

Structure, Stability, Electronic Properties and NMR-Shielding of the Cucurbit[6]uril–Spermine-Complex

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Abstract

Geometries, stabilities, electronic properties and NMR-shielding of cucurbit[6]uril–spermine host-ligand complexes are investigated with DFT calculations and compared to experimental results. Cucurbit[6]uril and spermine can form complexes with two different minimum energy geometries and corresponding characteristic differences in NMR shielding. The energetically preferred complex geometry has a perfect inversion symmetry and its proton NMR shielding agrees very well with experimental results. The cucurbit[6]uril host molecule shows a distinct geometrical flexibility in ligand binding which allows an induced fit of the spermine ligand. The energetic barrier for the rotation of spermine in the favourable complex is approximated to be in the order of a few kilocalories per mole.

Introduction

Cucurbit[6]uril is a macrocyclic ligand with a hydrophobic cavity accessible through two portals each formed by six carbonyl groups. The compound was first synthesized in 1905 by Behrend *et al.* [1] and rediscovered by Mock and coworkers in 1981 [2]. They observed that alkylamines, diamines and some polyamines form very stable complexes with cucurbit[6]uril [3]. From the measurement of the thermodynamic parameters for the reaction of different amines with cucurbit[6]uril more insight in the factors responsible for the complex formation was obtained [4]. Kinetic investigations of the complex formation of cucurbit[6]uril with amines gave detailed information about the individual reaction steps taking place during the inclusion of the amines into the cavity of cucurbit[6]uril [5, 6].

The cucurbit[6]uril complexes with polyamines have been used as starting materials for the formation of polyrotaxane nets in the solid state [7, 8]. The reaction of the complex between 1,6-diaminohexane and cucurbit[6]uril with benzoylchloride resulted in the formation of a monorotaxane [9]. Using the formation of real stopped polyrotaxanes became possible [10]. Instead of diamines also spermine was used for the synthesis of monorotaxanes

[11]. The fixation of spermine onto polyester films followed by the complex formation with cucurbit[6]uril and the final reaction of the terminal amino group with an aromatic carboxylic acid chloride resulted in the formation of so-called surface rotaxanes [12, 13]. One of the stopper groups is the polymer backbone and the other a defined chemical group.

The high stability constants of the spermine and spermidine complexes with cucurbit[6]uril enabled the additional formation of complexes with crown ethers bond at the terminal nitrogen atoms of these polyamines [14]. Thus the formation of a 2:1:1 complex between a crown ether, spermine and cucurbituril took place in solution. Just recently it was shown that the complexation of cucurbit[6]uril with spermidine and spermine enhances or reduces the activity of the polyamine on enzymatic reactions of DNA [15].

The complex between cucurbit[6]uril and spermine is an interesting starting material for further chemical reactions. Thus it is important to obtain a fundamental understanding of factors responsible for the chemical behaviour of this complex. In a recent study we investigated the cucurbit[n]uril family itself using DFT calculations [16]. Geometrical flexibility and a characteristic partial charge distribution are the basis of the well known complex building behaviour of this class of host molecules. In the present work we studied the cucurbit[6]uril–spermine complex in detail.

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Methods

The quantum chemical calculations were performed with Gaussian [17]. Molecular graphics were generated with GaussView [18]. Geometries were optimized with the semiempirical PM3 method and then refined with Density Functional Theory (DFT) using the B3LYP hybrid functional with the 6-31G(d) basis set. Calculation of nuclear magnetic shielding tensors for the optimized molecular geometries was performed with the Gauge-Independent Atomic Orbital (GIAO) method and the B3LYP/6-31G(d) model chemistry. Reported shifts are relative to those of optimized tetramethylsilane calculated with the same model chemistry [19–22]. The four amino groups of spermine are protonized in aqueous solutions. Therefore all calculations were performed with the protonized form.

