# Guest Exchange by a Partial Energy Ratchet in Water

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# Guest exchange by a partial energy ratchet in water.

Xue Yang,[a] Qian Cheng[b] Valerie Monnier,[c] Laurence Charles,[a] Hakim Karoui,[a] Olivier Ouari,[a] Didier Gigmes,[a] Ruibing Wang,*[b] Anthony Kermagoret,*[a], and David Bardelang*[a]

**Abstract:** Molecular machines are ubiquitous in nature and function away from equilibrium by consuming fuels to produce appropriate work. Chemists have recently excelled at mimicking the fantastic job performed by natural molecular machines with synthetic systems soluble in organic solvents. In efforts toward analogous systems working in water, we show that guest molecules can be exchanged in the synthetic macrocycle cucurbit[7]uril by involving kinetic traps, and in such a way as modulating energy wells and kinetic barriers using pH, light and redox stimuli. Ditolyl-viologen can also be exchanged using the best kinetic trap and interfaced with alginate thus affording pH-responsive blue, fluorescent hydrogels. With tunable rate and binding constants toward relevant guests, cucurbiturils may become excellent ring molecules for the construction of advanced molecular machines working in water.

Biological molecular motors are fascinating architectures performing highly specialized and crucial tasks for different types of cells. Proteins (and most often protein assemblies) involved in these machines function away from equilibrium to generate directional motion closely linked to ratchet type mechanisms.[1, 2, 3, 4] These features have allowed them to produce the work necessary for cell machinery such as that required for the directional transport of RNA in the ribosome,[5] for protein translocation across cell membranes,[6] or for muscle contraction.[7] While the working principles of natural molecular motors have started to be understood, chemists have begun to design and study increasingly complex artificial molecular machines.[8, 9, 10, 11, 12] The quest toward synthetic molecular motors,[13, 14, 15] has progressively resulted in a paradigm shift to out of equilibrium systems.[16, 17, 18, 19] Landmark achievements were obtained with interlocked structures (rotaxanes and catenanes) enabling to discover artificial unidirectional ring transport,[20, 21, 22] molecular pumps,[23, 24] or catalysis,[25] relying on energy ratchet[26] or information ratchet[27, 28] mechanisms, processing relevant fuel, and controlling the depth of energy wells and the height of kinetic barriers. However, we are not aware of artificial molecular machines featuring macrocycles working out-of-equilibrium in water.[29]

In 2000, the chemistry of the synthetic macrocycle cucurbit[6]uril dramatically expanded after the reports of lower and higher size homologues.[30, 31] Cucurbit[n]urils (CB[n])[32, 33, 34, 35, 36] have since then been used in a plethora of applications in water,[37, 38, 39, 40, 41, 42] including molecular machines[43, 44, 45] or more recently systems working away from equilibrium,[46, 47, 48] In about 20 years, key results were obtained by the teams of Isaacs, Kim, Kaifer and others illustrating the relevance of using CB[n] for self-sorting,[49, 50, 51, 52] stimuli-responsive systems,[42, 45, 53, 54, 55] or for kinetic versus thermodynamic control.[56, 57] In 2002,[58], [59] the inclusion of methyl-viologen in CB[7] was reported opening a new prolific interface. Later, pH was shown to trigger shuttling of CB[7] on and off over a viologen axle featuring carboxylate groups.[60] CB[7] was also demonstrated to be hardly expelled out of relevant threads carrying carboxylic acids at basic pH,[61, 62] when better partners are present.[63, 64] These systems highlight the frontier between pseudo-rotaxanes and rotaxanes that can sometimes be blurred.[65, 66, 67] These studies also showed that effective kinetic traps can be prepared in water, systems that can in principle be used to build assemblies working away from equilibrium.[68] Finally, Masson and co-workers set the challenge to build energy ratchets based on CB[n] in 2018.[68] Here we show that, by combining two guest molecules with CB[7] (Figure 1), the 1st responding to pH and the 2nd to oxidoreduction, CB[7] can be transiently transported out-of-equilibrium on a disfavored station thereby affording a partial energy ratchet in water. One of the key features of this system lies in a kinetic trap[69, 70, 71] where CB[7] is blocked on a viologen and cannot escape from it due to repulsive interactions between the two carbonyl rims of the host and the negatively charged carboxylate groups of the viologen thread.

The first guest 4,4'-bis(carboxyphenyl)-bipyridinium (Figure 1) possesses three potential stations for CB[7] binding: phenylene-viologen-phenylene (**PVP**). This compound was previously studied in the context of metal-organic rotaxane frameworks involving CB[7].[72] ^{1}H NMR titrations at near neutral pH showed that at 1 equiv. of CB[7], the host prefers binding station V (viologen) while at 2 equiv. of CB[7], two host molecules are on stations P (Figures S1 and S2), in line with previous reports.[62] Mass

