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Repulsive Interaction Can Be a Key Design Element of Molecular Rotary Motors

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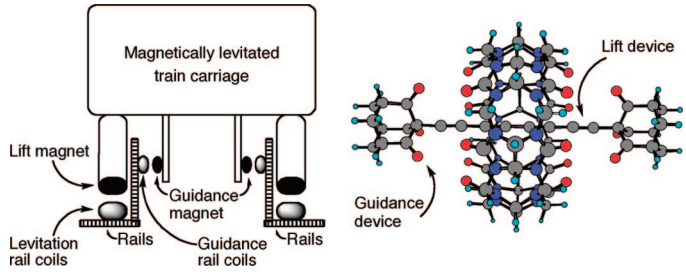

Low-barrier molecular rotary motors having rotaxane architecture can be constructed using a cucurbituril host and a polyyne guest serving as stator and rotator, respectively. The repulsive interaction between these components is supported by molecular mechanics calculations with model systems and experimentally verified by X-ray crystallography with several synthetic host−guest complexes, all suggesting that the diyne rod floats at the center of the macrocyclic host with no apparent van der Waals contacts between them. Further support for these interactions is suggested by microcalorimetry measurements.

Introduction

The hypothesis that molecular scale rotary motors[1] can be designed and constructed from synthetic components originated from the available structural information about the biological precedents,[2] such as the bacterial flagellar motor[3] and the ATP synthase,[4] which interconvert chemical energy and coordinated mechanical motion. For example, ATP synthase, which is the smallest known biological motor, is composed of a rotator within a stator, fuelled by a proton gradient to produce ATP. It can also operate reversibly to consume ATP and produce mechanical motion. Although through nature, we have learned that such devices are synthetically attainable, the actual design and synthesis of molecular rotary motors has been greatly inspired by the basic principles of physics, supramolecular chemistry, and mechanical engineering. Synthetic motors could offer considerable advantages in developing complex nanomachinery because they can tolerate a more diverse range of conditions than biological machines.

Most of the reported efforts to synthesize molecular rotary motors, including bevel gears, propellers, a three-propeller system, and molecular turnstiles,[5−9] have exploited intramolecular interactions with one molecular fragment rotating with

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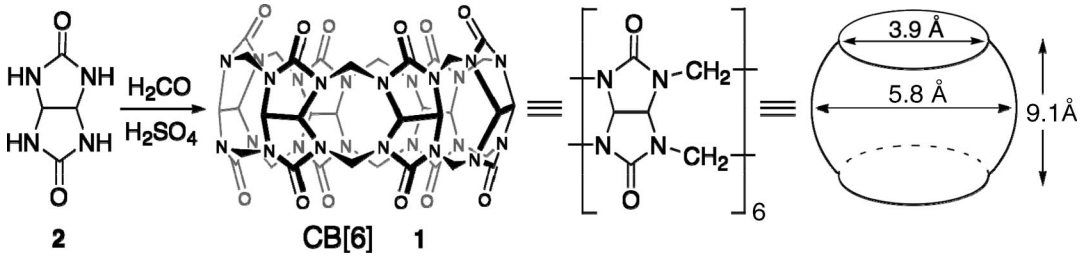
SCHEME 1. Cucurbit[6]uril, 1, and Its Precursor, Glycoluril, 2



respect to the rest of the molecule around one or two single bonds.[10] An alternative approach to such machines exploits the rotaxane's architecture,[11] which consists of a macrocyclic molecule hosting a linear guest molecule that is terminated by two bulky stoppers.[12,13]

Rotaxanes can exhibit three types of motion: rotation of a wheel around an axle (or a rotator inside a stator, which depends on the frame of reference), shuttling of the wheel along the axle in a piston-like motion,[14] and a pivoting motion, where the angle between the axle and the main axis of the host changes. Circumrotation in catenanes was also investigated.[15] External stimuli, such as light, thermal energy, or electrochemical energy, have been used to control the motion, including the threading/unthreading motion of pseudorotaxanes.[16−20] An external electric field has been shown to induce the rotation of a rotaxane wheel around its axle, demonstrating that rotaxanes could interconvert different types of energy and therefore may potentially be used as energy converters.[21]

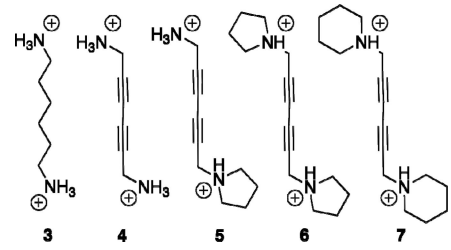
A relatively ignored but quite challenging design element is the need for high-speed rotation, which requires a low barrier for rotation.[18,22] One may use the macroscopic term "friction" metaphorically to describe rotation that involves very low energy barriers. We suggest that, in order to achieve minimal friction, the rotator−stator couple should repel one another. This strategy has not been pursued at the molecular level, except for the notion that repulsive interactions could lower the rotational barrier of methyl-sized molecular rotators.[23] In the macro world, however, this idea has already been applied for linear motion. For example, the dynamic stability of repulsive-force magnetic levitation (maglev) suspension systems has been exploited in designing high-speed trains.[24] One constant magnet on the maglev train carriage is positioned against a rail electromagnet for levitation and a second magnet on the train is positioned against another electromagnet on the L-shaped rails for directional control. All magnet pairs are kept at repulsive interactions.[25]

Here we report on host−guest molecules that could serve as synthetic building blocks for the construction of frictionless rotary motors. Our stator−rotator couple is based on the rotaxane-type architecture, with a macrocyclic cucurbituril host serving as the stator, and a rigid, polyyne guest serving as the rotator. We support the proposition of repulsive interaction between these two components by molecular mechanics calculations with model systems and by experimental data of microcalorimetry and X-ray crystallography.