To determine the geometries of the possible cucurbit[6]uril–spermine complexes spermine was threaded through cucurbit[6]uril in steps of 0.5 Å. Each start geometry was optimized with the semiempirical PM3 method. As a result cucurbit[6]uril and spermine formed a penetration complex or spermine was expelled from the cucurbit[6]uril cavity. All detected penetration complexes were then refined with the B3LYP/6-31G(d) model chemistry.

The choice of the model chemistry can be regarded as an acceptable compromise between accuracy and speed for this kind of quantum chemical calculations. Moreover there are additional restrictions that have to be taken into account: DFT methods are not able to describe dispersion effects. For this study the contribution of dispersion effects to the complex formation is estimated to be small in comparison to the strong electrostatic interactions. The well known basis set superposition error affects all electronic structure calculations with centered basis functions and is especially problematic in studies of weak intermolecular interactions. Therefore energetic differences must be dealt with caution. Solvent and dynamical effects are completely neglected. A possible influence of the solvent on the NMR results is discussed in the NMR section. The calculation of absolute NMR shifts is very sensitive to the applied model chemistry. In this study only the relative differences of shifts due to complex formation are of interest for comparison with experiment. These relative values often exhibit a favourable cancellation of errors and therefore are more accurate than the absolute ones. In summary the quantitative results have to be interpreted with care and can be regarded as approximate only.

Results and discussion

Optimized Geometries

The threading procedure with initial PM3 optimization and following B3LYP/6-31G(d) refinement resulted in only two minimum energy complex geometries denoted 1

and 2 (see Figure 1a). Geometry 2 is energetically favoured by -22.5 kcal/mol and shows a perfect C_i symmetry, i.e. the cucurbit[6]uril host molecule is distorted from its native D_{6h} symmetry into a C_i symmetry. This accounts for the geometrical flexibility of cucurbit[6]uril in ligand binding [16]. Spermine already has a native C_i symmetry. If thermodynamic control for the complex reaction is assumed a minimum energy difference in the order of -22.5 kcal/mol means that complex geometry 2 dominates nearly exclusively geometry 1 (the ratio of the concentrations of complex 2 to complex 1 is of order 10^{16} at room temperature). The energy of complex formation for cucurbit[6]uril and fully protonated spermine is -188.2 kcal/mol for complex 1 and -210.7 kcal/mol for complex 2 so that complex formation seems to be strongly energetically favoured. This accounts for the well known stability of the cucurbit[6]uril–spermine complex.

If the geometry of complexed cucurbit[6]uril is compared to its native geometry a significantly reduced size of the oxygen portals as well as a reduced intramolecular distance is noted (see Figure 1a and b). The approximated oxygen portal area is reduced from 33.7 to 28.9 Å² [16]. The distance of opposing oxygen atoms within a portal (the portal diameter) is reduced from 7.21 to 6.33/6.82/6.88 Å [16]. The intramolecular distance of the oxygen portals is reduced from 6.23 to 5.87/5.98 Å where the portal oxygen atoms that form the “H-bonds” (see below) with the amino groups of spermine (highlighted in green in Figure 1a) are slightly distorted out of plane [16]. In summary cucurbit[6]uril seems to behave like a “mechanical claw” when forming a penetration complex with spermine compared to its native geometry.

The interaction between the hydrogens of the “binding” spermine amino groups and the corresponding portal oxygen atoms (“H-bonds”, see Figure 1d) is assumed to be the primary energetic interaction that determines the symmetrical C_i geometry of complex 2. The O–H distances are of similar order (1.87/1.92 Å) and identical at both portals.

Electronic properties

The electron densities with mapped electrostatic potentials of complex 2 show the complementary electrostatic nature of both molecular species (see Figure 1e). The partially negative oxygen portals interact with the positively charged hydrogens of the spermine amino groups. The spermine methylene bridges that separate the amino groups fit in the relatively uncharged cavity of cucurbit[6]uril [16]. Due to the geometrical flexibility of cucurbit[6]uril the spermine “key” seems to induce a perfect fit with the cucurbit[6]uril “lock”.