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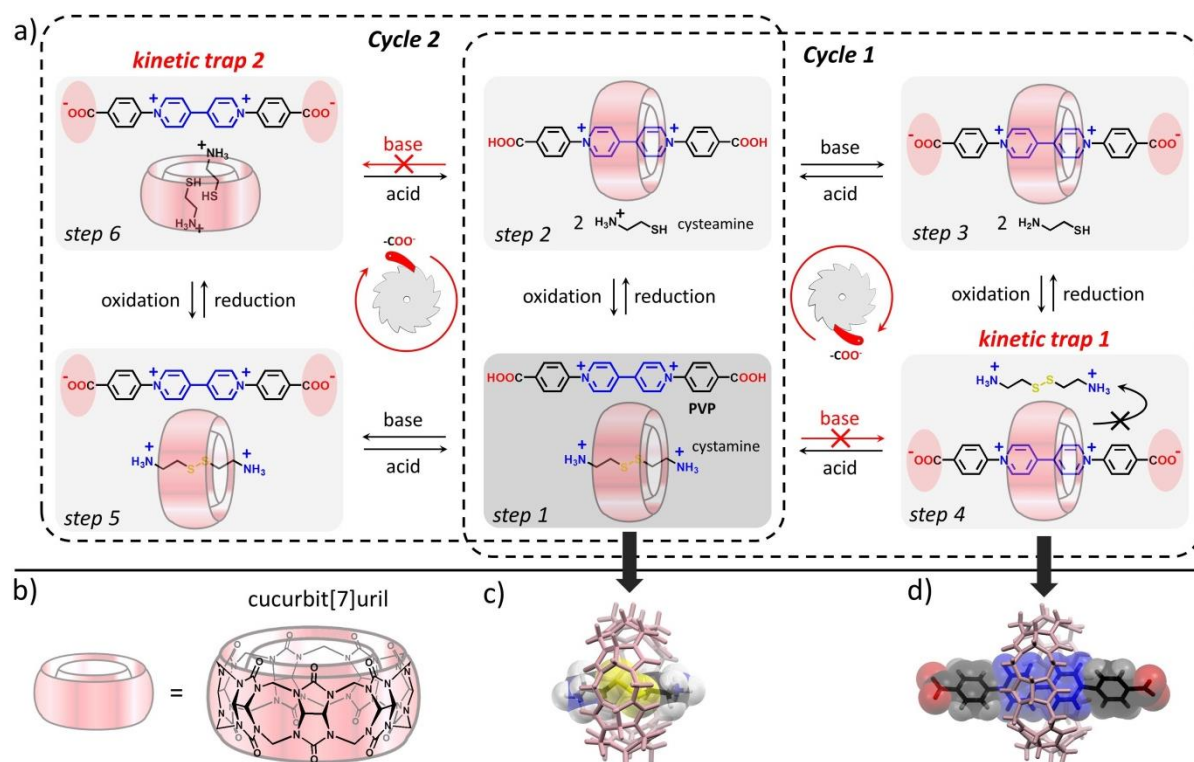
**Figure 1.** Cycles of guest exchange (a) mediated by two stimuli (pH and redox) featuring two kinetic traps (step 6: CB[7] cannot complex the viologen and step 4: CB[7] cannot escape viologen). Structure of (b) CB[7], DFT minimized structure (c) of the CB[7]•cystamine complex and X-ray structure (d) of the CB[7]•**PVP** complex.

spectrometry confirmed these results (Figures S3 and S4). Conversely, at basic pH, only one CB[7] can be bound on station V, leading to **PVP²⁻**•CB[7] (Figure S2). In contrast to **PVP**•CB[7], the **PVP²⁻**•CB[7] complex is stable when a better guest (i.e. (p-phenylenedimethylene) bis [trimethylammonium] **PMTA**) is added to the solution, as showed by ¹H NMR spectra (Figure S5). Actually increasing the pH of a **PVP**•CB[7] solution before addition of a competitor prevented CB[7] from escapement, suggesting that CB[7] could be kinetically trapped in line with previous reports.[73] However, CB[7] could be immediately released from **PVP** to bind the more thermodynamically favored guest after addition of trifluoroacetic acid (TFA, Figure S5).

Having shown that the kinetic barriers, for escapement of CB[7] in the **PVP**•CB[7] complex, could be tuned by pH, we focused on a guest competitor enabling the binding to be controlled by another stimulus. Disulfides were prime candidates for this purpose because the disulfide bridges can be reversibly cleaved using oxidoreduction and they can be crucial structural features of proteins.[74] After several unsuccessful tests with cystine (D, L, DL), methylated-4,4'-dithiodianiline, and methylated-cystamine (Figures S6 to S8), cystamine hydrochloride (Figure 1) turned to be ideal as its disulfide bridge could be reversibly cleaved by a redox process leading to cysteamine (Figure 1 and Figures S9 to S11) and binding constants toward CB[7] are compatible with the use of **PVP** (Figure 1). However, limitations inherent to some reactions impacting pH (so the **PVP** protonation state), or redox efficiencies being pH dependent have impeded fast

access to quantitative transformations. Nevertheless, after several tests involving different oxidants (30% $H_2O_2$, 30% $H_2O_2$/1 mol% NaI, 30% $H_2O_2$/1 mol% $I_2$, $O_2$, and KMnO$_4$/CuSO$_4$· 3$H_2O$), FeCl$_3$, NaI appeared ideal.[75] Likewise, we focused on finding reductants enabling quantitative transformations and tested DTT, $H_2$, and NaHSO$_3$ but TCEP afforded the best results. Kaifer and coworkers previously showed that reduction of cystamine could be dramatically decreased by complexation in CB[6].[76] We reasoned that cystamine binding in CB[7] could be less efficient enabling reduction/oxidation of included cystamine/cysteamine in a reasonable timeframe (Figures S10 and S11). We measured a binding constant for CB[7] toward cystamine of $K_a = 7.9 \times 10^7$ M⁻¹ by NMR (competitive binding, Figure S12). The binding of CB[7] toward **PVP** was previously reported to be $K_a \approx 3.8 \times 10^5$ M⁻¹.[72] A single-crystal X-ray structure of **PVP**•CB[7] (CCDC-2038656) and a DFT minimized structure for the cystamine•CB[7] complex confirmed the expected binding geometries (Figures 1c and 1d). Besides supramolecular p$K_a$ shifts displacing equilibria to protonated amines when complexed in CB[7],[77] cystamine and cysteamine were considered protonated (respective p$K_a$ values for first ionization of ~10.8[78] and ~8.3).[79]