Results and Discussions

Cucurbit[6]uril (CB[6], **1**)[26−28] is a macrocyclic cavitand, which is obtained by acid-catalyzed polycondensation of glycoluril, **2**, with formaldehyde (Scheme 1).[29] Its rigid structure, combined with a hydrophobic cavity and polar portals, renders the CB[*n*] cavitands good hosts for neutral molecules,[30,31] essentially any metal cation,[32−34] and, in particular, cations that can form hydrogen bonding, such as ammonium cations.[35,36]

SCHEME 2. Diammonium Guest Molecules



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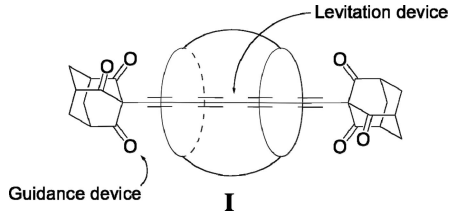
One of the best-known binders of **1** is the doubly protonated form of 1,6-diaminohexane, **3** (Scheme 2).[35] Three modes of attractive interaction probably contribute to the high affinity between **1** and **3** in water: the charge−dipole interaction between the ammonium group and the hexacarbonyl portal, hydrogen bonding between the same, and hydrophobic interaction between the hydrocarbon chain of **3** and the interior of **1**.[37,38] We anticipated that replacing the flexible hexamethylene chain of **3** by a rigid, hexadiyne fragment, as shown in **4**, would diminish the hydrophobic binding interaction and even lead to repulsive interaction between the diyne rod and the interior of **1** owing to the high electron density of both diyne and the interior of **1**.[39] Moreover, we expected that the 48 nonbonding electrons of the carbonyl oxygens of **1** and the filled π-orbitals of the 12 urea groups would repel the π-electrons of the diyne rod. Consequently, one could predict that, if a polyyne rod is inserted into the cavity of **1**, the repulsive interaction should keep it floating at the center of the cavity in perfect alignment with the 6-fold symmetry axis of **1**.

Our general rotaxane architecture requires a second mode of repulsive interaction between the two molecular partners, one that minimizes the friction between the portals of **1** and the bulky stoppers of the guest molecule. This requirement, which is analogous to the guidance device in the maglev train, could be achieved by designing stoppers equipped with a strong dipole moment that opposes the dipole moment of the portal, for example, the trioxoadamantyl group in structure **I** (Figure 1). Such repulsive interactions would maintain the two stopper groups floating at a maximal distance from the portals.



I

FIGURE 1. Potential components for a CB[6]-based molecular rotary motor.

In order to verify the above predictions, we carried out energy minimization of the hypothetical complexes **I**, **II**, and **III**, using MOLOC software[40] (Figure 2). The adamantyl groups in **II** represent a fully saturated hydrocarbon stoppers, whereas the triphenylmethyl groups in **III** represent a polyaromatic stopper. The calculated interatomic distances between the propargylic carbons C and C′ (denoted in red in Figure 2) and each of the carbonyl oxygen atoms of the adjacent portal of **1** (Table 1) indeed matched the above predictions. In structure **I**, which represents an extreme case of a dipole−dipole repulsive interaction, both stoppers are positioned at a maximal distance from the portal with equal interatomic distances between either C or C′ and any of the neighboring carbonyl oxygens (4.55−4.56 Å). In contrast, structure **II** represents a case in which there is some attractive interaction between the stopper and the near portal, resulting in nonsymmetrical positioning of **1** between the two stoppers: one stopper is closer to the portal (3.95 ± 0.01 Å), whereas the other stays at a much longer distance (5.25 ± 0.11 Å). Structure **III** represents an intermediate case, where **1** is positioned at roughly equal distances from the two stoppers (4.48 ± 0.23 and 4.62 ± 0.14 Å), but with a significant departure of the stoppers from the 6-fold axis of **1**. This situation probably reflects some attractive interaction between the aromatic rings and the portals.

An essential step toward experimentally verifying the calculated results was the synthesis of simpler complexes of **1** with diyne diammonium salts. Four 1,6-diaminohexa-2,4-diyne derivatives, **4**−**7** (Scheme 2), were prepared in order to study their binding to **1**. Such diammonium salts could serve as potential intermediates in the future preparation of the desired rotary motors. Compound **4** was prepared by oxidative Hay coupling of propargyl alcohol, followed by replacement of the hydroxy groups by phthalimide via the Mitsunobu reaction.[41] Compounds **6** and **7** were prepared by transforming propargyl bromide to the appropriate propargyl amine, followed by a modified Hay coupling under acidic conditions.[42] Compound **5** was synthesized by cross-coupling of *N*-propargyl proprionamide with 3-hydroxy-1-iodopropyne[43] using catalytic amounts of copper(I) iodide in pyrrolidine.[44] Mitsunobu substitution of the alcohol by pyrrolidine[45] and deprotection in refluxing aqueous hydrochloric acid afforded **5**.[46] All compounds were isolated and characterized in the form of their bis-hydrochloride salts.

