A Quantum-Mechanical Description of Macrocyclic Ring Rotation in Benzylic Amide [2]Catenanes

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Abstract: Catenanes can undergo rotation of one ring through the cavity of the other. Since macroscopic and molecular properties must clearly vary with the relative positions and orientations of the interlocked components, a complete understanding of the way that the rings rotate is of considerable importance. Here we show that low-dimensional quantum-mechanical modeling can yield rate constants and barriers similar to those obtained by temperature-dependent nuclear magnetic resonance experiments. Data from both non-hydrogen bond disrupting (e.g. $CDCl_3$) and hydrogen bond disrupting (e.g. $[D_6]DMSO$) solvents are well reproduced demonstrating the validity of the model. The successful simulation of the rates of circumrotations by entirely harmonic transition state theory originates from the description of the anharmonic levels of the systems through an effective harmonic frequency, not very different from twice the zero point energy. The nature of the model makes it extendable, in principle, to the calculation of properties dependent upon circumrotational activity.

Keywords: catenanes · kinetics · molecular dynamics · molecular modeling

Introduction

Many phenomena of biological or technological interest originate directly from submolecular motions; for example, the *trans–cis* isomerisation of a carbon–carbon double bond that triggers the visual signal or the solitonic behavior of electron transport in doped conjugated polyacetylenic semiconductors.[1] Other remarkably complicated dynamic processes can arise in organic systems with unusual molecular level architectures.[2–4] The components of catenanes and rotaxanes possess unique degrees of freedom for the constrained motion of one mechanically interlocked moiety with respect to another.[2h,i] The details of the relative motions of interlocked rings can be highly complicated, as demonstrated during the investigation of the structure and dynamics of several benzylic amide catenanes using molecular mechanics calculations.[3] That study provided the first complete theoretical description of the lowest energy pathway for the circumrotation of macrocycles in a catenane system, featuring a concerted sequence of several large-amplitude motions involving a host of rearrangements to minimise steric and electrostatic interactions through the formation/disruption of hydrogen bonds, π-electron stacks, CH-π electron complexes and amide rotamer interconversions. In spite of this complexity, unifying features were found for the description of the passing of successive fragments through the macrocyclic cavities. Analysis of the structural characteristics of the transition states located along the circumrotational pathway of three related catenanes furnished a comprehensive interpretation of the large variation of the dynamical behaviour observed in NMR experiments.

The fundamental and crucial question that arises from the mechanistic treatment of circumrotation is how complicated does the model have to be in order to derive useful information about the system? Is it possible to describe circumrotation in simple terms and reduce the inherently multiple dimensionality of the process to a more manageable size? The large masses involved in the motion, and perhaps the lack of a better conceptual framework, have thus far generally led to the dynamic behavior of mechanically interlocked systems being treated in a classical context.[3] Recently, however, it proved possible to provide a description of the "shuttling" process (constrained translation—not rotation—of a macrocycle between two sites along the axis of a thread in a rotaxane) with a quantum-mechanical model.[4]

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Herein we construct an analogous model with the aim of reducing the dimensionality of circumrotation in catenanes in a consistent way, capable of yielding barriers and rate constants similar to those determined by temperature-dependent nuclear magnetic resonance experiments. The fundamental attraction of the present model is that the same framework used to calculate the average kinetic energies—and hence the rate constants—could be extended to calculate any property dependent on the circumrotational activity and temperature.