We then investigated 1/1/1 mixtures of **PVP**/cystamine(or cysteamine)/CB[7] by ¹H NMR in $D_2O$ (Figures S13 to S23 for each step) tuning conditions to target quantitative conversions. The results, summarized in Figure 1, highlighted two directional cycles of transformations featuring two kinetic traps, and dependent on the sequence of stimuli applied (*cycle 1*: steps 1 → 2 → 3 →
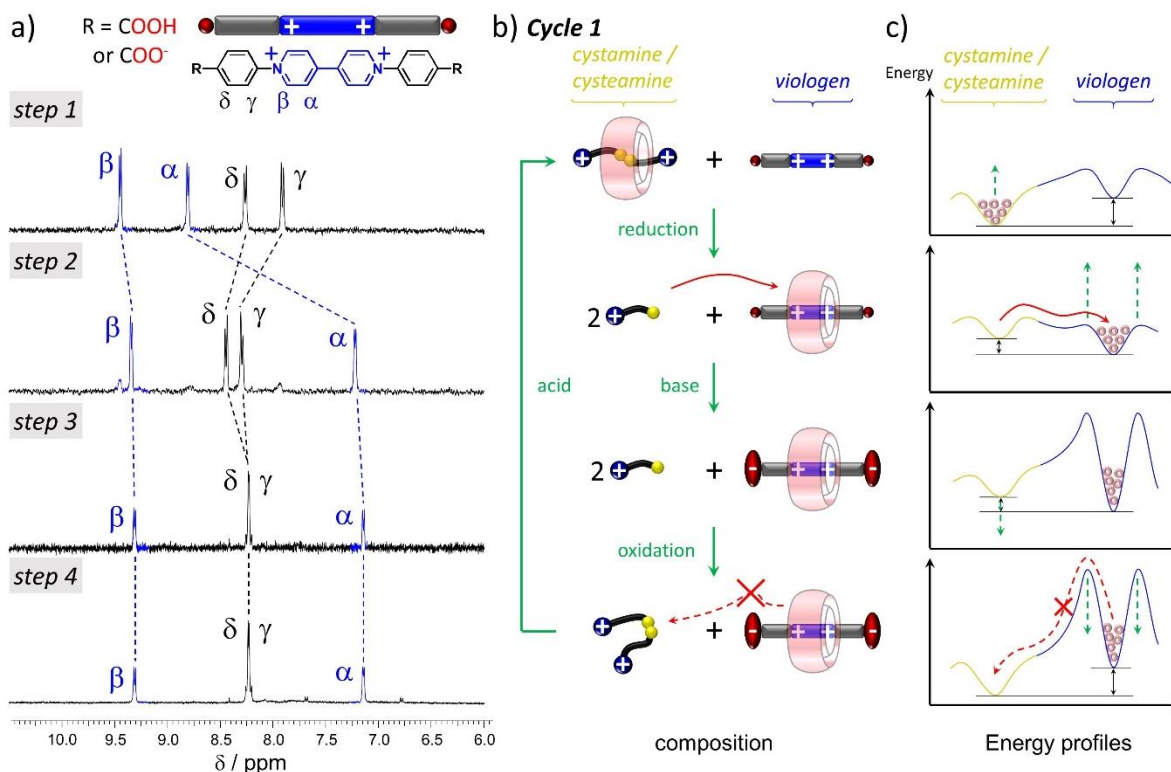
**Figure 2.** Aromatic region of $^1$H NMR spectra (a) of mixtures containing **PVP**, cystamine, cysteamine and CB[7] corresponding to *Cycle 1* (sequence $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$) of Figure 1 in D$_2$O, followed by (b) schematic representations of tube composition and (c) corresponding energy profiles.

$4 \rightarrow 1$ using the sequence: reduction, base, oxidation, acid; and *cycle 2*: steps $1 \rightarrow 5 \rightarrow 6 \rightarrow 2 \rightarrow 1$ using the sequence: base, reduction, acid, oxidation).

As the 2$^{nd}$ kinetic trap was not stable enough (vide infra), we focused on *kinetic trap 1* and performed the $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$ sequence in one NMR tube. *Cycle 1* started at step 1 upon the *random* mixing of the three components in D$_2$O. Balancing each stimulus by its counterpart, this sequence of steps did not result in net transport of CB[7] molecules that came back to their initial positions. Since addition of a base onto a **PVP**/cystamine•CB[7] solution (step 1) did not result into cystamine/**PVP$^{2-}$**•CB[7] (step 4), there should be only one way to reach this state ($1 \rightarrow 2 \rightarrow 3 \rightarrow 4$). This means that the sequence of steps $1 \rightarrow 4 \rightarrow 3 \rightarrow 2 \rightarrow 1$ is impossible to do.