Isothermal titration calorimetry (ITC) experiments afforded useful thermodynamic parameters of the host−guest affinities, including the binding constant (K_b), the binding stoichiometry (n), enthalpy (ΔH), and entropy (ΔS) of binding.[47] We carried out the titrations by loading the ITC sample cell with saturated aqueous solution of **1** (1.4 mL) and titrated it with a neutral aqueous solution of one of the diammonium salts, **3**, **4**, **6**, or **7** (3.3−5.0 mM). The heat generated during each injection was recorded (Figure 3), and the thermodynamic parameters (Table 2) were obtained from a nonlinear least-squares fit of the data to a one-site binding model.[47] Although binding constants between **1** and various diammonium salts have been previously determined either by NMR[36b] or by calorimetry in strongly acidic media (40−50% formic acid),[26] the reported data varied significantly because they are pH dependent.[28]

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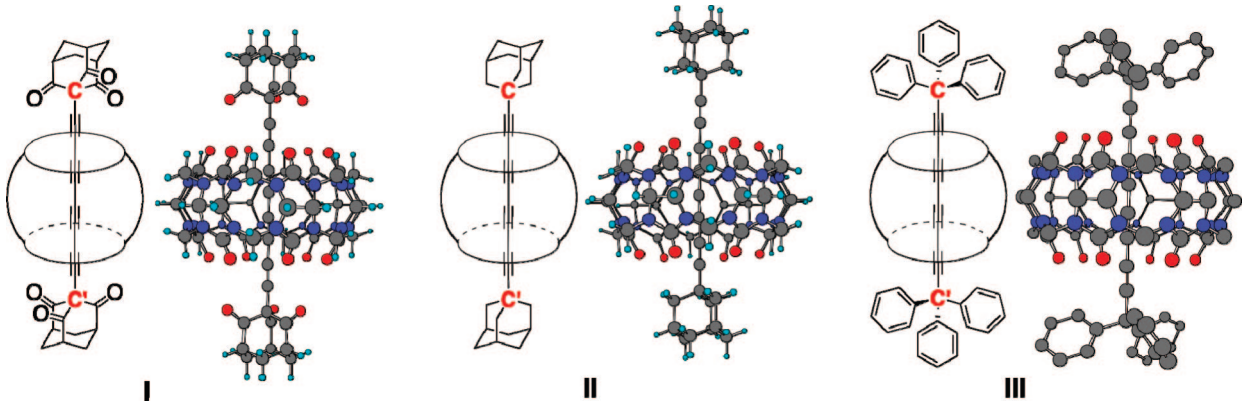


FIGURE 2. MOLOC calculated structures of complexes **I**, **II**, and **III**. Color code: red, oxygen; blue, nitrogen; gray, carbon; cyan, hydrogen. The propargylic carbons, C and C′, are denoted in red.

TABLE 1. Interatomic Distances between the Propargylic Carbons of the Guest, C, C′, and Each of the Six Carbonyl Oxygen Atoms on the Adjacent Portal of the Host, 1

atoms	I	II	III
C−O_1	4.55	5.33	4.51
C−O_2	4.55	5.36	4.52
C−O_3	4.55	5.24	4.57
C−O_4	4.55	5.28	4.23
C−O_5	4.56	5.16	4.68
C−O_6	4.56	5.18	4.37
average	**4.553 ± 0.007**	**5.25 ± 0.11**	**4.48 ± 0.23**
C′−O_7	4.56	3.95	4.7
C′−O_8	4.56	3.96	4.76
C′−O_9	4.55	3.96	4.61
C′−O_{10}	4.55	3.94	4.56
C′−O_{11}	4.55	3.94	4.6
C′−O_{12}	4.55	3.97	4.53
average	**4.553 ± 0.007**	**3.95 ± 0.01**	**4.62 ± 0.14**

Although all four compounds exhibit similar dissociation constants within the range of 2−7 μM, their ΔH and ΔS values of binding vary significantly. The significant gain of binding enthalpy in the case of **3**, in comparison with the smaller gains in the cases of **4**, **6**, and **7**, is counterbalanced by the large negative entropy term of **3** (ΔS = −85.77 J/mol·K), as compared with the positive terms of **4**, **6**, and **7** (ΔS = 98 − 39 J/mol·K). Apparently, complexation of **3** requires freezing multiple rotational and vibrational degrees of freedom, resulting in a large entropy penalty, which is not the case with the rigid guest molecules **4**, **6**, and **7**. Since complexation of a diamine ligand requires expulsion of 2−3 ordered water molecules[48] from the interior of the CB[6] to the bulk solution, the entropy of association could be positive, particularly in the case of rigid polyyne ligands. In addition, some of the entropy differences arise from reorganization of solvent molecules around both host and guest.

The comparison between **3** and **4** is of particular interest because both guests have two ammonium groups separated by a chain of six carbon atoms, yet their binding enthalpies are dramatically different (ΔH = −57.57 and −2.91 kJ/mol, respectively). We assume this difference to result from a strong hydrophobic interaction between the hexamethylene chain of **3** and the interior of **1**, which adds to the attractive interaction between the ammonium groups and the polar portals of **1**. In the case of **4**, however, the interaction between the diyne rod and the interior of **1** is probably repulsive, resulting in a very small net enthalpy gain.

TABLE 2. Thermodynamic Parameters Obtained from ITC Titration of 1 by a Guest Molecule in Water at 30 °C

guest	K_d (μM)	ΔH (kJ/mol)	ΔS (J/mol·K)
3	3.53 ± 0.30	−57.57 ± 0.38	−85.77 ± 1.43
4	2.28 ± 0.25	−2.91 ± 0.02	98.32 ± 0.91
6	3.36 ± 0.56	−15.56 ± 0.18	53.56 ± 1.51
7	6.80 ± 0.87	−18.63 ± 0.24	38.91 ± 1.32

Further support for our hypothesis about the special interaction between **1** and the bisammonium diyne guests was obtained from X-ray crystallography. Three inclusion complexes, namely, **8**, **9**, and **10** (Figure 4), were prepared by addition of **1** to aqueous solutions of diammonium salts **4**, **5**, and **7**, respectively. Formation of stable inclusion complexes was evident from their ^{1}H NMR spectra and MS (MALDI-TOF) data. All complexes were crystallized from the aqueous solution over 2−3 weeks, and their single crystals were studied by X-ray crystallography (Table 1S, Supporting Information).

