Reducing Molecular Shuttling to a Single Dimension**

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Many of the properties of organic materials that are of technological interest are fundamentally different than those of wholly inorganic systems. Amongst them are phenomena which originate from specific submolecular movements, for example, the solitonic behavior of electron transport in conjugated polyacetylenic semiconductors, where the doped molecules localize the extra particle over several unsaturated C–C bonds and an applied electric field makes the charge move along the chain.[1] Effectively a set of single and double bonds travel as a wave from one end of the molecule to the other, inextricably linking submolecular motion to a macroscopic phenomenon. Other remarkably complicated dynamic processes can arise in organic systems with unusual molecular-level architectures.[2–4] The mechanically interlocked components of catenanes and rotaxanes, for example, possess unique degrees of freedom with respect to each other that might be exploitable in nanoscale devices or "molecular machinery".[2h,i] However, great care must be taken when extrapolating ideas about motion from the macroscopic world to the molecular level, where the principle of microscopic reversibility and quantum effects operate.[3] As a result of the large masses involved, and perhaps because of the lack of a better framework, the dynamic behavior of mechanically interlocked systems has previously only been considered in a nearly classical context.[4]

Here we describe the "shuttling" process (translation of the macrocycle between specific sites along the axis of the thread in rotaxanes with two or more "stations"[5]) starting from a simple quantum-mechanical model, that is, the double minimum potential, which is used to calculate average kinetic energies and rate constants and finally, through the use of the partition function, the free energies of activation. This motion is particularly exciting because of its possible utility in switchable systems, where properties differ depending upon which station is occupied by the macrocycle, or in "nanomanipulations", in which shuttling could be used to fetch or deliver small molecules or clusters of atoms attached reversibly to the macrocycle. The success of the treatment provides a further tool for designing functional rotaxanes. It shows that at energies slightly above the activation barrier to shuttling, the probability density of the wavefunctions are largest in zones where they are small at lower energies. Effectively, therefore, just above the shuttling energy barrier the degree of occupancy of the stations and the route of shuttling are exchanged! Application of this model to peptide-based molecular shuttles, where information is available regarding the relationship between rates of shuttling and the distance between stations, shows good agreement between the calculated free energy barriers and rate constants and those obtained experimentally from temperature-dependent dynamic NMR studies.

In its lowest energy state, the macrocycle in a molecular shuttle (e.g. **1**) is located preferentially at one of the stations by intercomponent noncovalent bonding.[2h,i, 5] Whilst in the absence of threading movement of a macrocycle is unrestricted in all directions, in a shuttle translation of the macrocycle is essentially limited to along the vector of the thread. An actual quantum-mechanical calculation of this one-dimensional motion requires the description of the potential energy term, which is taken as the linear combination of a quadratic and a quartic term. The low dimensionality is justified by the timescale of the motion, which is several orders of magnitude slower than for the other molecular-level movements.

The generic double-minimum potential was selected using "Occam's razor". The most well known of such potentials is the quartic potential, which adds to the harmonic part (ax^2) a quartic component (bx^4). For certain ratios of coefficients a and b the potential energy curve forms two equivalent minima. Other functions use additional parameters and complicate unnecessarily the investigation without modifying the conclusions. The same potential is successful in simulating long-standing experimental results such as the inversion tunneling of ammonia.[6] A similar double-minimum potential has been recently used to analyze the Cope rearrangement,[7] which is a problem of ultrafast double minimum potential, as opposite to this very slow one. A potential with a seesaw-type behavior with the presence of multiple secondary minima could be introduced, but this is unnecessary for the issue addressed here. The present choice can also be thought as an average over all the possible shuttling pathways.

In the Schrödinger equation [Eq. (1)] m is the reduced mass, and E_i and ψ_i are the energies of the levels and the corresponding eigenfunctions (in a molecular orbital treatment, they would be the molecular orbitals). Variation of a and b affects the dynamics of the system, and they are adjusted with the intent of reproducing the observed rate constant of shuttling at room temperature k_{298}. This is estimated by thermal averaging of the microcanonical rates $k(E_i)$ [Eq. (2)], where $E_i > E_{\text{barrier}}$ (that is, only the levels above the barrier are considered), L is the distance between the turning points of the potential, and T is the kinetic energy.

