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Na^+ Ions Induce the Pirouetting Motion and Catalytic Activity of [2]Rotaxanes

Yong-Jay Lee,[a],‡ Kuang-Shun Liu,[a],‡ Chien-Chen Lai,[b] Yi-Hung Liu,[a] Shie-Ming Peng,[a] Richard P. Cheng*[a] and Sheng-Hsien Chiu*[a]

Dedication ((optional))

Abstract: We have prepared [2]rotaxanes whose behavior as switchable catalysts depends on their pirouetting motion, which can be controlled through the addition and removal of Na^+ ions. At least three sequential on/off cycles of a Michael reaction can be performed in situ when using the NaTFPB/[2.2.2]cryptand reagent pair to switch "on" and "off" the catalytic ability of the [2]rotaxanes.

Although the application of rotaxane structures in catalysis has been investigated for more than a decade,[1] only recently has the catalytic activity of [2]rotaxanes been controlled reversibly through management of translational motion (shuttling) between two well-arranged recognition sites.[2] In addition to shuttling, pirouetting (where the interlocked macrocyclic component circumrotates with respect to the threadlike unit) is another possible dynamic motion in a [2]rotaxane (Figure 1).[3] The number of pirouetting [2]rotaxane-based molecular switches has, however, remained limited,[4] mainly because it can be difficult to position two different binding sites within a single macrocyclic component and balance the binding energies of the two switchable states. Nevertheless, pirouetting motion will, by necessity, change the relative positions of functional groups in the threadlike and macrocyclic components, making such [2]rotaxanes candidate displayers of switchable catalytic activity (e.g., for two reacting species that are activated by functionalities in the different components of the [2]rotaxanes). Herein, we report small [2]rotaxanes that behave as switchable catalysts for the Michael addition of diethyl malonate to nitrostyrene,[5] with their Na^+-free and -complexed states being catalytically inactive and active, respectively. Using sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaTFPB) and [2.2.2]cryptand to introduce and remove the complexing Na^+ ions, respectively, the catalytic activity of the [2]rotaxane catalysts can be switched in situ between "on" and "off" states for at least three cycles—reflected in the Michael addition displaying three "go" and "stop" transitions in its reaction rates.

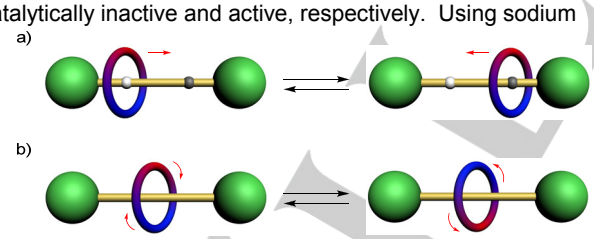
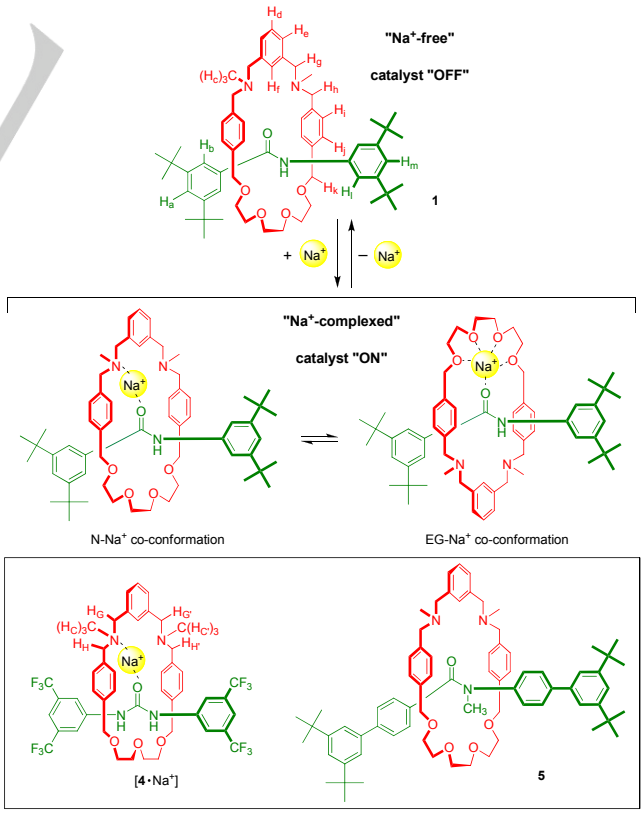