The present work stems from related quantum-mechanical modeling performed on a different motion of a macrocycle in a mechanically interlocked system.[4] The fundamental difference here is that we focus on constrained rotation, while before we considered constrained translation. The previous quantum-mechanical model was applied to peptide-based molecular shuttles, where data were available for the relationship between rates of shuttling and the inter-station distance. The results showed good agreement between the calculated free energy barriers and rate constants and those obtained experimentally from NMR studies.[3] The treatment also made evident that at energies slightly above the activation barrier to shuttling, the probability densities of the wavefunctions are larger in zones where they are small at lower energies. Effectively, just above the shuttling energy barrier, the degree of occupancy of the "stations" and the "routes of shuttling" are exchanged. The picture has many similarities with that of a cart rolling along a rollercoaster shaped like a double minimum potential. 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, the cart spends the longest time passing over it and, conversely, the greatest probability is to find the macrocycle 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. The model showed that longer spacers—characterized by the same barrier—take a longer time for the ring to travel. The mechanical analogy was found, however, only partially applicable: as the path elongates, the variation of the rate constants is determined by a quantum-mechanical effect, that is the increase of the density of states per unit of energy.

It is clear that many similarities should exist in the quantum-mechanical description of circumrotation in catenanes and shuttling in rotaxanes. Apart from the fact that in both cases a macrocycle is present, when circumrotation is limited to a rotation of less than 360° it effectively becomes shuttling, albeit along a curved pathway. In more detail, in the absence of mechanical interlocking, the macrocycle movement is unrestricted in all directions. In a catenane its rotation is essentially limited about an axis defined by a fragment—a few bonds—of the other ring. The motion is therefore two-dimensional (one dimension for each ring) although, in the end, full 360° rotation of either ring must be identical (in homocircuit catenanes such as **1**–**3**) to the same rotation of the other ring. Adiabatic separation of circumrotation from the other degrees of freedom is justified by the time scale of the motion that is several orders of magnitude slower than any other molecular movement. Separation of a (few) degree(s) of freedom is well known and has been frequently used in the study of large amplitude motions, for instance in the treatment of tunneling effects.[5] In an actual quantum-mechanical calculation the basic requisite is the description of the potential energy. In this case, the potential is periodic and is characterized by *at least* two barriers, one for the passing of the isophthaloyl group and the other for the passing of the *p*-xylyl fragment. The natural choice is therefore a periodic sinusoidal potential that is a function of an angle which must not be taken to be that of rigid rotation, rather, it is a coordinate that compounds all the effects, that is, structural rearrangements, encountered during the motion. The coupling between the rotation of either ring with that of the other is also assumed—in an equivalent of a "mean field approximation"—to be effectively included in the one-dimensional potential. This does not imply that the two rings move independently from each other, indeed if the other macrocycle were not present the motion would be free, but rather that each ring experiences along the rotation the average effect of the other. Other potential energy functions could be used along with additional parameters, for instance other secondary minima could be introduced, but they would unnecessarily complicate the investigation without modifying the conclusions that are reached at the end of this work. Success or failure of the treatment proves the validity of the assumptions and the approximations undertaken in the calculations. It is worth mentioning that the generic sinusoidal potential has found many applications in chemistry. Noteworthy in their simplicity and generality are the applications to the torsions of ethane and ethylene.[6]

Even with the simplifying assumptions outlined above, solution of the quantum-mechanical problem is challenging. The permutation group symmetry—not point group symmetry—of the system is, however, rather high and can provide further assistance.[7] The symmetry is dictated by four operations that are intrinsic to the rotation by an angle ϕ and do not modify the Hamiltonian. Apart from the identity, they are the $+\phi \rightarrow -\phi$ reflection, the $\phi \rightarrow \phi + \pi$ rotation, and the $\phi \rightarrow \pi\text{-}\phi$ roto-reflection. In the calculations, the potential energy function is constructed as a series of adjoining sinusoidal segments of the type given in Equation (1), where

$$\mathrm{V}(\varphi) = \frac{E_\mathrm{i}}{2}\left(\cos(\alpha\phi + \beta) + \frac{1}{2}\right) \tag{1}$$