The solid-state structure of complex **8** is centrosymmetric (Figure 4A,B), with the unit cell containing 1 complex, 12 water molecules, and 2 HSO_4^- counteranions. The complex unit is located on an inversion center at (1/2,1/2,1/2), and the ions and water molecules are arranged around this center. The ammonium groups take up three different positions with occupancies of 0.50, 0.25, and 0.25. This observation probably reflects facile rotation around the guest axis. In any of the three positions, the nitrogen atom forms hydrogen bonds with two water molecules and with four carbonyl oxygens at the portal of **1**: N(131)—O(4) = 2.855 Å, N(131)—O(6) = 2.956 Å, N(131)—O(8) = 2.842 Å, N(132)—O(6) = 2.875 Å, N(132)—O(8) = 2.933 Å, N(132)—O(10) = 2.888 Å, N(133)—O(1)* = 2.865 Å, N(133)—O(3)* = 2.871 Å, N(133)—O(8) = 2.961 Å. Nevertheless, it is also possible that the multiple occupancy of the nitrogen atoms in this structure reflects static positional disorder of the guest molecule. The asterisk denotes the inversion center at (1/2,1/2,1/2). Both HSO_4^- ions and water molecules occupy the cavities left by the nearly spherical complexes and form long hydrogen bond chains surrounding the complex units.

Several hydrogen bonds exist among water molecules O(9), O(10), O(11), O(12), and the HSO_4^- oxygens: O(9)—O(10) = 2.899 Å, O(9)—O(12) = 2.737 Å, O(10)—O(11) = 2.939 Å, O(11)—O(13) = 2.885 Å. In the HSO_4^- ion, the bond S(1)—O(16) = 1.560 Å is much longer than the other S—O bonds (the average distance is 1.438 Å), as expected from a

(48) Freeman, W. A. *Acta Crystallogr., Sect. B* **1984**, *40*, 382.
(49) *TEXRAY Structure Analysis Package*; MSC: 3200 Research Forest Drive, The Woodlands, TX 77381, 1999.