Figure 1. a) Shuttling and b) pirouetting (with the axle fixed for reference) motions of a [2]rotaxane.

We prepared the [2]rotaxane **1**, comprising the macrocyclic component **2**[6] and the dumbbell-shaped component **3**, through alkali metal ion–templated clipping of an imino macrocycle and subsequent reduction.[7] 2D COSY and NOESY experiments allowed us to identify most of the signals in the ^{1}H NMR spectra of the [2]rotaxane **1** in toluene-d_8 at 298 K (Figure 2, see Supporting Information for the full signal assignments). In the NOESY spectra, cross signals between the protons of the amido NH group and the tri(ethylene glycol) unit suggested that the dominating conformations of the [2]rotaxane **1** in toluene-d_8 featured these units in close proximity (Scheme 1). Such an orientation was evident in the solid state structure of the



Scheme 1. Structures of the [2]rotaxanes **1**, **4**, and **5**, and possible Na^+ ion–induced pirouetting motion of **1**.

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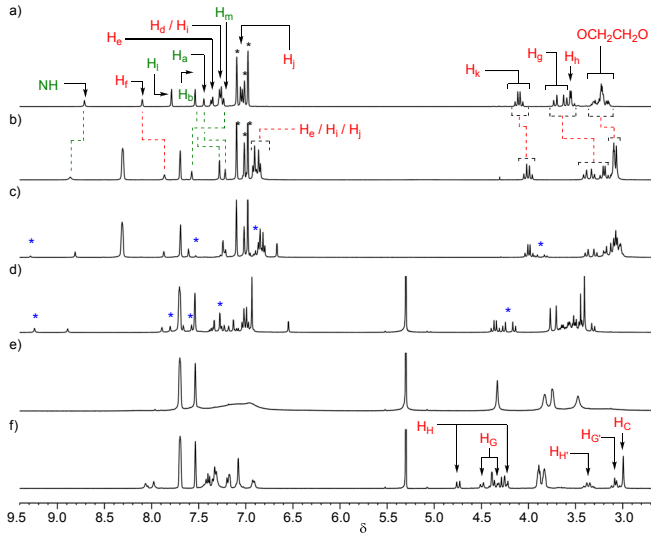


Figure 2. ^{1}H NMR spectra (400 MHz, 298 K) of a) the [2]rotaxane **1**; b, c) an equimolar mixture of the [2]rotaxane **1** and NaTFPB (10 mM) left at b) 298 K for 0 h and c) 308 K for 10 days; d) an equimolar mixture of the [2]rotaxane **1** and NaTFPB (10 mM) left at 298 K for 5 days; and e, f) an equimolar mixture of the [2]rotaxane **4** and NaTFPB (10 mM) left at 308 K for e) 0 h and f) 10 days. Solvents: (a–c) toluene-d_8; (d–f) CD_2Cl_2. Asterisk: signals that belong to the N-Na^+ co-conformers.