α and β are chosen to satisfy the symmetry and energy conditions which are $V(0) = V(\pi) = V(2\pi) = E_1$; $V(\pi/2) = V(3\pi/2) = E_2$ with $E_2 < E_1$; $V(\mathrm{c}\pi/2) = V(\pi - c\pi/2) = V(\pi + c\pi/2) = V(2\pi - c\pi/2) = 0$ and $E_\mathrm{i} = E_2$ for $c\pi/2 \leq V \leq \pi - c\pi/2$ and $c + \pi/2 \leq V \leq 2\pi - c\pi/2; 0 \leq V \leq c\pi/2$, $\pi - c\pi/2 \leq V \leq \pi + \mathrm{c}\pi/2$ and $2\pi - \mathrm{c}\pi/2 \leq V \leq 2\pi$ and $E_\mathrm{i} = E_1$; c was set to 0.45 to avoid the introduction of further symmetry that would arise if $c = 0.5$. All the integrals required by the numerical matrix solution of the Schrödinger equation were calculated by using an algebraic manipulator.

The rate constant of circumrotation at room temperature k_{298} was estimated by thermal averaging the microcanonical rates, $k(E_\mathrm{i})$ [Eq. (2)], where $E_i > E_\mathrm{barrier}$, that is only the levels

$$\langle k(E_\mathrm{i})^2 \rangle = \frac{\langle T \rangle}{4\pi 2} = -\frac{h^2}{16\pi^4 I^2}\left\langle \frac{\mathrm{d}^2}{\mathrm{d}\varphi^2} \right\rangle \tag{2}$$

above the barrier give rise to circumrotation (no tunneling), T is the kinetic energy operator, the bracket means calculation of the expectation value for the i-th level and I is the moment of inertia. 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, $<q^2> \geq <q>^2$. Importantly, the kinetic energy term operator can be replaced by any operator to yield circumrotation dependent properties. The free energy of activation $\Delta G^{\neq}$ was obtained by using the transition state theory (TST; [Eq. (3)])[8] relation where Q is the partition function given in Equation (4) (in this approach and within TST the partition function at the transition state is one).

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

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

Results and Discussion

The model illustrated in the previous section can be used to simulate the dynamical data of the catenanes with two different intents. The first is to reproduce the experimental rates of circumrotation and obtain the quantum mechanical barriers, the second is to drive the calculations to reproduce the Eyring-derived barriers and obtain, in turn, the quantum-mechanical rates of circumrotation. Coincidence—or near coincidence—of the results of the two approaches would prove the circumrotational action of these systems is an ideal case for the Eyring treatment and implicitly show that they satisfy its underlying conditions.[8] As an initial step for the whole treatment, Figure 1 shows a typical two-dimensional potential energy surface (PES) of the complete circumrotation of the two rings of a benzylic amide [2]catenane, where ϕ_1 and ϕ_2 obey the same conditions illustrated above for ϕ. The periodicity and the symmetry of the PES are striking and derive from the symmetry considerations and the assumptions outlined in the previous section. Apart from variations in the heights of the saddle points, the general features of this potential are common to the three catenanes and the two solvent systems. Table 1 shows the results of the fitting. Very similar rates of circumrotations and energy barriers were obtained starting both from the experimental rates of circumrotation and the Eyring theory derived barriers. Considering the exponential dependence of the rates on the barriers, the agreement can be deemed very satisfactory. Importantly, the experimental free energies of activation $\Delta G^{\neq}$ and rate constants k depend strongly not only on the molecular structure but also on the solvent used. Table 1 provides the calculated rate constants both for hydrogen bonding and non-hydrogen bonding solvents. Whilst solvent variation probably affects the microscopic detail of the dynamics of the system, in the present model, this is reflected only, and can only be reflected, in the energy barriers. The success in capturing the