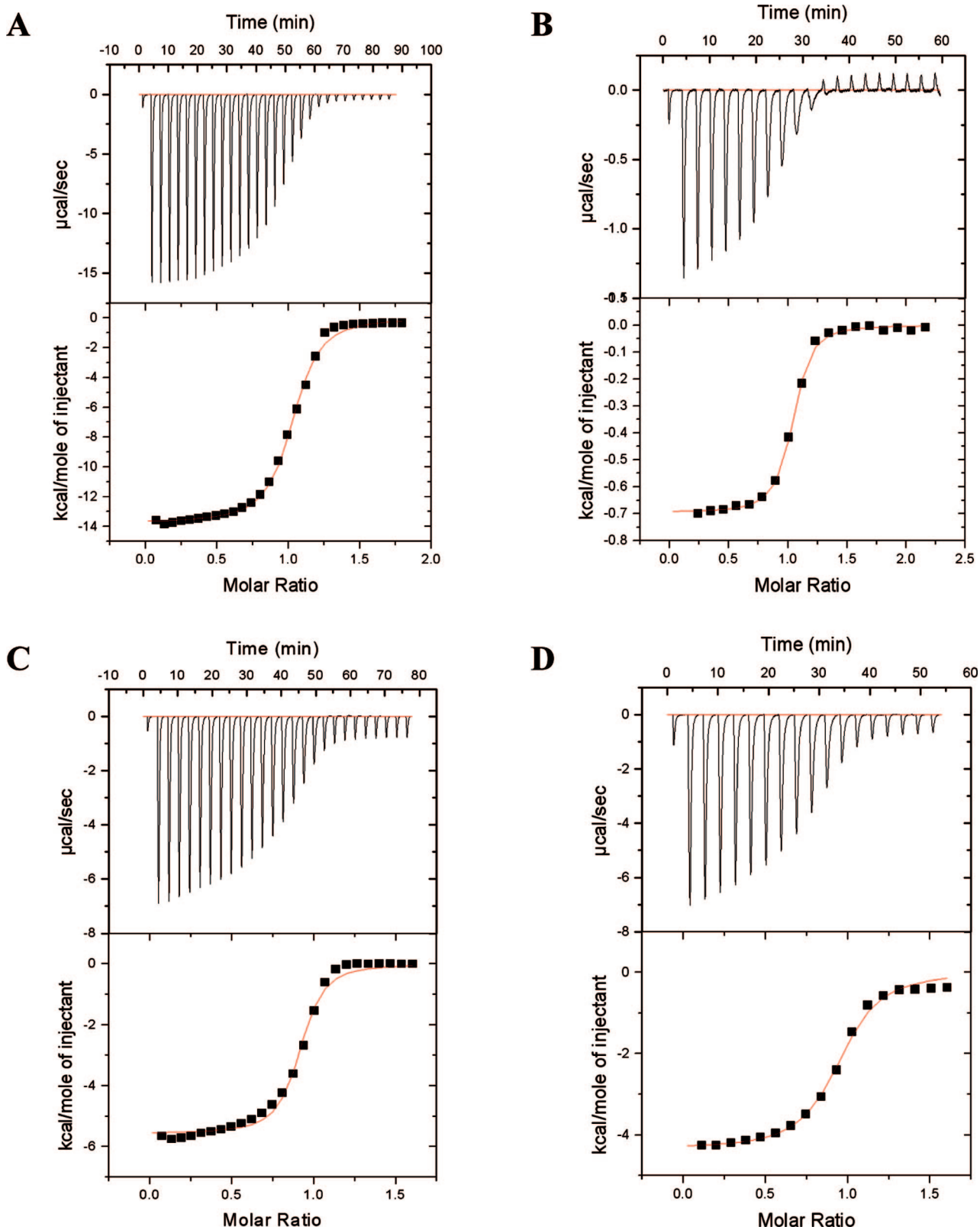


FIGURE 3. ITC titration of **1** (0.4 mM in water) with a diammonium ligand at 30 °C. (A) Ligand **3** (3.33 mM). (B) Ligand **4** (6 mM). (C) Ligand **6** (3.3 mM). (D) Ligand **7** (5.0 mM).

singly protonated sulfate ion. The guest axes of the complex units are all parallel in the crystal, as expected from the crystal structure. Most importantly, the diacetylene rod floats at the center of the macrocyclic host with no apparent van der Waals contacts between them (Figure 5). The existence of multiple rotamers with similar energy and steric demands suggests that rotation of the polyyne rotator within the CB stator is quite facile. Apparently, this motion is restricted in the solid state

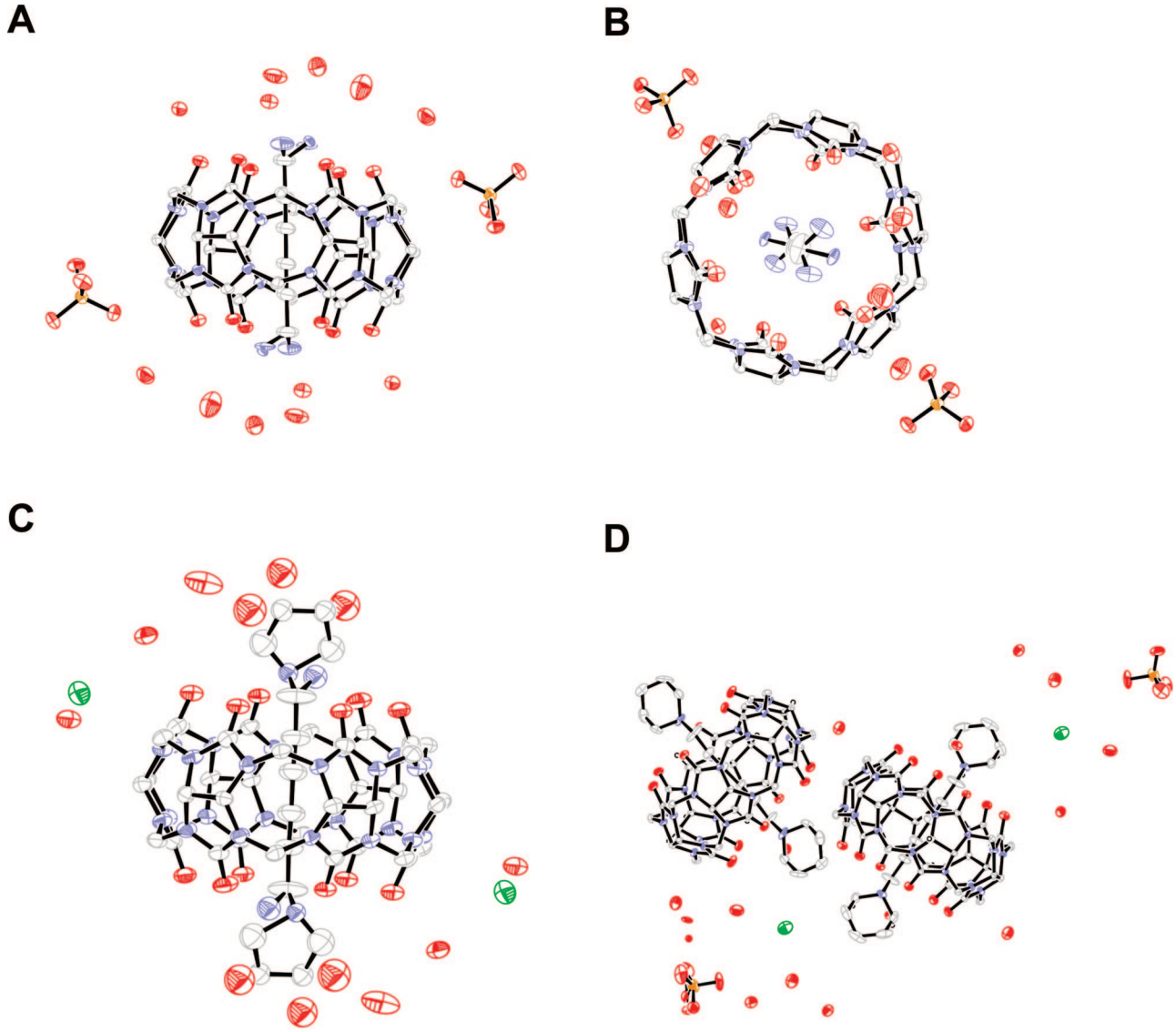


FIGURE 4. ORTEP pictures of the solid-state structure of inclusion complexes **8**: (A) side view, (B) top view, the picture shows superposition of three rotamers of the diamine guest); **9** (C) the picture shows superposition of two orientations of the diamine guest with respect to the host); and **10** (D). Color code: red, oxygen; blue, nitrogen; gray, carbon; brown, sulfur; green, chloride. Hydrogen atoms were omitted for clarity. The pictures show the complexes and part of their environment.

due to the fixed position of the counteranions and the network of hydrogen bonds, which includes all water molecules, counteranions, and ammonium cations.