[2]rotaxane **1**, with the macrocyclic component having its tri(ethylene glycol) unit hydrogen bonded to the NH unit of the amido group (Figure 3a).[8]

The ^{1}H NMR spectrum of a mixture of diethyl malonate (200 mM), nitrostyrene (100 mM), and the [2]rotaxane **1** (10 mM) in toluene-d_8 displayed (Figure 4a) no noticeable signals (expected at δ 4.22, 4.39, and 4.58) representing the Michael adduct after 72 h at 298 K. In contrast, the reaction occurred when this solution was treated with one equiv of NaTFPB, with a yield for the product of approximately 66% after 72 h at 298 K (Figure 4c), based on integration of signals in the ^{1}H NMR spectrum. We attempted similar experiments using both the free dumbbell-shaped molecule **3** and the free macrocycle **2** and their combinations with NaTFPB, but none of these control reactions proceeded at a rate comparable with that observed when using the mixture of Na^+ ions and the [2]rotaxane **1** as the catalyst (Table 1).[9]

The addition of one equiv of NaTFPB to a toluene-d_8 solution of the [2]rotaxane **1** (10 mM) caused significant changes to its ^{1}H NMR spectrum (Figure 2b). In the resulting NOESY spectrum, cross signals between the amido NH proton and the methyl (H_c) and aromatic (H_f) protons nearby the tertiary amino groups suggested that collaborative complexation of the tri(ethylene glycol) and amide C=O units to the Na^+ ion had occurred, a process that necessitated rotation (pirouetting) of the macrocyclic component relative to that of the free [2]rotaxane (Scheme 1). X-ray crystallographic analysis of single crystals,

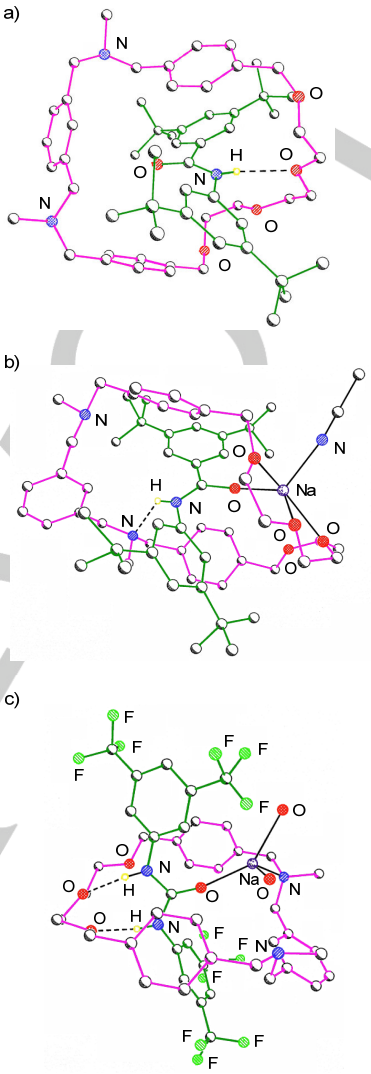


Figure 3. Ball-and-stick representations of the solid state structures of a) the [2]rotaxane **1**, b) the complex [**1**·Na·CH_3CN]$^+$, and c) the complex [**4**·Na·$2H_2O$]$^+$.

grown through liquid diffusion of hexanes into an equimolar solution of the [2]rotaxane **1** and NaTFPB in toluene/CH_3CN (99:1), confirmed the structure of such an "ethylene glycol" (EG)-Na^+ co- conformation (Figure 3b).

Interestingly, the ^{1}H NMR spectrum of an equimolar mixture of the [2]rotaxane **1** and NaTFPB in toluene-d_8 (10 mM) displayed a small new set of signals after heating at 308 K for 10 days (Figure 2c). The signals of this new species were more pronounced when we mixed **1** and NaTFPB in CD_2Cl_2 at 298 K for 5 days. The observation of 2D NOESY cross signals between the amido NH unit and protons of the tri(ethylene glycol) motif of the new species and a downfield shift of the signals for the protons adjacent to the tertiary amino groups (see Supporting Information for the full signal assignment), suggested that the tri(ethylene glycol) and amide units in this structure had a spatial alignment similar to that in the free [2]rotaxane **1**,