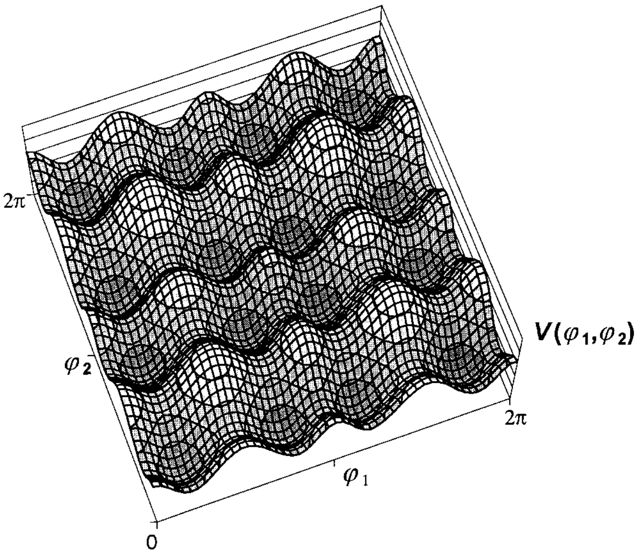
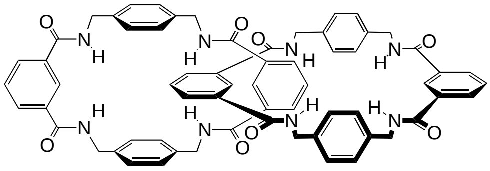


Figure 1. Potential energy surface of the circumrotational pathway.

Table 1. Experimental and quantum-mechanical energy barriers and rate constant, at 298 K, for the circumrotational action in three benzylic amide catenanes.



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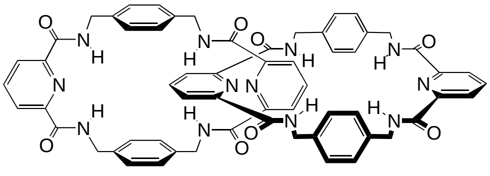

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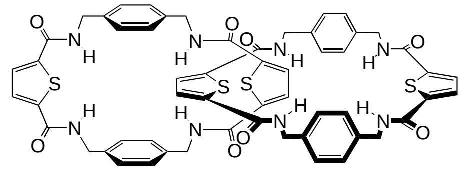

3

Compound[a]	k_{exp} [Hz]	$\Delta G^{\neq}_{\text{exp}}$ [kcal mol^{-1}]	k_{calcd} [Hz]	$\Delta G^{\neq}_{\text{calcd}}$ [kcal mol^{-1}]
1				
A	72	12.3	72.86	12.68 (10.81)[b]
		14.5		14.61 (12.74)
B	16000	–	15447	10.00 (8.04)
		11.3		11.43 (9.47)
2				
A	0.003	11.3	0.0033	12.78 (10.97)
		20.5		20.54 (18.73)
B	0.2	–	0.239	10.76 (8.90)
		17.9		18.01 (16.14)
3				
A	9600	–	10526	7.95 (5.95)
		11.6		11.70 (9.70)
B	28000	–	27269	7.01(4.97)
		11.0		11.06(9.02)

[a] A: measurements of k and $\Delta G^{\neq}$ were performed in $CDCl_3$, a non-hydrogen bond disrupting solvent. B: Measurements of k and $\Delta G^{\neq}$ were performed in $[D_6]$DMSO, a hydrogen bond disrupting solvent. [b] The potential energy barrier is given in parentheses.

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changes of the rates through modifications of energy barriers further strongly supports the validity of the model.

The agreement between experiment and theory confirms that the assumptions of the present model are reasonable and that a) the circumrotational motion can be separated from the other degrees of freedom, b) the effective coordinate of circumrotation can be described quite simply as a sinusoidal potential.