The structure of **9** is pseudo-centrosymmetric, with a unit cell that contains two such complexes (Figure 4C), each associated with two chloride counteranions and nine water molecules, all interconnected by hydrogen bonds. One complex is located on an inversion center at (0,0,1/2), but its guest, **5**, is disordered between two sites at the two portals, with each site being occupied either by a pyrrolidinium ring (50%) or by an ammonium group hydrogen bonded to a network of three water molecules, O(7), O(8), and O(12) (all together 50%). Only one hydrogen bond, N(13)—O(4) = 2.754 Å, is formed between the pyrrolidinium nitrogen and a carbonyl oxygen of **1**, whereas the ammonium nitrogen creates one hydrogen bond with a carbonyl oxygen, N(14)—O(5) = 2.806 Å, and two bonds with water molecules, N(14)—O(7) = 3.163 Å, N(14)—O(8) = 2.748 Å. The other water hydrogen bonds are as follows: O(7)—O(12) = 3.124 Å, O(8)—O(12) = 3.111 Å, and O(7)—O(9) = 2.856 Å, O(9)—O(10) = 2.779 Å. Other hydrogen bonds between water, carbonyl oxygens, and chloride ions were also observed: O(10)—O(3) ($-x$, $-y$, $1 - z$) = 2.957 Å, O(10)—Cl(1) = 3.158 Å, and Cl(1)—O(11) = 3.145 Å. Again, as in the case of **8**, the diyne rod in **9** floats at the center of **1** with no apparent van der Waals contacts.

The unit cell of **10** contains two inclusion complexes (Figure 4D). The asymmetric unit contains two complex unit halves, A and B (upper left and lower right in Figure 4D, respectively), located on inversion centers at (1, 1/2, 0) and (1/2, 0, 1/2), respectively, one HSO_4^- and one Cl^- counteranion and nine water molecules. The guest, **7**, is included inside the cavity of **1**, with its piperidinium nitrogen forming H-bonds with one carbonyl oxygen. The guest takes only one rotational position inside the cavity for both A and B halves, but binding differs with respect to the hydrogen bonding with the carbonyl oxygens: N(13A)—O(2A) = 2.870 Å, N(13B)—O(1B) = 2.884 Å, and N(13B)—O(3B) = 2.938 Å. Also, carbonyl oxygens are hydrogen bonded to water molecules as follows: O(1A)—O(10S)

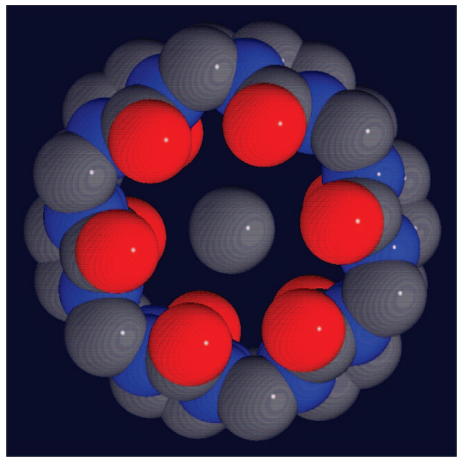


FIGURE 5. Space-filling presentation of **8** (top view) generated by the Chem-Ray molecular graphics program.[49] The nitrogen atoms of guest **4** were omitted for clarity.

= 2.845 Å, O(4A)—O(8S) = 2.881 Å, O(6A)—O(10S) = 2.828 Å, O(2B)—O(11S) = 2.783 Å, and O(4B)—O(11S) = 2.774 Å. Some hydrogen bonds are formed among the water molecules: O(5S)—O(7S) = 2.707 Å, O(7S)—O(9S) = 2.797 Å, O(11S)—O(9S)* = 2.721 Å, and also between ions and water molecules as follows: C(11)—O(7S) = 2.990 Å, C(11)—O(8S) = 3.012 Å, and O(3S)—O(5S) = 2.549 Å. The asterisk denotes the inversion center at (1/2,1/2,1/2). Within the unit cell, the guest axes of type A or B are aligned parallel through the inversion centers of the cell. Pairs of crystallographically independent types align in different directions. The HSO_4^- ion and the neighboring water molecule, O(13), are disordered between two sites. In contrast to the cases of **8** and **9**, the guest main axis in **10** is slightly distorted from perfect alignment with the main axis of the host, probably due to the crystal packing forces. A simple method was used to calculate the distortion angle using three points that form a triangle: the inversion center of **1**, the center of the portal of **1**, and the center of the propargylic carbon of guest, **7**. Thus, the deviation of the two axes from perfect alignment is 11.3° for complex A and 7.1° for complex B. This deviation is also manifested in nonsymmetrical positioning of the propargylic carbon within the portal of **1**. For complex A, the shortest contact is C(21A)—O(6A) = 3.03 Å and the longest contact is C(21A)—O(5A) = 4.32 Å. For complex B, the shortest contact is C(21B)—O(2B) = 3.15 Å and the longest contact is C(21B)—O(1B) = 3.73 Å.