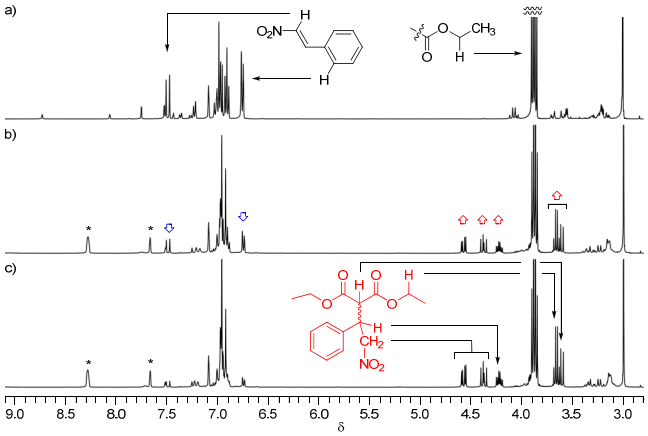


Figure 4. ^{1}H NMR spectra of the products of the Michael reactions catalyzed by a) the [2]rotaxane **1** after 72 h and b, c) the [2]rotaxane **1** and NaTFPB after b) 24 and c) 72 h. Asterisk: signals belong to TFPB anions.

implying that the Na^+ ion was likely to have complexed to the amide C=O and tertiary amino groups. We observed significantly lower catalytic activity for the Michael reaction after adding diethyl malonate (200 mM) and nitrostyrene (100 mM) to the above equilibrated equimolar mixture of the [2]rotaxane **1** and NaTFPB in CD_2Cl_2 (17% yield after 72 h at 298 K), compared with that of the fresh mixture (36% yield), implying

Table 1. Yields of Michael additions performed under various conditions.[a]

Entry	Rotaxane	Additive[b,c]	Solvent	% Yield[d]
1	**1**	—	Toluene-d_8	—
2	**1**	Na^+	Toluene-d_8	66
3	—	Na^+	Toluene-d_8	—
4	—	**2** + **3**	Toluene-d_8	—
5	—	**2** + **3** + Na^+	Toluene-d_8	2
6	**1**	Na^+	CD_2Cl_2	36
7	**1**	Na^+[e]	CD_2Cl_2	17
8	**4**	Na^+	Toluene-d_8	81
9	**4**	Na^+[f]	Toluene-d_8	74
10	**4**	Na^+	CD_2Cl_2	47
11	**4**	Na^+[f]	CD_2Cl_2	—
12	**5**	Na^+	Toluene-d_8	35

[a] Reaction of diethyl malonate (200 mM) and nitrostyrene (100 mM) at 298 K for 72 h. [b] Concentration of each additive was 10 mM. [c] Na^+ ions were added as TFPB salts. [d] Yields estimated based on integration of signals in ^{1}H NMR spectra, using the signal of the TFPB anion [δ 8.26 (toluene-d_8) or 7.70 (CD_2Cl_2)] as a reference. [e] [2]Rotaxane and Na^+ ions were pre-mixed at 298 K for 10 days. [f] [2]Rotaxane and Na^+ ions were pre-mixed at 308 K for 10 days.

that the new species was less catalytically effective. Similarly, we found that a CD_2Cl_2 solution of the urea-centered [2]rotaxane **4** and NaTFPB afforded broad ^{1}H NMR signals when freshly mixed, but gradually grew a new set of signals that predominated after heating at 308 K for 10 days. Negligible Michael product appeared 72 h after adding diethyl malonate (200 mM) and nitrostyrene (100 mM) to this equilibrated mixture (10 mM), suggesting that the new species was not catalytically active. The significant downfield shifts of one set of amine-adjacent protons relative to the other [H_C, H_G, H_H vs. $H_{C'}$ (not shown, δ = 1.92), $H_{G'}$, $H_{H'}$] suggested that the Na^+ ion coordinated to the amide C=O group and only one of the tertiary amino groups, and that the rate of exchange of the C=O-complexed Na^+ ion between the two tertiary amino groups was slow on the timescale of NMR spectroscopy under these conditions (Figure 2f, see Supporting Information for the full signal assignments). This N-Na^+ co-conformation was evident in the solid state structure of the complex [**4**·Na·2H_2O]$^+$ (Figure 3c).