The symmetrical highest occupied molecular orbital (HOMO) of complex 2 two is identical in shape to the HOMO of cucurbit[6]uril [16]. In contrast the lowest unoccupied molecular orbital (LUMO) is degenerated and identical in shape to virtual orbital 61 (LUMO + 3) of fully protonated spermine. There are also inner MOs with delocalized electron density spread over the whole

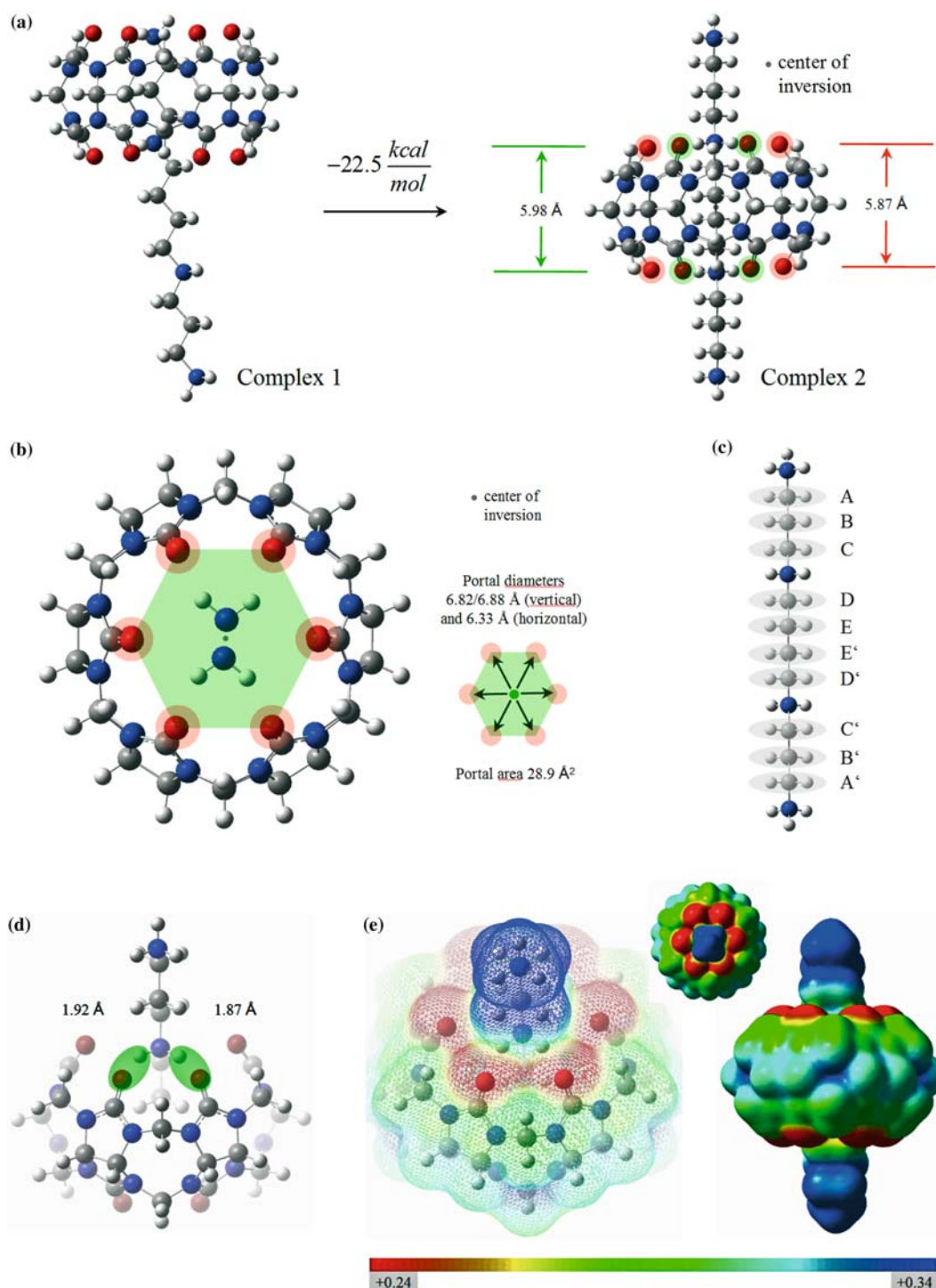


Figure 1. (a) Minimum energy geometries of cucurbit[6]uril-spermine. (b) Portal geometry of cucurbit[6]uril-spermine complex 2. Only the top and bottom “binding” amino groups of spermine are displayed. (c) Protonated spermine. (d) “H-bonds” of the cucurbit[6]uril-spermine complex 2. (e) Cucurbit[6]uril-spermine complex 2: Electrostatic potential mapped on the molecular “size surface” with electronic density isovalue of 0.002 a.u.

complex (see Figure 2a–d). These findings indicate an intense electronic interaction between cucurbit[6]uril and spermine which account for the highly negative complex formation energy.

NMR analysis

As far as NMR shielding is concerned the complex building reaction leads to differences in the shifts of the

proton and carbon signal groups due to the change in the chemical environment of the corresponding spins. These relative signal group differences between the cucurbit[6]uril-spermine complex and pure cucurbit[6]uril and pure spermine respectively are characteristic and allow a comparison of the calculated results with experimental data (see Figure 2e; experimental $^1\text{H-NMR}$ spectrum: 500 MHz, cucurbit[6]uril-spermine solved in D_2O , trimethylsilylpropionic acid sodium salt