$$\left(-\frac{h^2}{8\pi^2 m}\frac{d^2}{dx^2}+ax^2+bx^4\right)\psi_i = E_i\psi_i \qquad (1)$$

$$k(E_i)^2 = \frac{2}{mL^2}\langle T\rangle \qquad (2)$$

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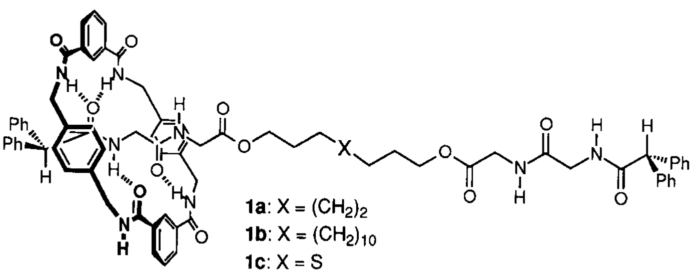
Equation (2) gives an upper value of the rate constants because the use of the kinetic energy implies squared velocities and, for any quantity q, $\langle q^2\rangle \geq \langle q\rangle^2$. The free energy of activation $\Delta G^{\neq}$ was obtained using the transition state theory (TST)[8] relation in Equation (3), where Q is the partition function defined in Equation (4) (in this approach and within TST the partition function at the transition state is unity).

$$\Delta G^{\neq} = E_{\text{barrier}} + k_B T \ln Q_{\text{min}} \tag{3}$$

$$Q = \sum_i e^{-\frac{E_i}{k_B T}} \tag{4}$$

In Table 1, the experimental rate constants and the Eyring-derived free activation energies for the peptide rotaxanes **1a–c** are shown. These systems were selected because of the versatility of the self-assembly reaction by which they are produced[5k, 9] and because recent work with solutions showed that elongation of the shuttling route by more than 10 Å only affects the shuttling frequency by one order of magnitude.[5k] In these two-station rotaxanes, the shuttling action might be thought of as commencing through the detachment of the ring from the hydrogen-bond network present at the station. The shuttle can then travel—subject to few additional constraints—all the way to the other station. The experimental free energies of activation $\Delta G^{\neq}$ and rate constants k depend weakly on the molecular structure and strongly on the solvent used, and confirm the intuitive picture that once the hydrogen bonds are broken, most of the effort is done. In agreement with a purely mechanical model, a longer chain length corresponds to a slower frequency of shuttling. However, that chemistry is not solely mechanics and with barriers of about 10 kcal mol^{-1} diffusion is only one component of the shuttling motion.



1a: X = $(CH_2)_2$
1b: X = $(CH_2)_{10}$
1c: X = S

Table 1 also provides the calculated rate constants as a function of the "walked" length. In the calculations, the length of the path was fixed, effectively reducing the number of fitting parameters to one. There is good agreement between experimental and calculated rates. The data for models 1–3 allow a disantanglement of the effect of route elongation on entropy and shuttling motion. The increase in the distance between the minima by 8 Å (without modification of ΔE; models 1 and 2) increases $\Delta G^{\neq}$ by 0.34 kcal mol^{-1} and decreases by nearly 50 % the rate. The remaining variation (model 3) necessary to achieve agreement with the experiment can be explained by slight variations of the transition state due to the addition of eight CH_2 groups.

The agreement between experiment and theory proves that the assumptions of the present model are reasonable and that 1) the shuttling motion can be separated from the other degrees of freedom and 2) the effective coordinate of shuttling can be described quite simply as a double-minimum potential. The further agreement of experimental and calculated activation free energies is also quite encouraging. The mechanical, expected, effect is now turned into a real chemical kinetics effect derived from the density of states per unit of energy. The increase in the density of states results in a larger value for $\Delta G^{\neq}$ despite the presence of a constant energy barrier (this is the difference between the minima and the maximum of the potential). The higher density of states found by the calculations for the longer shuttling pathway (Figure 1) can be understood if one considers that even in the particle-in-a-box model an increase of the size of the box—that is, elongation of the chain—gives more densely packed

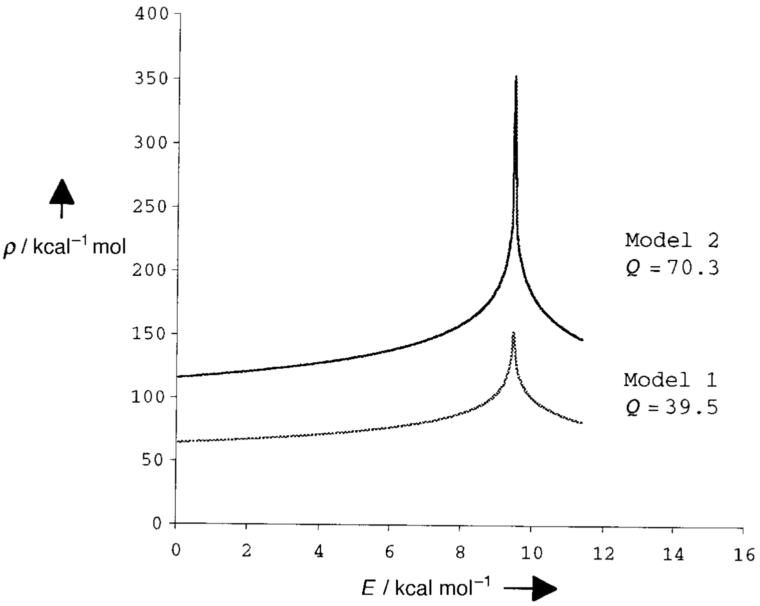


Figure 1. Density of states in models 1 and 2. Notice the cusp behavior, intrinsic to the solution of the quantum-mechanical equation.

