Conformational Control

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Shaping of a Conformationally Flexible Molecular Structure for Spectroscopy**

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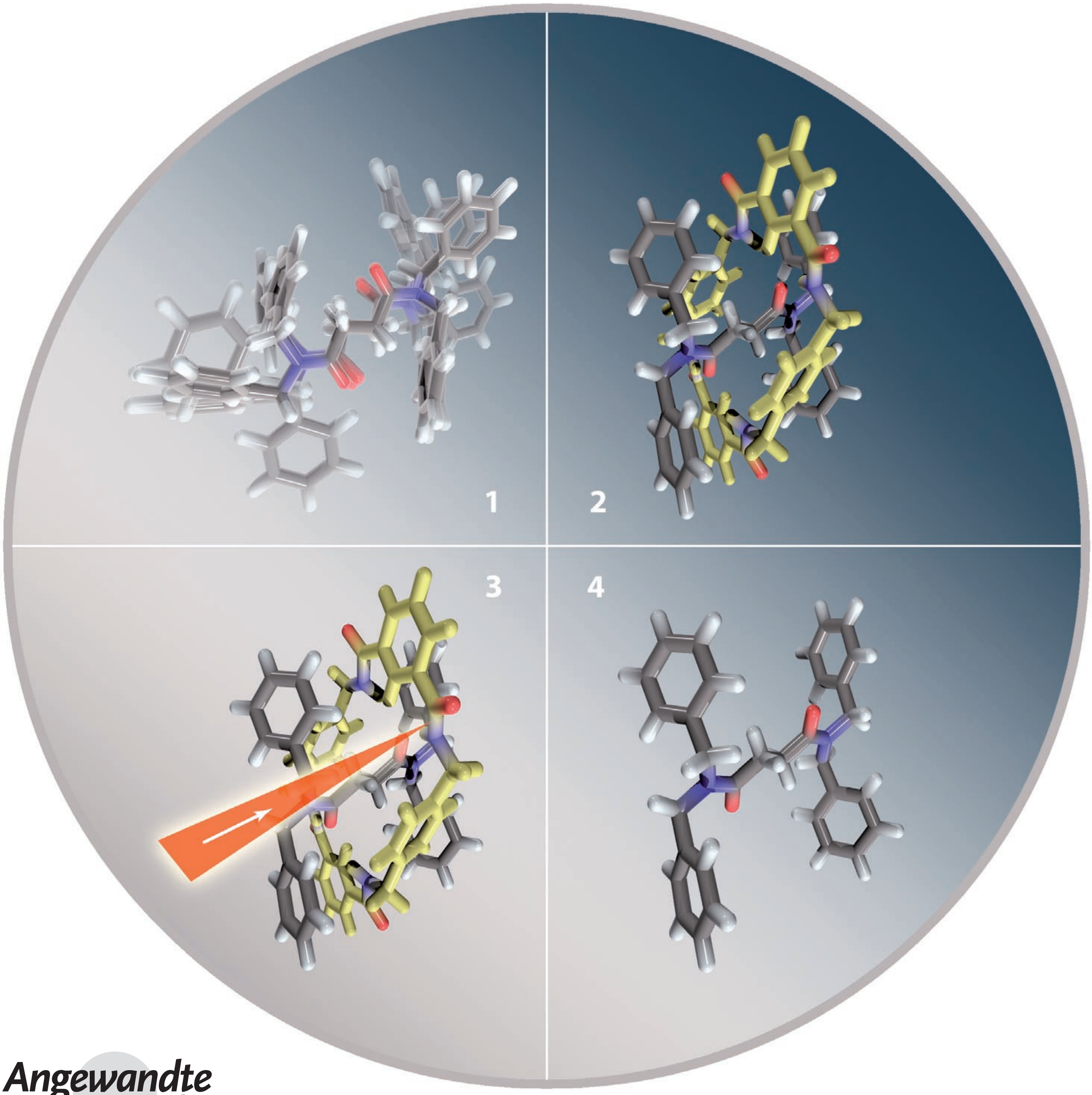

