure 1) and in the reduced state (generated by excitation with light), respectively. A coarse-grained (CG) model composed of charged rods (mimicking $\mathbf{1}^{6+}$) and spheres (PF_6^-) at the experimental density (0.1 mM) can then be used to unravel the interplay between entropic and electrostatic effects that favor the dispersion of the PF_6^- ions over the formation of a bonded state (see the Supporting Information). Extended CG simulations with DL_POLY2.16[10] during which the interaction between the rods and the spheres was strengthened progressively reveal that, when the binding energy between the rods and the spheres exceeds 13 kcal mol^{-1}, there is a dynamic exchange of the PF_6^- ions, although at least one anion is always bonded to the dumbbell. The high binding energy (compatible with the experimental estimate for the shuttling barrier of 12 kcal mol^{-1})[6] and the CG results indicate that the decomplexation of the counteranion is a slow event and hence it might limit the efficiency of the nanomachine, a finding that is in agreement with experimental observations on related systems.[5c,11]

Further analysis of the results from the QM study reveals that the strong interaction between the bistable rotaxane and the counteranions arises mainly from polarization effects and from a sizeable charge transfer (0.17e) from the PF_6^- ion to the axle. As these effects cannot be reproduced by an MM force field, in the following simulations we constrained the PF_6^- ions away from the dumbbell so as to focus solely on the contribution of the ring displacement to the overall shuttling rate. The time scale necessary to simulate the shuttling process directly is barely achievable even by MM simulations. However, a quantitative comparison with experiments can be obtained by calculating the MM free-energy profile and then the shuttling relaxation time by solving the Fokker–Planck equation.[12] The ring displacement can be easily described by considering the projection of the center of mass of ring R on the axle of the dumbbell. The free-energy profile along this collective variable (L; Figure 2) can then be readily calculated by using the weighted histogram analysis method[13] (see the Supporting Information for further details). The relative stabilities of the two co-conformers in both oxidation states (Figure 2) agrees perfectly with the experimental estimates,[14] whilst no relevant barrier for the ring displacement from A_1^+

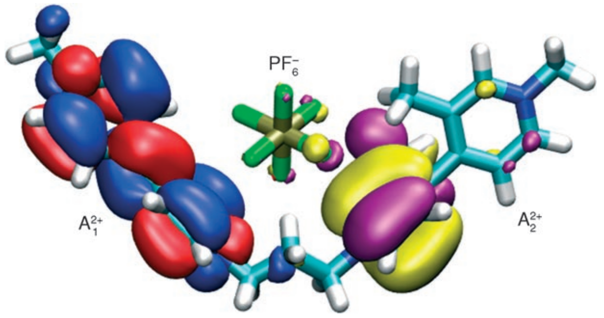

Figure 1. Graphical representation of the highest occupied molecular orbital (HOMO, yellow/purple) and lowest unoccupied molecular orbital (LUMO, red/blue) for the complex formed between a PF_6^- ion and the A_1^{2+} and A_2^{2+} stations. The LUMO is located on A_1^{2+}, in agreement with the experimentally determined electron affinity of the two stations. The strong interaction between A_2^{2+} and the PF_6^- ion is evidenced by the localization of the HOMO on both fragments. To reduce the computational workload, only the PF_6^- ion and the charged stations have been considered. Preliminary calculations including the macrocycle suggest a further increase in the binding energy.

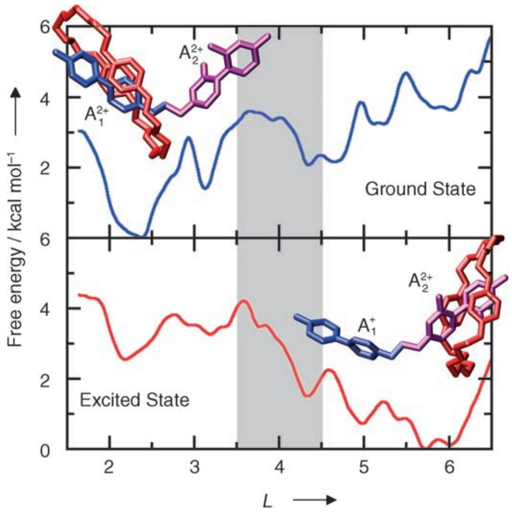

Figure 2. Free-energy profile computed for the oxidized (ground) state (top; see Scheme 1 a) and the reduced state generated by photoexcitation (bottom; see Scheme 1 c) of $\mathbf{1}^{6+}$ as a function of a collective variable (L) which describes the position of the ring along the axle of the dumbbell. The shaded area indicates the region in which the ring R encircles the hinge between A_1 (left) and A_2 (right). The insets show the typical atomic arrangements corresponding to the two co-conformers. For the calculations, the rotaxane was placed in a box of approximately 560 nm^3 filled with acetonitrile molecules (ca. 36000 atoms). The simulations were performed with the all-atom AMBER99[18] force field and the NAMD[19] code at 300 K and 1 bar. The overall simulation time for the calculation of the free energy was more than 200 ns, and the statistical analysis of the data confirms that all the orthogonal degrees of freedom are correctly sampled and that the accuracy of the profile is on the order of $k_B T$.

(Figure 2, bottom) was evident. We then used these free energies as inputs for a statistical description of the dynamics of L by using the Fokker–Planck equation (see the Supporting Information). The calculated time constant for the shuttling of the ring from A_1^+ to A_2^{2+} is approximately 20 ns at 300 K, which is more than 2000 times faster than the measured value (47 μs[6]). Given the complexity and flexibility of the system, this is an unexpected result: it suggests that ring displacement is not hindering the shuttling process, and hence is not crucial for determining the efficiency of the molecular machine.[15]

In summary, the free-energy calculations confirm the experimental findings on the relative stability of the different co-conformations in the two oxidation states of the bistable rotaxane. However, the observed shuttling kinetics cannot be reproduced computationally if the role of the counteranions is not explicitly taken into account. We have indeed shown that the anions are strongly bonded to the axle of the dumbbell component, and that their decomplexation from the rotaxane framework may be the rate-limiting step in the translational isomerization process. We have also demonstrated that the shuttling movement is almost barrierless in the absence of the counteranions. Therefore, if the interaction between the positively charged rotaxane and its counteranions could be weakened, for example, by changing the nature of the solvent or the counteranion, this molecular shuttle might work as a fast-switching, power-stroke nanomachine.[16,17] Experiments in this direction are not straightforward because of solubility issues and difficulties related to counteranion exchange with $\mathbf{1}^{6+}$. Nonetheless, experiments are already underway to test this hypothesis.

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