Table 1. Experimental[5k] and quantum-mechanical energy barriers [kcal mol^{-1}] and frequencies [s^{-1}] for the shuttling of peptide rotaxanes **1a–c**.

Rotaxane	Frequency$_{\text{exp}}$	$\Delta G^{\neq}_{\text{exp}}$	Model	Route [Å][a]	ΔE	Frequency$_{\text{calcd}}$	$\Delta G^{\neq}_{\text{calcd}}$
1a	37000	11.2 ± 0.3	1	10.0 (14.14)	9.49	37121	11.67
			2	18.0 (25.45)	9.49	20032	12.01
1b	5200	12.4 ± 0.3	3	18.0 (25.46)	10.39	5213	12.87
1c	62000	10.9 ± 0.3	4	10.0 (14.14)	9.19	62721	11.37

[a] The distance between the minima; the distance between the turning points is given in parentheses. The potential energy was $V_n = a_n x^2 + b_n x^4$ ($n = 1, 2, 3, 4$; $a_1 = -0.527476$, $b_1 = 1.05495 \times 10^{18}$, $a_2 = -0.162801$, $b_2 = 0.100495 \times 10^{18}$, $a_3 = -0.178240$, $b_3 = 0.110025 \times 10^{18}$, $a_4 = -0.510802$, $b_4 = 1.02160 \times 10^{18}$; units are a_n in J m^{-2}, b_n in J m^{-4}.

levels. The cusp behavior at $E = E_{\text{barrier}}$ is a quantum-mechanical effect that could not have been anticipated without solution of Equation (1). The closer to one another the levels are, the more readily are they thermally populated or, in other words, the larger is the partition function Q and hence $\Delta G^{\neq}$. As one may have expected, therefore, addition of CH_2 groups in the peptide rotaxanes does not change the intrinsic barrier of the shuttling and, importantly, the mechanical model is here substituted by a kinetic one whose parameters can be obtained by molecular calculations.

The agreement of the model calculations warrants a more detailed investigation of the quantum system, whose features become of fundamental importance to the overall understanding of the behavior of molecular shuttles. Figure 2 shows the squares of the wavefunctions of three energy levels where the behavior of the shuttle changes significantly. At low energies, probed only at low temperatures, the system is localized as expected at the minima; that is, the shuttle is statistically located at either one of the stations. However, when the barrier is overcome, the highest probability of finding the macrocycle moves away from the minima, and it is most likely to be found at the top of the barrier. Effectively, the populations of the stations and spacer unit of the thread are switched in this energy regime. This finding must not be taken to mean that the probability becomes localized at the center of the route as the temperature increases, but the realization that the macrocycle becomes preferentially located somewhere along the thread besides the ground-state stations should clearly be bourne in mind when considering possible conditions where rotaxanes could be used in nanomanipulations or devices. At higher energies, the probability distribution again resembles closely the classical one with maxima at the two turning points.

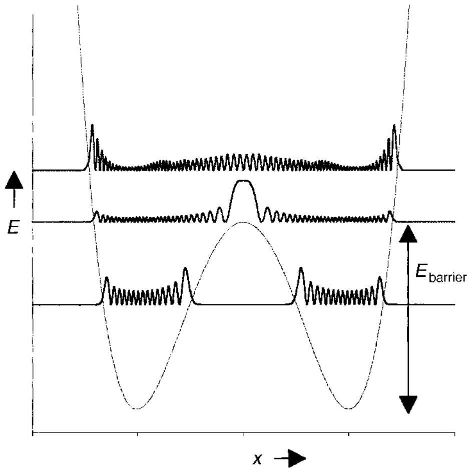


Figure 2. Potential energy curve and square of the wavefunction for three selected levels: At energies lower than the barrier, the ring sits at either one of the stations, at energies just above the barrier, the degree of occupancy of route and stations are reversed. At higher energies, the probability resembles that of a classic oscillator and population of the low energy stations is again favored. x = position.

The shuttling motion in rotaxanes is in many respects a complicated classical motion which can, however, as shown here, be reduced to a one-dimensional quantum-mechanically based one. The picture that emerges has many similarities with that of a cart rolling along a roller coaster shaped like the double-minimum potential depicted in Figure 2. At energies below the transition state, the cart/macrocycle sits around one of the two minima; when its energy is barely sufficient to overcome the barrier, it spends the longest time passing over it and the greatest probability is to find it at or near the top of the barrier; when the energy is much higher, the turning points, where the classical particle has to slow down, are where it is preferentially located! (We thank one of the referees for this analogy.) The kinetics of the process can be similarly appraised from the model. A longer spacer means that the ring takes a longer time to walk; however, the mechanical analogy cannot be carried too far because kinetics with a barrier of more than 10 kcal mol^{-1} is not only a matter of diffusion. The variation of the rate constants is therefore explained in terms of an increase in the activation free energy with the chain elongation. This, in turn, is a typically quantum-mechanical effect caused by the increase of the density of states per unit of energy with the shuttling route.