Thus, we found two co-conformations for the Na^+-complexed [2]rotaxane **1** in toluene-d_8, presumably with the major EG-Na^+ co-conformation being catalytically active and the minor N-Na^+ co-conformation being catalytically inactive in a low-polarity solvent. We cannot dismiss, however, the possibility that some other unidentified rotational co-conformations were also catalytically active; therefore, we are inclined not to ascribe the catalytic activity of the complex solely to the EG-Na^+ co-conformation but consider it as a property of the whole "complexed" state. In other words, introducing Na^+ ions to a solution of the [2]rotaxane **1** in toluene-d_8 immediately resulted in pirouetting motion of the interlocked macrocyclic component and generated a catalytically active Na^+-complexed state distinct from the original catalytically inactive Na^+-free state.

The addition of [2.2.2]cryptand (10 mM), a tight binder for Na^+ ions, to the solution of diethyl malonate (200 mM),

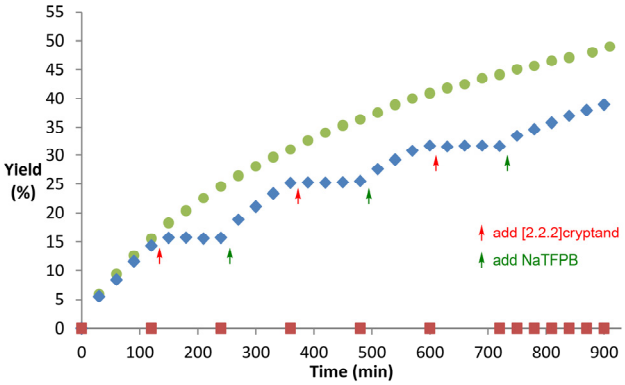
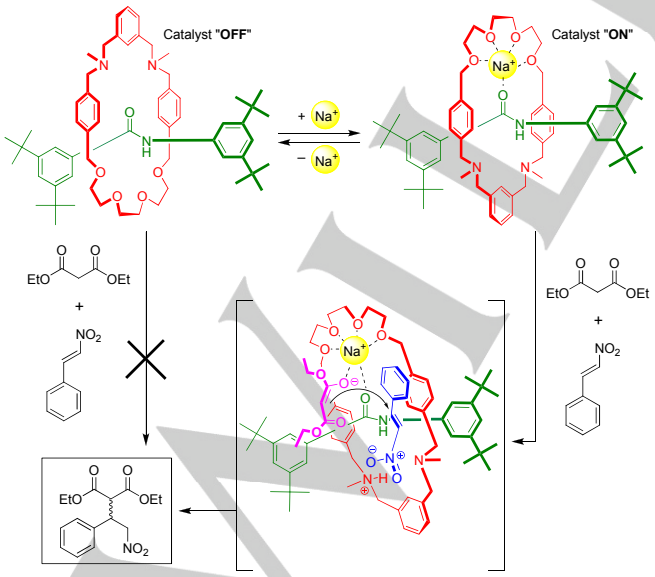


Figure 5. Yields of Michael product formed from diethyl malonate (200 mM) and nitrostyrene (100 mM) in toluene-d_8 when using a) the [2]rotaxane **1** (10 mM, ■) and b) an equimolar mixture of the [2]rotaxane **1** and NaTFPB (10 mM, ●) as the catalyst; c) sequential addition of [2.2.2]cryptand (10 mM) and NaTFPB (10 mM) to the mixture in (b), revealing three "on"/"off" switching cycles (◆).

nitrostyrene (100 mM), the [2]rotaxane **1** (10 mM), and NaTFPB (10 mM) in toluene-d_8 switched off the reaction immediately. We observed no noticeable rate increases for the reactions of diethyl malonate (200 mM) and nitrostyrene (100 mM) in toluene-d_8 in the presence of only NaTFPB (10 mM), only [2.2.2]cryptand (10 mM), or a mixture of NaTFPB and [2.2.2]cryptand (10 mM), suggesting that the reversible operation of the catalyst over multiple cycles should be possible without having to precisely control of the amounts of added Na^+ and [2.2.2]cryptand.