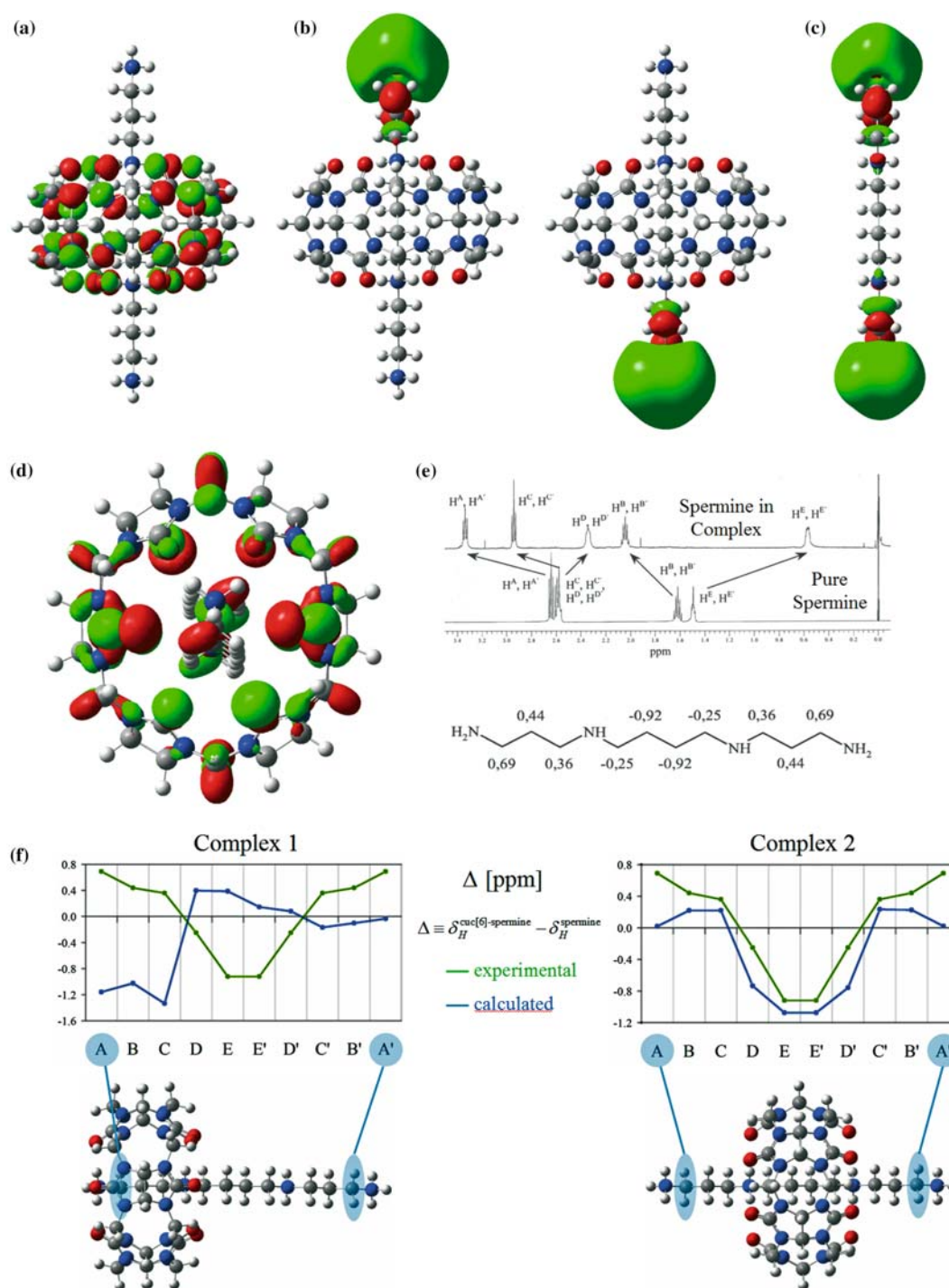


Figure 2. (a) HOMO of cucurbit[6]uril-spermine complex 2. (b) Degenerated LUMOs of cucurbit[6]uril-spermine complex 2. (c) MO 61 (LUMO+3) of protonized spermine. (d) MO 245 (HOMO-70) of cucurbit[6]uril-spermine complex 2. (e) Experimental ¹H-signal group differences of spermine in complex and pure spermine. (f) Calculated versus experimental ¹H-signal group differences of spermine in complex and pure spermine.

used as an internal standard for 0 ppm). For discrimination of complex 1 and 2 as well as comparison with experimental data the spermine proton signal groups denoted A–E are discussed only (see Figure 1c). Results are listed in Table 1 and visualized in Figure 2e and f. The calculated proton signal group differences of complex 2 agree well with experiment whereas the difference pattern of complex 1 is in distinct disagreement. The deviations in the proton signal group difference pattern

between complex 2 and experiment especially for signal group A/A' can be traced to solvent effects which are not taken into account in the DFT calculation of the isolated complex.

Rotational barrier estimation

Due to the flexibility of cucurbit[6]uril the spermine ligand is likely to perform rotations within the

Table 1. Calculated and experimental relative ^1H -NMR signal group differences for spermine signal groups A–E (see Figure 1c) between cucurbit[6]uril-spermine complex and pure spermine (in ppm)

Spermine proton signal group	A/A'	B/B'	C/C'	D/D'	E/E'
Experimental ^1H -signal group differences [ppm] (see Figure 2e)	0.69/0.69	0.44/0.44	0.36/0.36	-0.25/-0.25	-0.92/-0.92
Calculated ^1H -signal group differences of complex 1 [ppm]	-1.16/-0.03	-1.03/-0.10	-1.33/-0.17	0.40/0.08	0.39/0.15
Calculated ^1H -signal group differences of complex 2 [ppm]	0.02/0.02	0.22/0.23	0.22/0.23	-0.73/-0.76	-1.07/-1.07