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High-resolution electronic excitation spectroscopy can provide unprecedented levels of experimental detail with regards to molecular potential energy surfaces, structure, and dynamics.[1–3] The power of this technique stems from the high sensitivity of excitation spectra to molecular shape (i.e. conformation) and the very narrow line widths which can be resolved with ideal substrates in such experiments. Unfortunately, the sensitivity to conformation means that high resolution results are only obtained when probing relatively small molecules with few internal degrees of freedom, or by manipulating conformation populations by redistributing the internal molecular energy. Increasing size, complexity and/or the number of accessible conformations (i.e. flexibility) of a molecule, along with introducing practical difficulties on cooling large molecules in a molecular beam, rapidly leads to the broadening of the excitation spectra and the loss of detailed spectral features. Herein we demonstrate an experiment that overcomes these problems by the active modification of the molecular potential energy surface. We exploit the architecture of a [2]rotaxane,[4–12] a composite molecule consisting of a macrocycle mechanically locked onto a dumbbell-shaped thread, and use noncovalent intercomponent interactions to heavily influence the conformational phase space of the latter, thus shaping or molding the molecular structure. The removal of the macrocycle in situ then allows the spectroscopic investigation of the liberated thread in its molded conformation. The thread is a relatively complex (and what would normally be flexible) molecule, which apparently remains confined to the restricted number of conformations imposed by the rotaxane during the course of the experiment.

Rotaxane **1** (Figure 1 b) consists of a benzylic amide macrocycle that is mechanically locked onto a succinamide-based thread (diamide **2**), Figure 1 a, and held in position by a network of hydrogen bonds and two bulky stoppers. Rotaxanes and catenanes based on this motif have been used to construct molecular shuttles[6,9,10,13] and motors.[14–16] The coconformational behavior of **1**, and particularly the angle and distance between the carbonyl groups of the macrocycle with respect to those of the thread, has been studied in detail by time-resolved two-dimensional IR spectroscopy.[17]

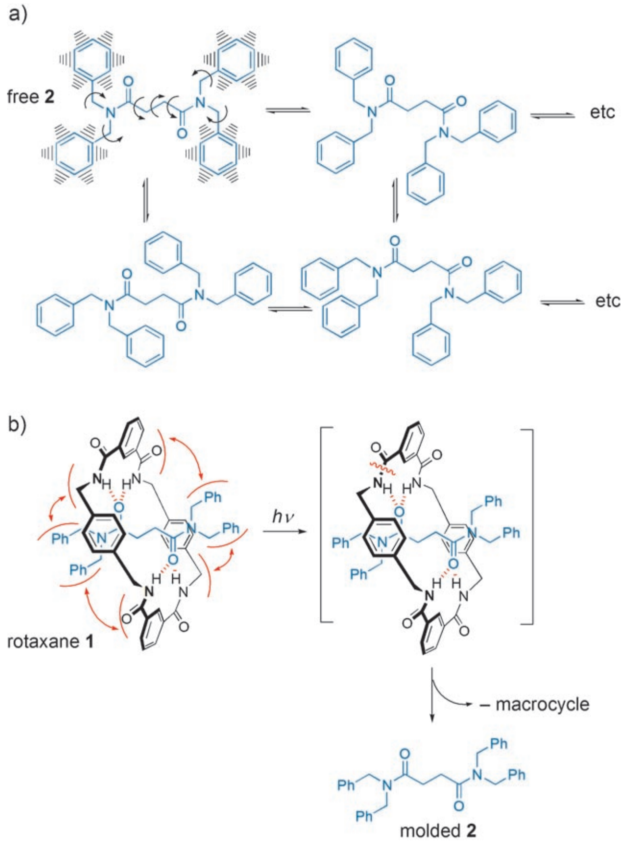

Figure 1. Architecture of a molecular-shaping device. a) A conformationally flexible diamide, free **2**. b) Incorporation of **2** into rotaxane **1** severely restricts the conformations that the diamide can adopt. Light-induced cleavage of the macrocycle in the gas phase leaves the free diamide in its conformationally shaped form, molded **2**. See text for details.

The experiments presented herein measure high-resolution UV spectra of molecules seeded into an argon supersonic expansion upon laser desorption from a graphite substrate.[18,19] In the expansion, the molecules are cooled rotationally and vibrationally, and remain trapped in the potential energy basin of one of the many conformations accessed at the temperature of ablation. We subsequently probed the conformations by (1+1) mass-resolved resonance enhanced two-photon ionization (R2PI) to obtain their mass-selected vibronic excitation spectra.