$^1$H NMR spectra for the $1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow 1$ sequence are presented on Figure 2. Reduction (balance breaking 1) of cystamine (steps $1 \rightarrow 2$) to cysteamine led CB[7] to bind **PVP** as revealed by the strong upfield shift for the signal of $\alpha$ protons.[72] These results are in line with a change in the energy profile (Figure 2c) leading to a guest exchange toward a new energetically stable CB[7] complex thanks to Brownian motion. Raising the pH (unlinking stimulus, steps $2 \rightarrow 3$) blocked CB[7] on the viologen, increasing kinetic barriers and thus preventing subsequent release, while only slightly affecting the signals of the guest. Then oxidation of cysteamine (balance breaking 2) to regenerate cystamine (steps $3 \rightarrow 4$) could have incited CB[7] to move on the best binder (cystamine). However, this was not possible because

CB[7] was kinetically trapped on **PVP$^{2-}$** (Figure 1), as observed by signals in the aromatic region which are virtually unchanged. Step 4 thus corresponds to an out-of-equilibrium system where CB[7] is trapped energetically uphill. Kinetic experiments for the **PVP$^{2-}$**•CB[7]/cystamine system (step 4) showed that the CB[7] escapement is pH dependent (Figure S24). At pH 7.8, ring escapement took place in a few days (Figure S24a) while at pH 10.8, CB[7] was released on cystamine only after heating at 75 °C for several hours (Figure S24b). The pH dependence for the CB[7] escapement from **PVP$^{2-}$**•CB[7] is presumably due to equilibria between the -COOH and -COO$^-$ forms of **PVP$^{2-}$** at lower pH (Figure S25). We believe that (at least) one -COOH function transiently occurring in the **PVP$^{2-}$**•CB[7] complex largely drops the kinetic (electrostatic) barrier at relevant pH, favoring CB[7] escapement through the carboxylic acid functions of **PVP** (Figure S25). The addition of an acid (linking stimulus) completed *cycle 1* by enabling CB[7] to be released and to complex cystamine. Additionally, we found that light could be used as another stimulus[80] for the escapement step. Inspired by the photochromic properties of crystals of CB[7]•**PVP**•Zn,[72] we prepared a solution corresponding to *kinetic trap 1* (step 4) and placed it under UV light. NMR spectroscopy revealed about complete CB[7] escapement from **PVP$^{2-}$** and binding of cystamine (Figure 3a) after irradiation at 254 nm for 15 minutes. We observed a color change from yellow to green during irradiation that we assigned to the generation of a colored radical cation of viologen. UV-vis spectroscopy showed a shoulder in the 430-440 nm

region caused by CB[7] (Figure S26). EPR spectroscopy showed under UV irradiation a pattern with many couplings typical of a viologen radical cation supporting that a viologen[+•] radical transiently formed (Figure 3c). Currently, the source of the electron donor remains unclear,[81, 82] but if at least one electron was to jump from one carboxylate group of PVP[2-], a negative charge would be removed, thereby decreasing the kinetic barrier for dethreading. While methylviologen and its complex with CB[7] showed no EPR signal under UV irradiation, EPR of PVP[2-] solutions showed a weak signal (Figure S27) suggesting that the benzoate group could be the electron source whereas that of PVP[2-]•CB[7] showed a green colour and a symmetric EPR spectrum (Figure S27).
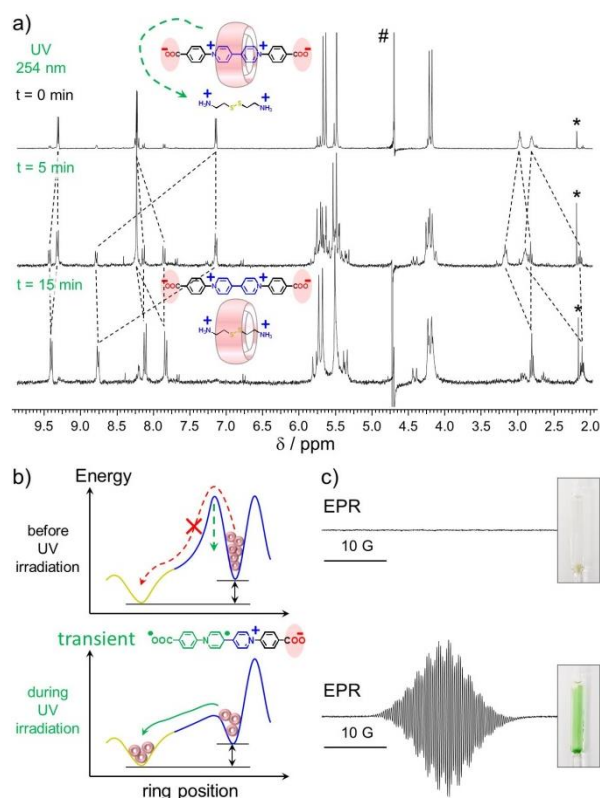


*Figure 3.* Ring escapement triggered by UV light irradiation (a) followed by NMR ([PVP] = 0.8 mM, 1 equiv. CB[7], 4 equiv. NaOH, and 1 equiv. cystamine in this order; *: acetone, #: HOD) with color changes suggesting (b) formation of a transient PVP radical form as could be checked (c) by EPR spectroscopy (inset: center of quartz flat cell, $\lambda_{irr}$ = 365 nm).