Figure 2 shows the deviation from perfect, or equal, harmonic spacing of the energy levels associated to the potential of Figure 1, as a function of the energy. Such spacing governs the partition function Q which is ultimately responsible for the rates of circumrotation. In agreement with the trend observed in the calculations of the shuttling in rotaxanes,[4] catastrophic changes occur at the energies of the two barriers. Notice that the cusp behavior at $E = E_{barrier}$ shared also by the constrained translation,[4] is a quantum-mechanical effect that could not have been anticipated without solution of the Schrödinger equation. Importantly, the closer to one another the levels, the more easily they are thermally populated, and the larger the partition function Q and hence ΔG^{+}. The anharmonic behavior of Figure 2 is readily explained if one considers that at the PES minimum the motion of the rings only slightly deviates from the pure harmonic regime. As the energy increases, the effect of the anharmonicity of the potential appears and the spacing between the levels decreases until the potential maximum, with very dense levels, is reached. Above the maxima, one-dimensional barrierless rotation occurs. In this regime, level spacing goes up with the square of the quantum number of the level and therefore strongly deviates, in the opposite way of that observed below the barrier, from the equal energy separation of the harmonic oscillator regime.

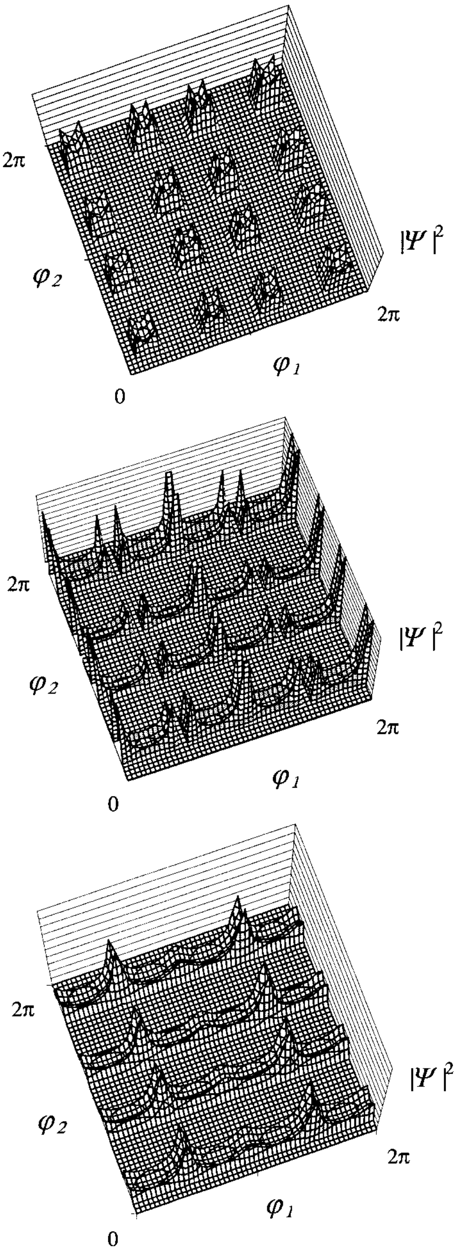

Figure 2. Deviation from harmonic spacing of the energy levels of the potential energy surface of the circumrotational pathway.

Importantly, the strong deviations from harmonicity seem to counter the ability to simulate the rates of circumrotation in non-hydrogen bonding solvents within a harmonic description of the transition state theory (TST) that was recently achieved.[3b] It should, however, be borne in mind that in the TST only the temperature-dependent partition function is required. Table 2 shows the values of harmonic frequency required to give the same value of the partition function at room temperature obtained by using the energy levels of the potential. Significantly, such values are very close to twice the zero point energy. The agreement between the two has fundamental practical consequences. So long as the partition function of circumrotation is well simulated by an effective harmonic frequency, the harmonic TST treatment can provide accurate results.

Table 2. Effective harmonic wavenumber[a] $\tilde{\nu}$ [cm^{-1}] and twice the zero point energy (2 × zpe, [cm^{-1}] for the six cases considered in Table 1.

	$\tilde{\nu}$	2 × zpe
1 A	8.65	8.96
1 B	7.44	7.72
2 A	9.56	9.91
2 B	8.74	9.05
3 A	6.93	7.21
3 B	6.48	6.77

[a] The effective harmonic wavenumber is defined as the frequency which gives the same partition function of that calculated from the energy levels of the sinusoidal potential.