Figure 2 shows the gas-phase UV excitation spectrum of the laser-desorbed succinamide thread, free **2**. The molecule has four identical phenyl groups that act as UV chromophores. Accordingly, the spectrum in effect duplicates that of alkyl-substituted benzenes.[20] However, the full-width at half maximum (FWHM) of the resonances is much larger (about 30 cm^{-1}) than would be expected for a single conformation. Conformational broadening, a lack of complete cooling in the

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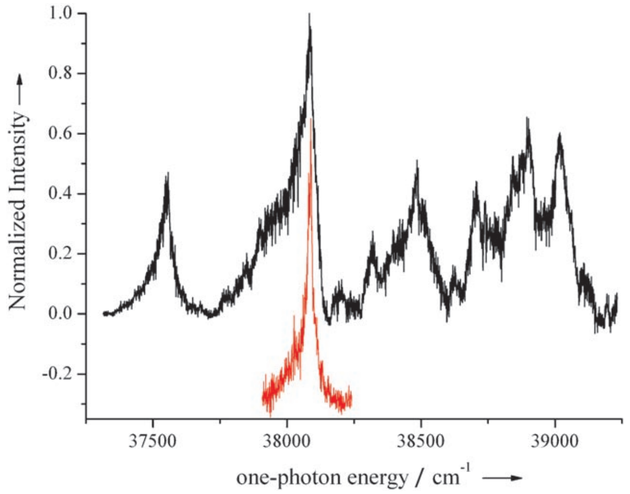

Figure 2. Resonance enhanced two-photon ionization spectrum of free **2** in the energy region 37250–39250 cm^{-1}. The resonances in the excitation spectrum are broad, with a FWHM of about 20–40 cm^{-1}. The red insert displays a part of the excitation spectrum that has been obtained under maximum optimized laser desorption and extensive averaging conditions (see Figure 5 a and accompanying text).

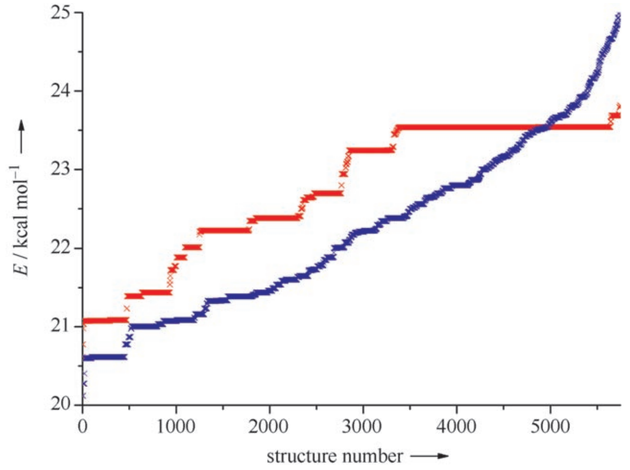

Figure 3. Energies of the optimized thread, free **2** (blue) and molded **2** (red). Conformations result from sampling during the three rapid annealing dynamics.

jet, or inequivalence of the phenyls incorporated in the thread could cause the broad peaks. The latter explanation is readily excluded by experiments performed on a slightly modified thread, free **3**, with only one UV chromophore, and the other phenyl groups replaced by cyclohexane groups (see the Supporting Information). The broad nature of the resonances most likely reflects the presence of many low-lying conformations of similar energy (see Figure 1 a), and is not surprising considering the shape, structure, and size of the thread. Molecular simulations confirm this picture.

Full mapping of the potential energy surface of rotaxane **1** and free **2** is not feasible. Herein we performed a series of annealings of the molecule from high temperatures (either 1200 or 400 K) using Molecular Dynamics (see the Supporting Information) aimed at exploring the minima of the potential energy surfaces. The two temperatures represent the effective temperature of ablation and a transient temperature reached during the initial cooling. The temperature was brought down to 0 K in 500000 steps of 0.5 fs, that is, 0.25 ns. During the annealing, structures were sampled every 0.1 ps and subjected to geometry optimization. Because of the rapid annealing, the sampling is non-Boltzmann and is biased by the conformations that are populated at high temperature. Figure 3 shows the distribution of the optimized structures of free **2** and of molded **2**. The latter was extracted from rotaxane **1** and subsequently optimized. Within a couple of kcal mol^{-1}, there is a very large number of different conformations that contribute to the broad linewidth observed experimentally. A striking difference of behavior of free **2** and molded **2** emerges. Whereas the conformations of free **2** form a continuum, the conformations of molded **2** are limited to only few discrete cases. The continuum of states for free **2** gives rise to the broader linewidths.