In any case, CB[7] seems largely promoting formation or stabilization of a viologen centred free radical of PVP. While more work is necessary to ascertain the nature of the electron donor, a new cycle passing through the two kinetic traps could in principle be build relying on light and redox stimuli (Figure S28).

As mentioned above, the addition of a base from step 1 did not lead to step 4. However, this process generated a new mixture enabling to enter *Cycle 2* (step 5, Figure 1) where cystamine was still included in CB[7] in the presence of PVP[2-] (Figure S20). Reduction from Step 5 generated the short lived *kinetic trap 2* since the potentially released CB[7] would in principle hardly go

through free PVP[2-] because of unfavorable interactions of carboxylate groups with CB[7]. However, isolation of step 6 was difficult due to the relatively fast threading of PVP[2-] after few minutes (Figure S22), rapidly leading to step 2.

One important feature of complexations by CB[*n*] in water is the often-reported high value for binding constants. For *cycle 1*, we could thus transform each step almost quantitatively. Even if there was no net ring transport after the cycle, the efficiency of ring transport and the faculty to return to its initial position ("reset")[83] suggests that such systems could in principle be used to build efficient, rotatory molecular motors in water.

Finally, we tried to realize a full cycle: 1 → 5 → 6 → 2 → 3 → 4 → 1 using two balance breaking stimuli (reduction and oxidation), and four linking / unlinking stimuli (base and acid, Figure 1). The complexation of the guests could be mainly controlled and is in line with Figure 4.
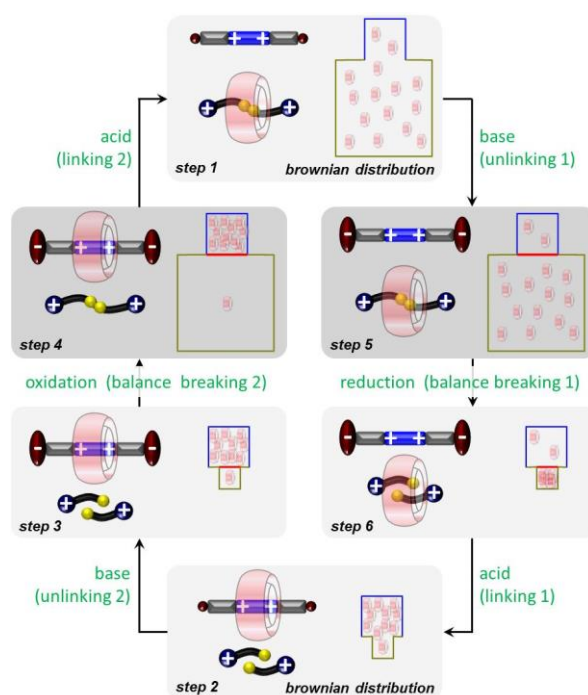


*Figure 4.* Full cycle featuring all steps of Figure 1.

However, transformations were not quantitative due to the presence of bases early in this cycle and perturbing the following steps (see comments in Figure S29). The CB[7] distribution in this full cycle is schematically presented in Figure 4 where the size of the boxes (the blue one for PVP and the yellow one for cystamine/cysteamine) illustrates the binding affinity for the guests. If we consider conditions transforming step 5 in step 4 (hosts and guests are identical but the CB[7] distributions are opposed), CB[7] could be transported on a disfavored guest, reminding a two-state Brownian flip-flop working by a partial energy ratchet mechanism.[26, 83]

To determine if a related system trapped away from equilibrium could be interfaced with a useful material, we searched for competitive fluorescent compounds being better binder than PVP and compatible with formation of hydrogels. After several attempts, we found that di-tolyl-viologen (DTV) was good for this purpose (Figure 5) making fluorescent DTV•(CB[7])$_2$ 1:2 complexes.[84]
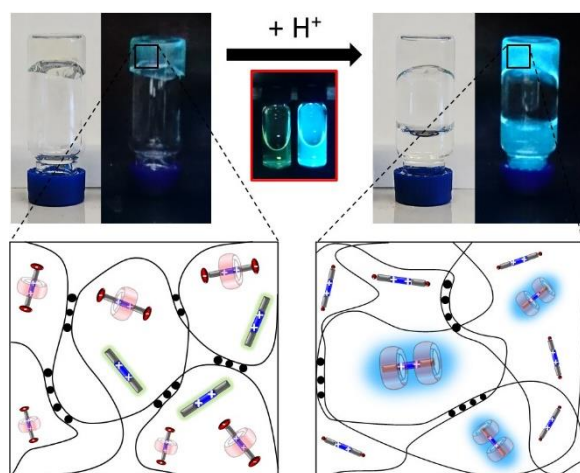
**Figure 5.** Hydrogels featuring the **PVP²⁻•CB[7]** kinetic trap and **DTV** showing weak emission (left) in basic conditions but strong fluorescence (right) after contact with an acidic solution as a result of CB[7] release and subsequent capture by **DTV** (red borders inset: identical solutions before (left) and after (right) acid addition without alginate and $CaCl_2$).