Through integration of signals in the ^{1}H NMR spectra belonging to the reaction product, we could estimate the progress of the reaction by monitoring the concentration of the product (using the signal for trichloroethene at δ 5.62 as the internal standard). As displayed in Figure 5, the addition of NaTFPB (10 mM) to a mixture of diethyl malonate (200 mM), nitrostyrene (100 mM), and the [2]rotaxane **1** (10 mM) in toluene-d_8 accelerated the reaction significantly; the reaction was "stopped" after 2 h, after the formation of the product in 16% yield, through the addition of one equiv of [2.2.2]cryptand. No noticeable increase in product yield occurred in this solution over the next 2 h, but the reaction was triggered again by adding NaTFPB, with the yield of the product reaching 25% after another 2 h, and then "stopped" again by adding [2.2.2]cryptand. We performed another on/off cycle using the same reaction mixture, with timely sequential additions of NaTFPB (10 mM) and [2.2.2]cryptand (10 mM), thereby increasing the yield of the product to 31%. Thus, in the presence of the [2]rotaxane **1**, the Michael addition could be triggered and shut down for, at least, three cycles, through in situ addition and removal, respectively, of Na^+ ions.

Because steric crowding in the [2]rotaxane **1** would presumably not allow the amido NH unit to interact with the substrate properly, and because the [2]rotaxane **5** (Scheme 1), which does not have an amido NH group, was also catalytically active for the same Michael reaction when complexed with an Na^+ ion in toluene-d_8, it is very unlikely that the reaction proceeded through Na^+ ion–induced activation of diethyl malonate and nitrostyrene through spatial proximity to the amido NH and tertiary amino units, respectively, as has been proposed for a related bifunctional organocatalyst.[10] Based on the solid state structure in Figure 2b, the complex [**1**·Na]$^+$ has a replaceable MeCN ligand. Thus, we suggest a mechanism for catalysis involving coordination of deprotonated diethyl malonate to the Na^+ ion, positioning it in close proximity to the nitrostyrene molecule activated through coordination to the protonated tertiary amino group nearby (Scheme 2).[11]



Scheme 2. Pirouetting motion of the macrocyclic component of the [2]rotaxane **1** after complexation to a Na^+ ion, and a possible mechanism for the catalytic Michael reaction.

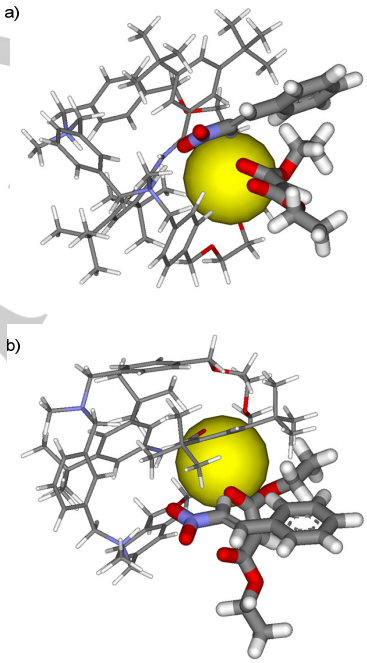


Figure 6. Model of [**1**·Na]$^+$ with the enolate of diethyl malonate coordinated to the Na^+ ion and the molecule of nitrostyrene hydrogen-bonded to one of the protonated tertiary amino groups. The (a) side view and (b) top view of the model reveal a structure capable to facilitate bond formation between the enolate and nitrostyrene. The [2]rotaxane is depicted with thin sticks; the enolate of diethyl malonate and nitrostyrene with thick sticks; the Na^+ ion in CPK form (C: gray; H: white; N: blue; O: red; Na: yellow).