The accessible conformations of diamide **2** can be influenced by making it part of the [2]rotaxane **1** shown in Figure 1 b. In such a system, the conformational freedom of the thread is decreased by hydrogen bonding, π stacking, and steric interactions with the macrocycle, which restricts the number of accessible conformations of **2**. During the expansion in a supersonic beam, the internal energy of the rotaxane is reduced, and the thread is restrained to the conformation(s) dictated by the macrocycle. The instantaneous removal of the macrocycle (see below) releases a thread effectively molded by the macrocycle, and thus generates diamide **2** in a form, molded **2**, that has fewer conformations than those observed for free **2**. However, at room temperature the distribution of conformers of the liberated thread would be restored back to that of the free-thread ground state. By cooling in the supersonic expansion of the rotaxane, this redistribution is no longer (or is only partly) possible, and the thread is locked into the conformations present after removal of the macrocycle (i.e., molded **2**).

The experimental implementation of this approach is demonstrated in Figures 4 and 5. Figure 4 a depicts the time-of-flight mass spectrum of rotaxane **1** having a photocleavable macrocycle. The spectrum was obtained with nonresonant two-photon ionization at 193 nm, and shows a strong peak at the mass of the rotaxane **1** molecular ion (1008 amu). Thus it is possible to bring the intact rotaxane into the gas phase. Separate experiments at 193 nm on the thread (not shown) show that, under the same conditions as employed in Figure 4 a, the thread is also nonresonantly ionized by two photons. The absence of a peak in the time-of-flight spectrum of rotaxane **1** at the mass of the thread (476 amu) thus demonstrates that a) there is no free thread present in the sample as an impurity, and b) laser desorption does not produce partial dissociation of rotaxane **1** into thread **2**.[21] Additional support for the latter conclusion is found in the observation that the relative intensities of the peaks in the time-of-flight spectrum are independent of the intensity of the desorption laser.

To remove the macrocycle from rotaxane **1** in situ, we employed a laser beam with a wavelength of about 265 nm

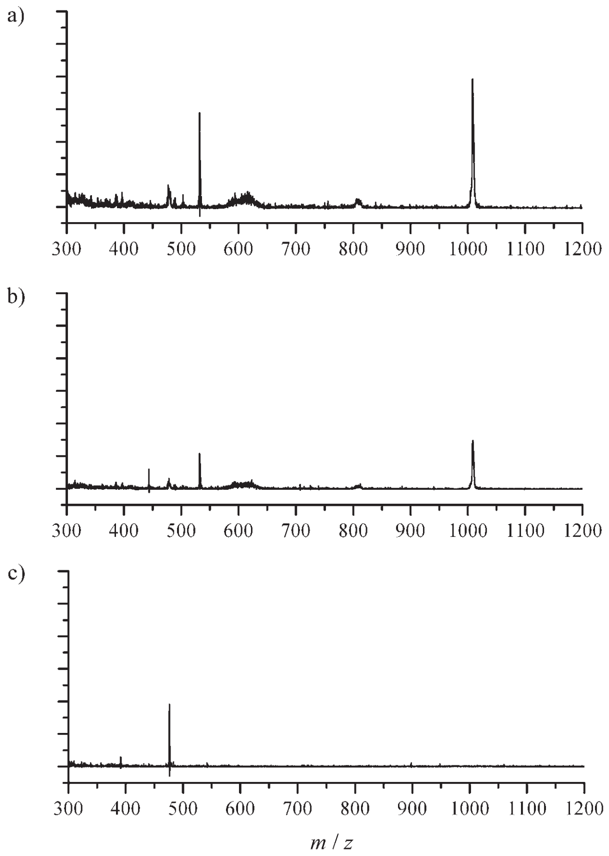

Figure 4. Photoionization mass spectra of laser-desorbed, jet-cooled rotaxane **1**. a) Spectrum obtained after nonresonant two-photon ionization at 193 nm. The peak at 1008 amu corresponds to the parent mass of the intact rotaxane. b) Spectrum after dissociation of the macrocycle by 265-nm excitation, followed after 100 ns by ionization of the species present in the molecular beam by non-resonant two-photon ionization at 193 nm. c) Spectrum after resonant two-photon ionization at 262.5 nm. Spectra (a) and (b) have the same vertical axis, and were obtained with the same intensity of the 193 nm beam. Spectra (b) and (c) were recorded with the same intensity of the 265 nm and 262.5 nm beam, respectively, but their vertical scales differ.