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Enantioselective Reactions of Configurationally Unstable α-Thiobenzyllithium Compounds[**]

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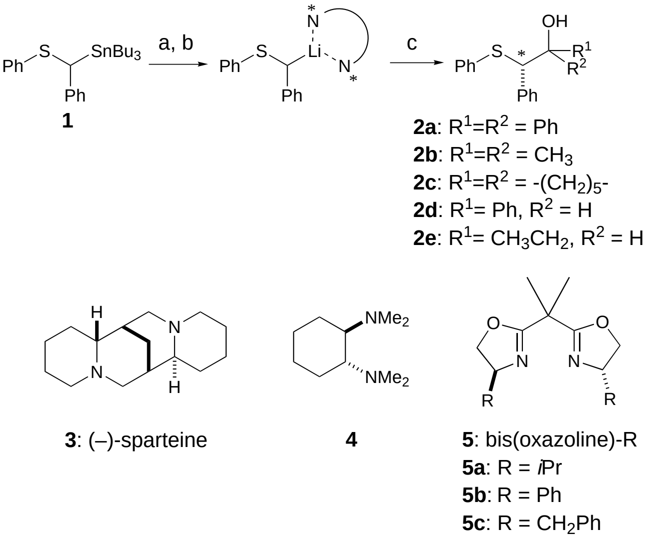
Asymmetric induction that arises from organolithium substrates complexed to chiral ligands has emerged as an efficient and powerful method. Since Hoppe et al. showed a high enantioenrichment could be achieved in a lithiation reaction to provide α-oxygen-substituted dipole-stabilized carbanions,[1] the enantioselective reactions of dipole-stabilized α-heterocarbanions have been the subject of extensive studies.[2] These reactions generally afford products with high enantioselectivity through asymmetric deprotonation. However, α-thiocarbanions do not give products with such enantioselectivity,[3] possibly because these carbanions are configurationally unstable and rapidly racemize even at temperatures as low as $-78\,^{\circ}\mathrm{C}$.[4–6] Racemization of the α-selenocarbanions also occurs,[4,7] but Hoffmann et al. have succeeded in achieving good enantioselectivities through a dynamic thermodynamic resolution in the reactions of non-dipole-stabilized α-selenocarbanions.[8] More recently, Nakai and Tomooka's group has reported highly enantioselective reactions of α-oxyorganolithium compounds.[9] Enantioselective reactions of α-thiocarbanions using asymmetrically deprotonated η^6-arene(tricarbonyl)chromium complexes have been reported.[10] There are, however, no reports on the intermolecular enantioselective reaction of α-sulfenyl carbanions derived from primary benzyl sulfides. The α-sulfenyl carbanion may be more unstable than the α-selenocarbanion,[4] and a high level of chiral induction could be realized through the asymmetric substitution process[2a] that is controlled either by the intermediate lithium carbanion/chiral ligand complex or by the transition state of the complex–electrophile interaction. We report herein the first highly stereoselective asymmetric substitution reactions of primary α-sulfenyl carbanions.

First we examined the reaction of α-lithio aryl benzyl sulfides with various electrophiles in cumene.[11] α-Lithiobenzyl phenyl sulfide was prepared from phenyl α-(tributylstannyl)benzyl sulfide (**1**) since reactions starting with benzyl phenyl sulfide often gave products with high stereoselectivity but in yields of less than 40%. Several chiral ligands, (−)-sparteine (**3**), (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine (**4**), and 2,2-bis{2-[(4*S*)-substituted-1,3-oxazolinyl]}-propanes[12] **5a–c**, were examined (Scheme 1). The yields and enantioselectivities obtained in these reactions are shown in Table 1.



Scheme 1. a) *n*BuLi (1.15 equiv), cumene, $-78\,^{\circ}\mathrm{C}$; b) chiral ligand (1.2 equiv), 1 h; c) electrophile, temperatures used are given in Table 1.

Ligands **3** and **4** provided the thio alcohol **2a** in low enantioselectivity from the reaction of lithiated **1** with benzophenone. The results are noteworthy since these chiral ligands often give high enantioselectivities in the reactions of α-heterocarbanions.[1,2,8] However, bisoxazolines showed excellent chiral induction. In particular, **5a** gave (*S*)-thio alcohols **2a**, **2b**, and **2c** in the reactions of lithiated **1** with

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