In summary, we propose a new approach for the design of a frictionless rotator—stator couple. The specific example is based on a rotaxane-type architecture with a cucurbituril host and a polyyne guest. The feasibility of the key design element, which is the repulsive interaction between these components, is supported by molecular mechanics calculations with model systems and by X-ray crystallographic data from three synthetic inclusion complexes, all suggesting that the diyne rod floats at the center of the macrocyclic host with no apparent van der Waals contacts between them. Further support for these interactions is provided by microcalorimetry measurements. Synthetic work toward low friction molecular rotary motors is currently underway in our laboratories.

Experimental Section

Hexa-2,4-diyne-1,6-diammonium dichloride, 4. Hexa-2,4-diyne-1,6-diamine was prepared using the literature procedure. The product was recrystallized from methanol/diethyl ether to give **4** (74% yield) as a brown solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.74 (br s, 6H), 3.9 (d, J = 6 Hz, 4H); ^{13}C NMR (75.44 MHz, DMSO-d_6) δ 73.4, 69.1, 28.6 ppm.

Inclusion Complex of 1 with Hexa-2,4-diyne-1,6-diammonium bis-hydrosulfate, 8. An aqueous solution of **1** was added to a solution of diammonium salt, **4**, in water. The mixture was stirred overnight at room temperature, then filtered, and the filtrate was concentrated to give the crude product, which was dissolved in a minimum amount of water. Methanol was slowly added, and the resulting precipitate was filtered and washed with methanol and dried to give the inclusion complex **8**. Apparently, compound **1**, which was used for this preparation, was contaminated with sulfuric acid, a fact that resulted in incorporating hydrosulfate anions within the crystal of **8**: ^{1}H NMR (300 MHz, D_2O) δ 5.73 (d, 12H), 5.58 (s, 12H), 4.04 (d, 12H), 3.8 (s, 4H).

1,6-Dipiperidinium-2,4-hexadiyne dichloride, 7. Preparation was carried out as reported earlier.[42] 1,6-Dipiperidino-2,4-hexadiyne was dissolved in ethanol and was treated with concentrated hydrochloric acid until the pH of the solution reached 2. Then the product was recrystallized from ethanol/diethyl ether to give 0.7 g (44% yield): ^{1}H NMR (300 M Hz, D_2O) δ 1.46 (m, 2H), 1.70 (m, 6H), 1.94 (m, 4H), 3.05 (t, 4H), 3.59 (d, 4H), 4.10 (s, 4H); ^{13}C NMR spectra (75.44 MHz, D_2O) δ 72.0, 68.4, 52.5, 45.8, 22.4, 20.2 ppm; MS (CI) m/z 245.2 (M + 1).

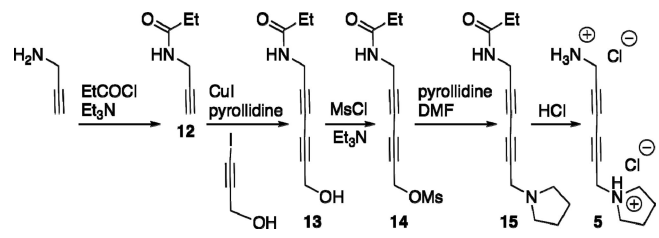
Inclusion Complex of 1 with 1,6-Dipiperidinium-2,4-hexadiyne dichloride, 10. An aqueous solution of **1** was added to a solution of 1,6-dipiperidinium-2,4-hexadiyne dichloride in water; the mixture was stirred for 15 min with gentle heating with a heat gun, then filtered with a microfilter, and acetone was added until precipitation occurred. The mixture was left overnight at room temperature and then centrifuged; the solid was washed with acetone, and the same procedure was repeated to give the pure inclusion complex, **10**: ^{1}H NMR (300 MHz, D_2O) δ 5.68 (m, 12H), 5.59 (s, 12H), 4.39 (m, 12H), 3.78 (s, 4H) 2.97 (m, 12H), 1.72 (m, 6H), 1.52 (m, 2H); ^{13}C NMR (75.44 MHz, D_2O) δ 156.2, 71.5 68.5, 52.2, 49.5, 46.1, 23.2, 21.1 ppm; MS (MALDI-TOF) m/z 1242 (M).

1,6-Dipyrrolidinium-2,4-hexadiyne dichloride, 6. Preparation was carried out as reported earlier.[42] 1,6-Dipyrrolidino-2,4-hexadiyne was dissolved in ethanol, and concentrated HCl was added to reach pH 2. The product was recrystallized from ethanol/diethyl ether (0.6 g, 55%): ^{1}H NMR (300 MHz, D_2O) δ 1.74 (t, 8H), 2.53 (t, 8H), 3.43 (t, 4H); ^{13}C NMR (75.44 MHz, D_2O) δ 70.7, 69.0, 53.4, 43.2, 22.6 ppm; MS (CI) m/z 217 (M + 1).

Inclusion Complex of 1 with 1,6-Dipyrrolidinium-2,4-hexadiyne dichloride, 11. This complex was prepared by using the above-described procedure for preparing **10**: ^{1}H NMR (300 MHz, D_2O) δ 5.53 (d, 12H, J = 15.6 Hz), 5.32 (s, 12H), 4.07 (d, J = 15.6 Hz, 12H), 4.08 (s, 4H) 3.11 (m, 4H), 1.94 (br, 8H), 1.8 (br, 4H); MS (MALDI-TOF) m/z 1214 (M).

1-Ammonium-6-pyrrolidinium-hexa-2,4-diynye dichloride, 5 (Scheme. 3).