fired 100 ns before the 193 nm probe beam. Dissociation wavelength and timing refer to the particular conditions employed in recording the spectrum shown in Figure 4b. In separate experiments, we varied the wavelength of the dissociation laser and the time delay between dissociation and probe laser, but this did not lead to discernible differences. Upon absorption of a 265 nm photon, the macrocycle is photodissociated (see the Supporting Information), and the liberated but molded thread is produced (molded **2**). Figure 4b shows the time-of-flight spectrum of the rotaxane probed at 193 nm after removal of the macrocycle. The *m*/*z* 1008 peak for the rotaxane is depleted by up to 75%, as is the macrocycle peak at *m*/*z* 532. Both peaks decrease owing to photodissociation of the macrocycle upon 265-nm absorption. Figure 4c shows the effect of turning off the 193 nm laser and tuning the dissociation laser to 262.5 nm (ca. 38200 cm^{-1}), a wavelength that is resonant with the thread (Figure 2). This spectrum only shows a peak at the mass of the thread (476 amu) that is liberated by photodissociation of the macrocycle. From the absence of peaks at higher masses, we can conclude that under these experimental conditions, one-photon photodissociation overwhelmingly dominates the excitation dynamics of rotaxane **1**, and does not leave any room for a noticeable contribution of direct two-photon ionization.

As a measure for the efficiency of the conformational shaping process, the R2PI excitation spectrum of the thread was investigated. Figure 5a shows part of the excitation spectrum of the pristine thread molecule, free **2**, that was recorded under laser desorption conditions optimized to give resonances with the smallest possible width.[22] It thus is slightly different from the corresponding region in Figure 2. Figure 5b shows the analogous part of the spectrum after the macrocycle is removed (i.e., molded **2**). This spectrum was obtained by monitoring the mass of the thread in the time-of-flight spectrum of Figure 4c under the same optimized laser desorption conditions employed for Figure 5a. It is clear that the two spectra are considerably different, as is most directly visible in the red wing of the 38085 cm^{-1} region. In a more extensive analysis, we find that Figure 5a and b can be fitted quite adequately by the sum of two Gaussian functions that we associate with the distribution of accessible conformations. Both Gaussian distributions significantly more narrow for molded **2** than for free **2**. Moreover, the low-energy Gaussian distribution of molded **2** is shifted towards higher excitation energies.

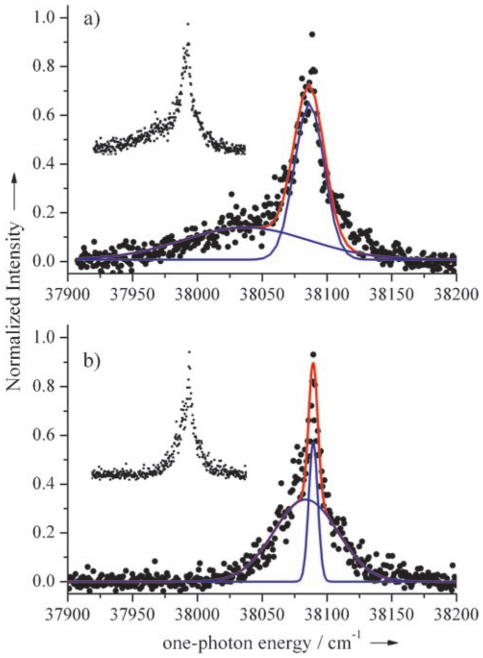

Figure 5. a) Enlarged excitation spectrum of the conformationally flexible diamide thread, free **2**. b) The same region of the excitation spectrum for the thread molded **2** that has been generated from rotaxane **1** after photodissociation of the benzylic amide macrocycle. Each spectrum is fitted to a sum (red) of two Gaussian distributions (blue). The insets display the same but unfitted data.