Indeed, after checking that **DTV** was a better CB[7] binder by NMR (Figure S30), we prepared solutions featuring the **PVP²⁻•CB[7]** trap in the presence of **DTV**. As expected only a very weak fluorescence was observed as a result of CB[7] staying trapped out-of-equilibrium. After HCl addition, the solution became intense blue fluorescent as a result of CB[7] release and trapping by **DTV** (Figure 5 inset).[84] Further work established the compatibility of this system with alginate/$Ca^{2+}$ hydrogels (Figure 5) resulting in materials possessing supramolecular systems trapped away from equilibrium, but sensitive to pH changes as can be seen by large fluorescence changes. The controlled release of CB[7] in moderately acidic environments may facilitate the specific sequestration of polyamine for possible cancer treatments.[85]

In conclusion, we have shown that the complexation of CB[7] toward two carefully designed guests could be well controlled by tuning energy wells and kinetic barriers thanks to appropriate stimuli. These experiments show that cucurbiturils can be used to afford long-lived kinetic traps in water where the ring compound can be set to bind less favoured guests in the presence of better partners. An interesting feature of this system is the relative complexity that is generated from simple molecules, and the possibility to interface it with fluorescent compounds and hydrogels. With their excellent and tuneable rate and binding constants, we anticipate that many more molecular machines using ratchet mechanisms[86] will be prepared in water using cucurbiturils in the future, especially if they can be organized, or interfaced with other systems to generate useful work.[87]

## *Acknowledgements*

[1]     D. Baker, D. A. Agard, *Biochemistry* **1994**, *33*, 7505-7509.
[2]     E. A. Galburt, J. M. R. Parrondo, S. W. Grill, *Biophys. Chem.* **2011**, *157*, 43-47.
[3]     D. Chowdhury, *Phys. Rep.* **2013**, *529*, 1-197.
[4]     B. Lau, O. Kedem, J. Schwabacher, D. Kwasnieski, E. A. Weiss, *Mater. Horiz.* **2017**, *4*, 310-318.
[5]     H. F. Noller, L. Lancaster, J. Zhou, S. Mohan, *Nat. Struct. Mol. Biol.* **2017**, *24*, 1021-1027.
[6]     A. R. Osborne, T. A. Rapoport, B. van den Berg, *Annu. Rev. Cell Dev. Biol.* **2005**, *21*, 529-550.
[7]     M. Takano, T. P. Terada, M. Sasai, *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 7769-7774.
[8]     M. A. Watson, S. L. Cockroft, *Chem. Soc. Rev.* **2016**, *45*, 6118-6129.
[9]     J. V. Hernandez, E. R. Kay, D. A. Leigh, *Science* **2004**, *306*, 1532-1537.
[10]    M. von Delius, E. M. Geertsema, D. A. Leigh, *Nat. Chem.* **2010**, *2*, 96-101.
[11]    H. Hess, J. L. Ross, *Chem. Soc. Rev.* **2017**, *46*, 5570-5587.
[12]    Y. Qiu, B. Song, C. Pezzato, D. Shen, W. Liu, L. Zhang, Y. Feng, Q.-H. Guo, K. Cai, W. Li, H. Chen, M. T. Nguyen, Y. Shi, C. Cheng, R. D. Astumian, X. Li, J. F. Stoddart, *Science* **2020**, *368*, 1247-1253.
[13]    S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan, A. L. Nussbaumer, *Chem. Rev.* **2015**, *115*, 10081-10206.
[14]    E. R. Kay, D. A. Leigh, F. Zerbetto, *Angew. Chem., Int. Ed.* **2007**, *46*, 72-191.
[15]    S. Kassem, T. van Leeuwen, A. S. Lubbe, M. R. Wilson, B. L. Feringa, D. A. Leigh, *Chem. Soc. Rev.* **2017**, *46*, 2592-2621.
[16]    C. Cheng, P. R. McGonigal, J. F. Stoddart, R. D. Astumian, *ACS Nano* **2015**, *9*, 8672-8688.
[17]    C. Pezzato, C. Cheng, J. F. Stoddart, R. D. Astumian, *Chem. Soc. Rev.* **2017**, *46*, 5491-5507.
[18]    R. D. Astumian, *Phys. Chem. Chem. Phys.* **2007**, *9*, 5067-5083.
[19]    Q. Li, G. Fuks, E. Moulin, M. Maaloum, M. Rawiso, I. Kulic, J. T. Foy, N. Giuseppone, *Nat. Nanotechnol.* **2015**, *10*, 161-165.
[20]    M. R. Wilson, J. Solà, A. Carlone, S. M. Goldup, N. Lebrasseur, D. A. Leigh, *Nature* **2016**, *534*, 235-240.
[21]    C. Cheng, P. R. McGonigal, W.-G. Liu, H. Li, N. A. Vermeulen, C. Ke, M. Frasconi, C. L. Stern, W. A. Goddard, III, J. F. Stoddart, *J. Am. Chem. Soc.* **2014**, *136*, 14702-14705.
[22]    Z. Meng, J.-F. Xiang, C.-F. Chen, *J. Am. Chem. Soc.* **2016**, *138*, 5652-5658.
[23]    C. Cheng, P. R. McGonigal, S. T. Schneebeli, H. Li, N. A. Vermeulen, C. Ke, J. F. Stoddart, *Nat. Nanotechnol.* **2015**, *10*, 547-553.
[24]    S. Erbas-Cakmak, S. D. P. Fielden, U. Karaca, D. A. Leigh, C. T. McTernan, D. J. Tetlow, M. R. Wilson, *Science* **2017**, *358*, 340-343.