SCHEME 3. Synthetic Scheme for Obtaining *N*-6-Pyrrolidiniumhexa-2,4-diynyl ammonium dichloride, 5



***N*-Propargyl propionamide, 12.** Triethyl amine (19 mL, 0.14 mol) was added to a solution of propargyl amine (5 g, 0.09 mol) in dichloromethane (DCM, 50 mL), cooled to 0 °C, after which a

solution of propionyl chloride (9.4 mL, 0.109 mol) in DCM (50 mL) was added dropwise, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water (20 mL), the organic layer was collected, and the aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4, concentrated, and finally purified by flash column chromatography (silica gel, 20% ethyl acetate in hexane) to give **12** (7.4 g, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.27 (br s, 1H), 4.01 (dd, J = 4.5, 3 Hz, 2H), 2.23 (q, J = 9.5 Hz, 2H), 2.21 (t, J = 6.5 Hz, 1H), 1.13 (t, J = 9.5 Hz, 3H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 173.6, 79.7, 71.2, 29.2, 28.9, 9.5 ppm.

***N*-(6-Hydroxyhexa-2,4-diynyl)propionamide, 13.** Copper iodide (104 mg, 0.5 mmol) was added to a stirred solution of iodopropargyl alcohol[43] (1 g, 5.5 mmol) and **12** (11 mmol) in pyrrolidine (5 mL) at 0 °C under argon. The mixture was stirred at room temperature for 30 min, quenched with aqueous ammonium chloride, and extracted with diethyl ether. The organic extract was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, 40% ethyl acetate in hexane), to give **13** as a colorless solid (58%): ^{1}H NMR (300 MHz, DMSO) δ 8.29 (br t, J = 4.8 Hz, 1H), 5.41 (t, J = 5.4 Hz, 1H), 4.15 (d, J = 5.7 Hz, 2H), 3.97 (d, J = 5.4 Hz, 2H), 2.1 (q, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.44 MHz, DMSO) δ 172.8, 78.6, 77.3, 67.9, 65.6, 49.3, 28.4, 28.2, 9.7 ppm.

6-(Propionamido)hexa-2,4-diynyl methanesulfonate, 14. Triethyl amine (0.5 mL, 3.6 mmol) and methanesulfonyl chloride (0.23 mL, 2.9 mmol) were added to a solution of **13** (0.4 g, 2.4 mmol) in DCM (5 mL) at 0 °C; the mixture was stirred at room temperature for 1.5 h, quenched with water (10 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layer was washed with aqueous $NaHCO_3$ solution, water, and brine, dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, 50% ethyl acetate in hexane) to give **14** (0.51 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (br s, 1H), 4.97 (s, 2H), 4.21 (m, 2H), 3.19 (s, 3H), 2.30 (q, J = 6.5 Hz, 2H), 1.21 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 174.0, 78.7, 73.9, 69.8, 66.6, 58.1, 39.4, 29.9, 29.7, 9.9 ppm.

***N*-(6-(Pyrrolidin-1-yl)hexa-2,4-diynyl)propionamide, 15.** [45] Pyrrolidine (0.14 mL, 1.65 mmol) was added to a stirred solution of **14** (0.2 g, 0.82 mmol) in DMF (2 mL), and the reaction mixture was stirred at room temperature until completion (monitored by TLC), then quenched by water (8 mL), and extracted with ether (3 × 30 mL). The ether layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, 40% ethyl acetate in hexane) to give **14** (0.098 g, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (br s, 1H), 4.03 (d, J = 4.5 Hz, 2H), 3.42 (s, 2H), 2.54 (m, 4H), 2.16 (q, J = 6.5 Hz, 2H), 1.73 (m, 4H), 1.08 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75.44 MHz, $CDCl_3$) δ 173.6, 74.7, 73.5, 68.5, 67.2, 52.2, 43.2, 29.4, 29.0, 23.6, 9.5 ppm.

***N*-6-Pyrrolidiniumhexa-2,4-diynyl ammonium dichloride, 5.** [46] Propionamide **15** (0.098 g, 0.45 mmol) was mixed with aqueous HCl (8 M, 4 mL), and the solution was refluxed overnight, allowed to cool to room temperature, and extracted with DCM (2 × 10 mL). Next, the aqueous part was separated, and the water was evaporated. The residue was dissolved in MeOH and precipitated out with ether. Finally, the precipitate was filtered and dried to give **5** (0.80 g, 76%): ^{1}H NMR (400 MHz, D_2O) δ 4.23 (s, 2H), 3.96 (s, 2H), 3.67 (m, 2H), 3.22 (m, 2H), 2.15 (m, 2H), 2.01 (m, 2H); ^{13}C NMR (75.44 MHz, D_2O) δ 73.3, 73.1, 71.2, 70.4, 55.4, 45.3, 31.1, 24.6 ppm.

Inclusion Complex of 1 with 5 and 9. The same procedure described above for the preparation of complex **8** was followed; the inclusion complex **9** was prepared from **1** and **5**: ^{1}H NMR (400 MHz, D_2O) δ 7.37 (br s, 1H), 7.24 (br s, 3H), 5.57 (2d, J = 13.5 Hz, 12H), 5.48 (s, 12H), 4.34 (2d, J = 13 Hz, 12H), 4.34 (m, 2H), 4.18 (m, 2H), 3.83 (m, 2H), 3.09 (m, 2H), 2.02 (m, 4H).

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Supporting Information Available: General experimental procedures for synthetic, microcalorimetry, and X-ray structure studies; table of crystallographic data and refinement details; tables of atom coordinates of MOLOC calculations of complexes **I**, **II**, and **III**; NMR spectra for compounds **8**, **10**, and **11**; and separate cif files for compound **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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