To examine the feasibility of such a mechanism, we used molecular mechanics[12] to construct (Figure 6) a model based on the crystal structure of [**1**·Na·MeCN]$^+$. We replaced the MeCN ligand with the enolate of diethyl malonate, and introduced a molecule of nitrostyrene, hydrogen-bonded through its nitro group to a protonated tertiary amino group on the [2]rotaxane.[10] The system was initially minimized with a distance restraint to bring the enolate and the nitrostyrene into close proximity. After equilibration through dynamics, followed by minimization, the system was ultimately minimized without

the distance restraint. The resulting model reveals that [**1**·Na]$^+$ could simultaneously accommodate both the enolate (Michael donor) and a molecule of nitrostyrene (Michael acceptor) in close proximity. Furthermore, the distance between the enolate carbon atom and the β-carbon atom of nitrostyrene was 4.89 Å, making it highly likely that such bond formation could further occur to give the experimentally observed product.

We have demonstrated that the [2]rotaxane **1** can be operated reversibly between catalytically active Na$^+$-complexed and inactive Na$^+$-free states through the addition and removal, respectively, of Na$^+$ ions. At least three sequential on/off cycles of a Michael reaction can be performed in situ when using the NaTFPB/[2.2.2]cryptand reagent pair to switch "on" and "off" the catalytic ability of the [2]rotaxane. Our discovery of a pirouetting [2]rotaxane displaying switchable catalytic activity is a step toward the design of interlocked catalysts displaying more complicated functions in organic synthesis.

Acknowledgements ((optional))

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Keywords: alkali metal ion • catalysis • Michael addition • molecular switch • pirouetting • rotaxane

[1] a) Y. Tachibana, N. Kihara, T. Takata, *J. Am. Chem. Soc.* **2004**, *126*, 3438–3439; b) G. Hattori, T. Hori, Y. Miyake, Y. Nishibayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12930–12931; c) J. Berná, M. Alajarín, R.-A. Orenes, *J. Am. Chem. Soc.* **2010**, *132*, 10741–10747; d) Y. Suzaki, K. Shimada, E. Chihara, T. Saito, Y. Tsuchido, K. Osakada, *Org. Lett.* **2011**, *13*, 3774–3777; e) C. B. Caputo, K. Zhu, V. N. Vukotic, S. J. Loeb, D. W. Stephan, *Angew. Chem.* **2013**, *125*, 994–997; *Angew. Chem. Int. Ed.* **2013**, *52*, 960–963; f) C.-S. Kwan, A. S. C. Chan, K. C.-F. Leung, *Org. Lett.*, **2016**, *18*, 976–979; g) M. Galli, J. E. M. Lewis, S. M. Goldup, *Angew. Chem.* **2015**, *127*, 13749–13753; *Angew. Chem. Int. Ed.* **2015**, *54*, 13545–13549.

[2] a) V. Blanco, A. Carlone, K. D. Hänni, D. A. Leigh, B. Lewandowski, *Angew. Chem.* **2012**, *124*, 5256–5259; *Angew. Chem. Int. Ed.* **2012**, *51*, 5166–5169; b) V. Blanco, D. A. Leigh, U. Lewandowska, B. Lewandowski, V. Marcos, *J. Am. Chem. Soc.* **2014**, *136*, 15775–15780; c) V. Blanco, D. A. Leigh, V. Marcos, J. A. Morales-Serna, A. L. Nussbaumer, *J. Am. Chem. Soc.* **2014**, *136*, 4905–4908; d) D. A. Leigh, V. Marcos, M. R. Wilson, *ACS Catal.* **2014**, *4*, 4490–4497.

[3] a) M. Pons, O. Millet, *Prog. Nucl. Magn. Reson. Spectrosc.* **2001**, *38*, 267–324; b) S. A. **Vignon**, J. F. **Stoddart,** *Collect. Czech. Chem. Commun.* **2005**, *70*, 1493–1576; c) A. Mateo-Alonso, G. M. A. Rahman, C. Ehli, D. M. Guldi, G. Fioravanti, M. Marcaccio, F. Paolucci, M. Prato, *Photochem. Photobiol. Sci.* **2006**, *5*, 1173–1176.