[25] C. Biagini, S. D. P. Fielden, D. A. Leigh, F. Schaufelberger, S. Di Stefano, D. Thomas, *Angew. Chem., Int. Ed.* **2019**, *58*, 9876-9880.

[26] M. N. Chatterjee, E. R. Kay, D. A. Leigh, *J. Am. Chem. Soc.* **2006**, *128*, 4058-4073.

[27] V. Serreli, C.-F. Lee, E. R. Kay, D. A. Leigh, *Nature* **2007**, *445*, 523-527.

[28] R. D. Astumian, *Nat. Commun.* **2019**, *10*, 1-14.

[29] A. Hashidzume, A. Kuse, T. Oshikiri, S. Adachi, M. Okumura, H. Yamaguchi, A. Harada, *Sci. Rep.* **2018**, *8*, 1-8.

[30] J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi, K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540-541.

[31] A. I. Day, A. P. Arnold, R. J. Blanch, *WO2000068232A1*, (Unisearch Limited, Australia), **2000**.

[32] J. Lagona, P. Mukhopadhyay, S. Chakrabarti, L. Isaacs, *Angew. Chem., Int. Ed.* **2005**, *44*, 4844-4870.

[33] S. J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio, O. A. Scherman, *Chem. Rev.* **2015**, *115*, 12320-12406.

[34] J. W. Lee, S. Samal, N. Selvapalam, H.-J. Kim, K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621-630.

[35] K. I. Assaf, W. M. Nau, *Chem. Soc. Rev.* **2015**, *44*, 394-418.

[36] E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah, X. Lu, *RSC Adv.* **2012**, *2*, 1213-1247.

[37] A. Hennig, H. Bakirci, W. M. Nau, *Nat. Methods* **2007**, *4*, 629-632.

[38] U. Rauwald, O. A. Scherman, *Angew. Chem., Int. Ed.* **2008**, *47*, 3950-3953.

[39] J. M. Chinai, A. B. Taylor, L. M. Ryno, N. D. Hargreaves, C. A. Morris, P. J. Hart, A. R. Urbach, *J. Am. Chem. Soc.* **2011**, *133*, 8810-8813.

[40] W. Wang, A. E. Kaifer, *Angew. Chem., Int. Ed.* **2006**, *45*, 7042-7046.

[41] M. Raeisi, K. Kotturi, I. del Valle, J. Schulz, P. Dornblut, E. Masson, *J. Am. Chem. Soc.* **2018**, *140*, 3371-3377.

[42] L. Isaacs, *Acc. Chem. Res.* **2014**, *47*, 2052-2062.

[43] W. S. Jeon, E. Kim, Y. H. Ko, I. Hwang, J. W. Lee, S.-Y. Kim, H.-J. Kim, K. Kim, *Angew. Chem., Int. Ed.* **2005**, *44*, 87-91.

[44] W. S. Jeon, A. Y. Ziganshina, J. W. Lee, Y. H. Ko, J.-K. Kang, C. Lee, K. Kim, *Angew. Chem., Int. Ed.* **2003**, *42*, 4097-4100.

[45] J. W. Lee, I. Hwang, W. S. Jeon, Y. H. Ko, S. Sakamoto, K. Yamaguchi, K. Kim, *Chem. - Asian J.* **2008**, *3*, 1277-1283.

[46] S. Choi, R. D. Mukhopadhyay, Y. Kim, I.-C. Hwang, W. Hwang, S. K. Ghosh, K. Baek, K. Kim, *Angew. Chem., Int. Ed.* **2019**, *58*, 16850-16853.

[47] P. Dowari, S. Das, B. Pramanik, D. Das, *Chem. Commun.* **2019**, *55*, 14119-14122.

[48] I. Hwang, R. D. Mukhopadhyay, P. Dhasaiyan, S. Choi, S.-Y. Kim, Y. H. Ko, K. Baek, K. Kim, *Nat. Chem.* **2020**, *12*, 808-813.

[49] S. Liu, C. Ruspic, P. Mukhopadhyay, S. Chakrabarti, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2005**, *127*, 15959-15967.

[50] E. Masson, X. Lu, X. Ling, D. L. Patchell, *Org. Lett.* **2009**, *11*, 3798-3801.

[51] H. Barbero, N. A. Thompson, E. Masson, *J. Am. Chem. Soc.* **2020**, *142*, 867-873.

[52] G. Wu, Z. Huang, O. A. Scherman, *Angew. Chem., Int. Ed.* **2020**, *59*, 15963-15967.

[53] I. Hwang, W. S. Jeon, H.-J. Kim, D. Kim, H. Kim, N. Selvapalam, N. Fujita, S. Shinkai, K. Kim, *Angew. Chem., Int. Ed.* **2007**, *46*, 210-213.

[54] A. E. Kaifer, *Acc. Chem. Res.* **2014**, *47*, 2160-2167.

[55] G. Bergamini, A. Fermi, M. Marchini, M. Locritani, A. Credi, M. Venturi, F. Negri, P. Ceroni, M. Baroncini, *Chem. - Eur. J.* **2014**, *20*, 7054-7060.

[56] P. Mukhopadhyay, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2006**, *128*, 14093-14102.

[57] M. H. Tootoonchi, S. Yi, A. E. Kaifer, *J. Am. Chem. Soc.* **2013**, *135*, 10804-10809.