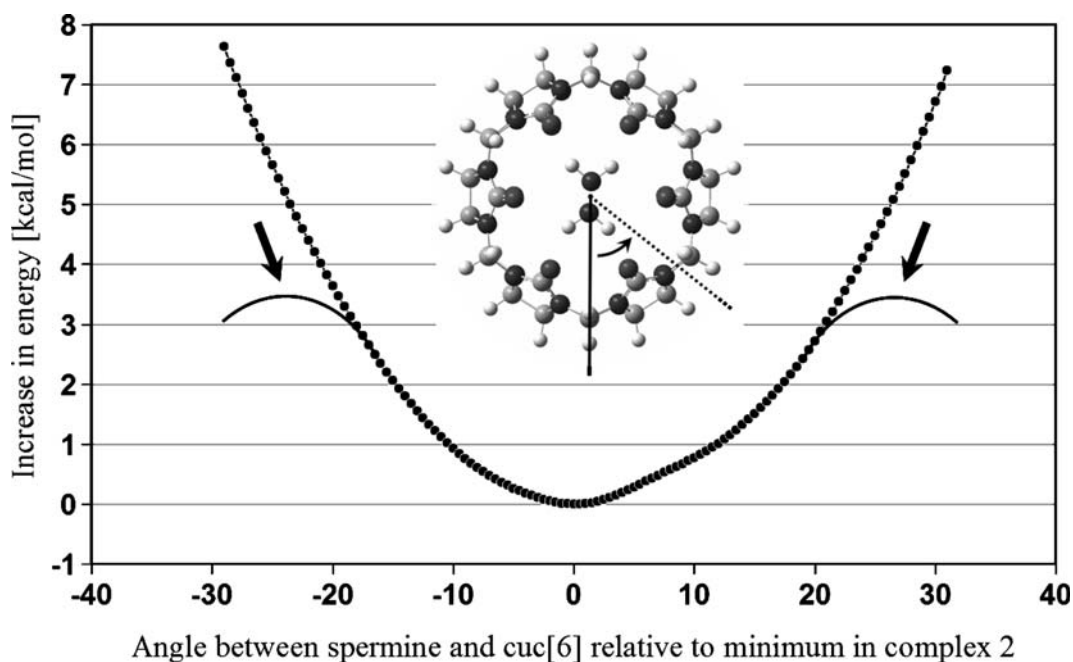


Figure 3. Calculated rotation of “static” spermine within “static” cucurbit[6]uril. The assumed “real” rotational barrier is indicated with the arrows. Each point is the result of a single point calculation of a cucurbit[6]uril-spermine complex geometry with a fixed angle between cucurbit[6]uril and rotated spermine. The minimum energy complex 2 corresponds to angle 0. The angle is sketched in the molecule drawing, the axis of rotation is perpendicular.

cucurbit[6]uril host molecule. An approximated “static” estimation of the associated rotational energetic barrier is given in Figure 3. For the calculations the angle between a “static” spermine and “static” cucurbit[6]uril (both with conformations identical to those of complex 2) was incremented relative to the energetic minimum of complex 2: The energies of the resulting complex geometries with rotated spermine were determined with single point calculations. The resulting “static” rotational energy path lies well above the real minimum rotational energy path with adapting geometries of both spermine and cucurbit[6]uril. As indicated in Figure 3 the real rotational barrier can be estimated to be in the order of a few kilocalories per mole so that spermine is likely to exhibit rotations within the cucurbit[6]uril host at room temperature.

Conclusions and prospects

The DFT calculations for cucurbit[6]uril-spermine allowed promising insights into some characteristics of the complex formation of cucurbit[6]uril with the spermine ligand. The complex can be regarded as a perfect induced fit of spermine with cucurbit[6]uril which results

in a very stable and symmetric combination. Due to its distinct geometrical flexibility cucurbit[6]uril acts like a “mechanical claw”. Both molecules are mutual complementary with regard to their electrostatic surface characteristics and a special contribution to the electronic interaction can be attributed to the interplay of spermine amino groups and the cucurbit[6]uril portal oxygen atoms. The energetically favoured calculated complex geometry can be shown to agree well with experimental NMR results so that an overall plausible picture is attained. The energetic barrier for spermine rotations within the cucurbit[6]uril host molecule can be estimated to be so small that these rotations are to occur at room temperature.

The described treatment of host-ligand complex formation for cucurbit[6]uril and spermine encourage further theoretical investigations of the interesting chemistry of cucurbit[n]uril family of molecules.

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