Whilst the general behavior of the levels and the dynamics of these complicated molecules is now better understood, its quantum component emerges and analysis of the system wavefunctions becomes of fundamental interest. In Figure 3, one can see the squares of the wavefunctions of three selected levels. At low energies, probed only by low temperatures, the system is localized at the minima where each macrocycle circumscribes one of the amide groups of the other. When the first barrier is overcome, the highest probability to find the macrocycle moves away from the -CONHCH$_2$- group and the macrocycle is most probably found around one of the five- or six-membered rings. Surmounting the second barrier pro-

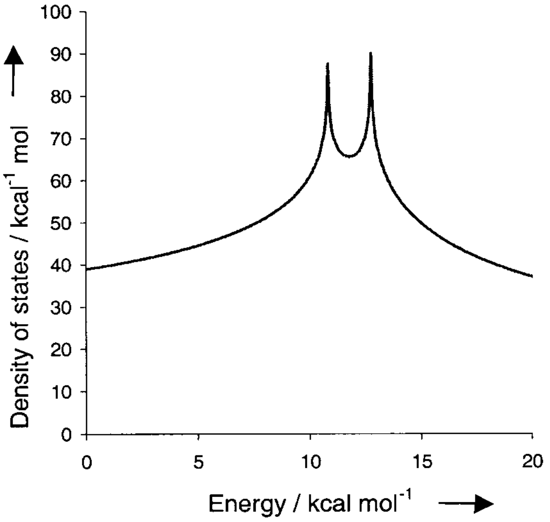

Figure 3. Square of the wavefunction for three selected levels: At energies lower than the barrier, the rings sit at either one of the stations, at energies just above the barrier, the degree of occupancy of route and stations are reversed. At higher energies, the probability resembles that of a classic oscillator and population of the low energy stations is again favored.

duces the same kind of behavior. Effectively, in terms of probability, stations and the routes connecting them are switched by increasing the energy of the system. The analogy of a cart on a rollercoaster previously used to describe the constrained translational motion of a macrocycle is even more relevant here where the potential, that is the rollercoaster, has a series of hills and troughs.

The present treatment has an interesting implication; the coalescence of the NMR signals at high temperatures.[3a] In rough terms, the spectral position of an NMR signal is given by the atomic chemical shift which may vary along each, infinitesimal, stretch averaged over the circumrotational pathway. The contribution of each "segment" has to be weighed over the probability of having the system in it. If the probability is low, the final contribution to the overall response is low. In reality, one should use an equivalent of Equation (2) to calculate the expectation value, where, the operator would be the chemical shift expressed as a function of the circumrotational coordinate. The accurate calculation of chemical shifts is a recent development and is not yet practical for systems of this size. However, the possibility of reducing the complexity of the special degree of freedom of catenanes to a model manageable in quantum-mechanical calculations, and its accurate description of the molecules dynamics in different conditions, opens the way to simulate any molecular property affected by circumrotation.

Conclusion

In benzylic amide catenanes, the circumrotation must—to a fair approximation—be describable in a classical manner. In agreement with this idea, activation energies and rate constants derived quantistically are in good agreement with the experimental rate constants and the barriers obtained by applying Eyring theory to the NMR data. The quantum-mechanical treatment offers, however, further remarkable insight into dynamics of these systems. In analogy to the case of shuttling in rotaxanes, the probability density to locate the macrocycle closely resembles the behavior of a rollercoaster cart slowly surmounting the top of the loops when its energy is comparable to the potential energy of the saddle point. In this sense, the coalescence of the NMR peaks with the temperature increase is therefore not only due to rapid exchange of the stations of the rings but is also caused by their most probable location which, at energies just above the barrier, is at a five- or six-membered ring. Finally, the treatment also explains the successful simulation of the rates of circumrotation by transition state theory in the harmonic approximation which is ultimately due to the possibility of effectively simulating the partition function of the highly anharmonically spaced levels of the circumrotational potential in terms of an effective harmonic vibration.

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