[58] W. Ong, M. Gómez-Kaifer, A. E. Kaifer, *Org. Lett.* **2002**, *4*, 1791-1794.

[59] H.-J. Kim, W. S. Jeon, Y. H. Ko, K. Kim, *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 5007-5011.

[60] V. Sindelar, S. Silvi, A. E. Kaifer, *Chem. Commun.* **2006**, 2185-2187.

[61] I. Neira, M. D. García, C. Peinador, A. E. Kaifer, *J. Org. Chem.* **2019**, *84*, 2325-2329.

[62] H. Shi, K. Zhang, R.-L. Lin, W.-Q. Sun, X.-F. Chu, X.-H. Liu, J.-X. Liu, *Asian J. Org. Chem.* **2019**, *8*, 339-343.

[63] R. A. Luna-Ixmatlahua, A. Carrasco-Ruiz, R. Cervantes, A. Vela, J. Tiburcio, *Chem. - Eur. J.* **2019**, *25*, 14042-14047.

[64] A. Carrasco-Ruiz, J. Tiburcio, *Org. Lett.* **2015**, *17*, 1858-1861.

[65] J. O. Jeppesen, S. A. Vignon, J. F. Stoddart, *Chem. - Eur. J.* **2003**, *9*, 4611-4625.

[66] J. O. Jeppesen, J. Becher, J. F. Stoddart, *Org. Lett.* **2002**, *4*, 557-560.

[67] P. R. Ashton, I. Baxter, M. C. T. Fyfe, F. M. Raymo, N. Spencer, J. F. Stoddart, A. J. P. White, D. J. Williams, *J. Am. Chem. Soc.* **1998**, *120*, 2297-2307.

[68] E. Masson, M. Raeisi, K. Kotturi, *Isr. J. Chem.* **2018**, *58*, 413-434.

[69] L. Liu, N. Nouvel, O. A. Scherman, *Chem. Commun.* **2009**, 3243-3245.

[70] H. Chen, Z. Huang, H. Wu, J.-F. Xu, X. Zhang, *Angew. Chem., Int. Ed.* **2017**, *56*, 16575-16578.

[71] O. Danylyuk, V. P. Fedin, V. Sashuk, *Chem. Commun.* **2013**, *49*, 1859-1861.

[72] X. Yang, M. Giorgi, H. Karoui, D. Gigmes, V. Hornebecq, O. Ouari, A. Kermagoret, D. Bardelang, *Chem. Commun.* **2019**, *55*, 13824-13827.

[73] Y. Zheng, A. E. Kaifer, *J. Org. Chem.* **2020**, *85*, 10240–10244.

[74] M. Góngora-Benítez, J. Tulla-Puche, F. Albericio, *Chem. Rev.* **2014**, *114*, 901-926.

[75] N. Iranpoor, B. Zeynizadeh, *Synthesis* **1999**, 49-50.

[76] L. Strimbu Berbeci, W. Wang, A. E. Kaifer, *Org. Lett.* **2008**, *10*, 3721-3724.

[77] N. i. Saleh, A. L. Koner, W. M. Nau, *Angew. Chem., Int. Ed.* **2008**, *47*, 5398-5401.

[78] E. Katz, M. Lion-Dagan, I. Willner, *J. Electroanal. Chem.* **1996**, *408*, 107-112.

[79] L. Riauba, G. Niaura, O. Eicher-Lorka, E. Butkus, *J. Phys. Chem. A* **2006**, *110*, 13394-13404.

[80] A. Seco, A. M. Diniz, J. Sarrato, H. Mourão, H. Cruz, A. J. Parola, N. Basilio, *Pure Appl. Chem.* **2020**, *92*, 301-313.

[81] G. Brunet, E. A. Suturina, G. P. C. George, J. S. Ovens, P. Richardson, C. Bucher, M. Murugesu, *Chem. - Eur. J.* **2020**, 10.1002/chem.202003073.

[82] J.-J. Liu, Y.-F. Guan, M.-J. Lin, C.-C. Huang, W.-X. Dai, *Cryst. Growth Des.* **2016**, *16*, 2836-2842.

[83] M. Baroncini, S. Silvi, A. Credi, *Chem. Rev.* **2020**, *120*, 200-268.

[84] M. Freitag, L. Gundlach, P. Piotrowiak, E. Galoppini, *J. Am. Chem. Soc.* **2012**, *134*, 3358-3366.

[85] J. Chen, H. Ni, Z. Meng, J. Wang, X. Huang, Y. Dong, C. Sun, Y. Zhang, L. Cui, J. Li, X. Jia, Q. Meng, C. Li, *Nat. Commun.* **2019**, *10*, 3546.

[86] R. D. Astumian, *Nat. Nanotechnol.* **2012**, *7*, 684-688.

[87] I. Aprahamian, *ACS Cent. Sci.* **2020**, *6*, 347-358.

Cucurbiturils can be prime components to build energy ratchets in water.
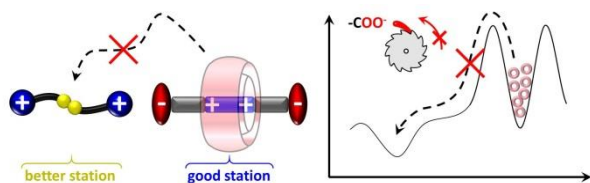
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