[4] a) L. Raehm, J.-M. Kern, J.-P. Sauvage, *Chem. Eur. J.* **1999**, *5*, 3310–3317; b) L. M. Hancock, P. D. Beer, *Chem. Commun.* **2011**, *47*, 6012–6014; c) I. Murgu, J. M. Baumes, J. Eberhard, J. J. Gassensmith, E. Arunkumar, B. D. Smith, *J. Org. Chem.* **2011**, *76*, 688–691; d) P. Farràs, E. C. Escudero-Adán, C. Viñas, F. Teixidor, *Inorg. Chem.* **2014**, *53*, 8654–8661; e) E. Coronado, P. Gavina, J. Ponce, S. Tatay, *Chem. Eur. J.* **2014**, *20*, 6939–6950.

[5] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658–7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496–7504; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; d) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; e) J. Wang, B. L. Feringa, *Science* **2011**, *331*, 1429–1432; f) C. Najera, J. M. Sansano, E. Gomez-Bengoa, *Pure Appl. Chem.* **2016**, *88*, 561–578; g) L. Yang, L. Zhao, Z. Zhou, C. He, H. Sun, C. Duan, *Dalton Trans.* **2017**, *46*, 4086-4092.

[6] Y.-J. Lee, T.-H. Ho, C.-C. Lai, S.-H. Chiu, *Org. Biomol. Chem.* **2016**, *14*, 1153–1160.

[7] T.-H. Ho, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu, *Chem. Eur. J.* **2014**, *20*, 4563–4567.

[8] CCDC-1511677, -1539017 and -1539018 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Because of the limited solubility of NaTFPB in toluene, the association constant for the interaction of the [2]rotaxane **1** with Na$^+$ (as TFPB salt) was determined in a mixture of CH_2Cl_2 and CH_3CN (97:3), using isothermal titration calorimetry (ITC); the value obtained from the means of three independent experiments was $(1.3 \pm 0.4) \times 10^5$ M^{-1}.

[10] (a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.*, **2005**, *127*, 119–125; b) A. Hamza, G. Schubert, T. Soós, I Pápai, *J. Am. Chem. Soc.*, **2006**, *128*, 13151–13160; c) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.* **2012**, *77*, 9813–9825.

[11] Although it is unlikely that the catalytic activity of the [2]rotaxane results from an increase in the basicity of the tertiary amino groups after undergoing the pirouetting motion, measuring the basicity of the tertiary amino groups in the Na$^+$-complexed [2]rotaxane is not straightforward so we cannot dismiss such a possibility.

[12] The structure was minimized using the Merck Molecular Force Field (MMFF) as implemented in Discovery Studio 2.1 (Accelrys, CA) by steepest descent followed by conjugated gradient protocols. See Supporting Information for the details.

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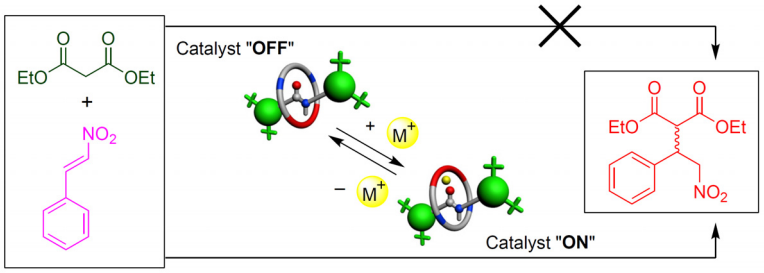

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Na^+ Ions Induce the Pirouetting Motion and Catalytic Activity of [2]Rotaxanes

The catalytic activity of the [2]rotaxane catalysts can be switched between “on” and “off” states over at least three different cycles through *in situ* addition and removal of Na^+ ions.