The excitation spectrum of the thread thus changes dramatically when it is embedded in the benzylic amide macrocycle, and the macrocycle is removed in the collision-free part of the expansion by photodissociative absorption. Because the conformational freedom of the thread has now effectively been diminished by its incorporation in the rotaxane, the width of the resonant features and the accessible excitation energies are reduced considerably. This reduction in width leads us to conclude that photodissociation of the macrocycle does not warm up the thread, and that the major part of the energy that goes into the rotaxane is only used to release the macrocycle. In Figure 5, the reduction in the width of the resonances is demonstrated using the vibronic band in the excitation spectrum that has the largest intensity. A similar reduction is observed for the other resonances in the excitation spectrum, in particular the origin transition around 37500 cm^{-1}, albeit less pronounced owing to their lower signal-to-noise ratio.

The free thread has a high density of conformations, which is readily apparent in the calculations. Once it is embedded in the macrocycle, their number is substantially reduced. A second search aimed at locating the global minimum for rotaxane **1** and free **2** was set up. This search involved initial 0.5-ns equilibration at 700 K. The five lowest-energy structures were then run at 278 K for a further 0.5 ns, and then the ten lowest-energy structures were then annealed from 278 to 20 K in 500000 steps of 0.5 fs. The three lowest-energy structures were finally used as input, each for a 2.5-ns run at 20 K for 2500000 steps of 0.1 fs; for each run, 10000 thread structures were isolated from their macrocycle and optimized (simply optimized for free **2**). Within 1.5 $kcal\,mol^{-1}$, there are only three conformations of rotaxane **1**: the second lowest has a relative energy of 0.6 $kcal\,mol^{-1}$, and the third lowest is 1.4 $kcal\,mol^{-1}$ higher. This is at variance with the behavior of free **2**, for which three conformations are already found within 0.5 $kcal\,mol^{-1}$.

Figure 6 shows the three lowest-energy structures of molded **2** and of free **2**. If the thread is part of the rotaxane, the macrocycle prevents the most favorable interaction between the phenyl groups of the thread to be realized. The optimized structures of molded **2** are accordingly distinctly different from those obtained at low energies for free **2**, the energy difference between the most stable free **2** and molded **2** structure being about 5 $kcal\,mol^{-1}$.

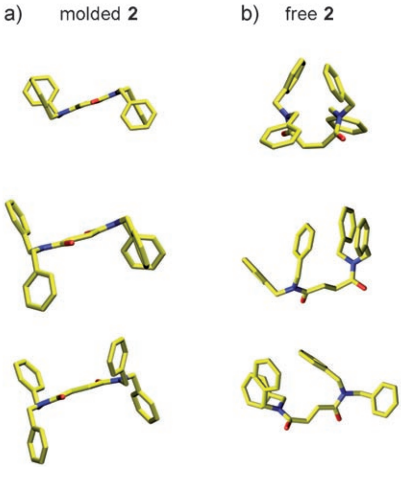

Figure 6. a) The three lowest-energy structures of liberated thread, molded **2**. b) the three lowest-energy structures of free **2**.

The present study shows that the rotaxane architecture has the potential to control, change, and decrease the number of conformations of an encapsulated and interlocked molecular structure. The synthesis of the macrocycles of these rotaxanes is very tolerant towards structural modifications. Through the use of mechanical interlocking auxiliaries[23] it is possible to embed practically any linear molecule in a variety of macrocycles so that their conformational and dynamical properties can be controlled. This provides a novel method to influence conformational dynamics, not by external stimuli or with new spectroscopic techniques, but through the manipulation of structure using noncovalent interactions by an artificial molecular chaperone.

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[21] The photoionization mass spectra in Figure 4a and b show a number of small but broad peaks. These peaks derive from minor fragmentation of ions in the flight tube after ionization of the rotaxane, and can thus not be directly related to the m/z ratio on the x axis.

[22] Optimization of the desorption conditions primarily involves the reduction of the power of the desorption laser and adjusting the position of the sample bar with respect to the nozzle. Although fine-tuning these parameters leads to a reduction of the width of the resonances, it reduces at the same time considerably the signal-to-noise ratio of the signal, and thus leads to extensive signal averaging.

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