

## Supporting Information

### A pH-driven ring translocation switch against cancer cells

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## Experimental procedures

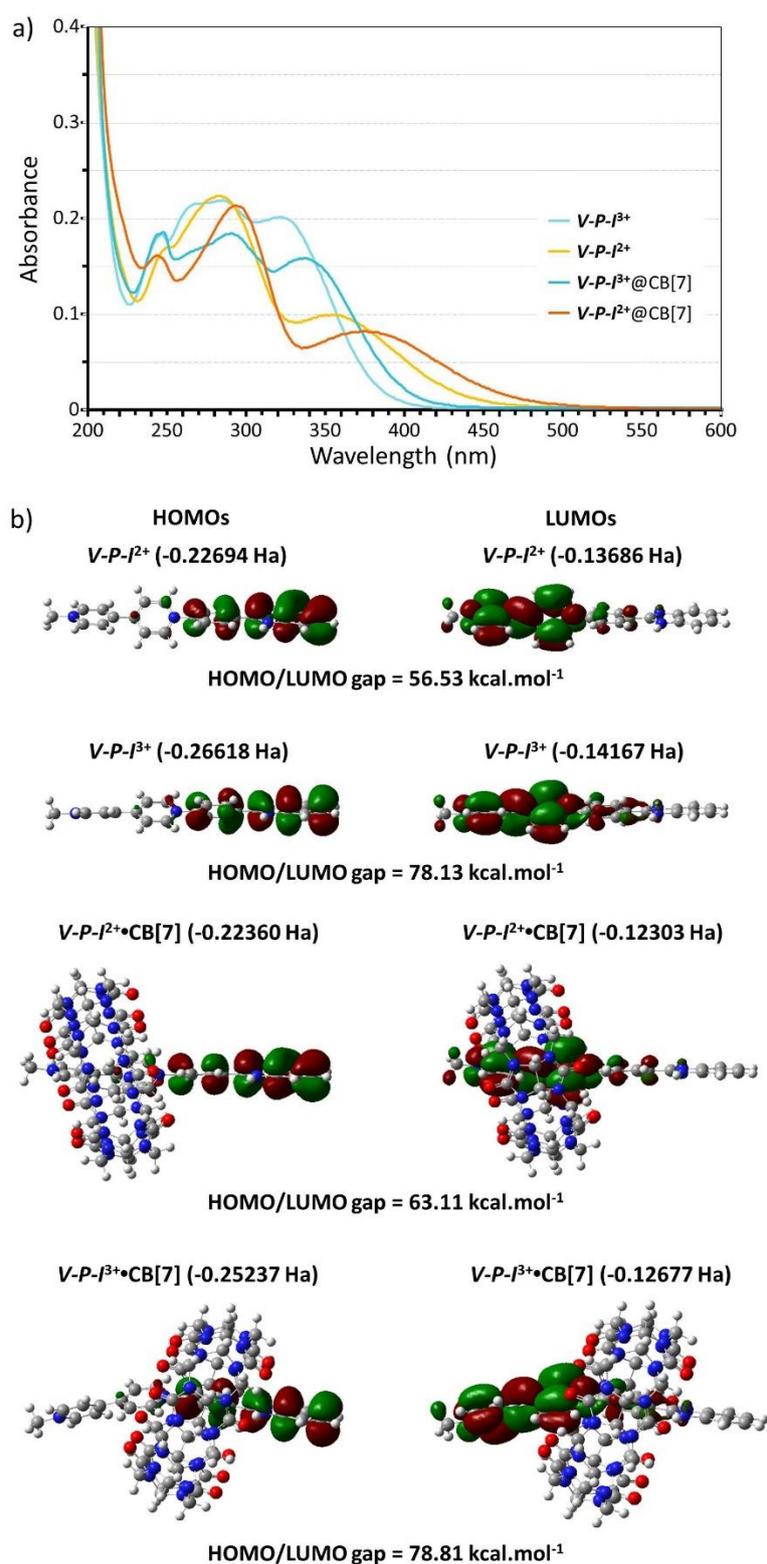
**1/ Chemical compounds.** The chemicals: D<sub>2</sub>O, trifluoroacetic acid-D (TFA), and Amberlite®IRA 400 chloride form were purchased from commercial sources (Aldrich, Acros or TCI) and used without further purification. Compound 1-butyl-3-methylimidazolium hexafluorophosphate was purchased from Aldrich and modified into 1-Butyl-3-methylimidazolium chloride (BMIC) using Amberlite®IRA 400 chloride form. CB[7] was prepared according to a previous paper<sup>[1]</sup> with extra caution regarding remaining trace acid since batches not pure enough (pH of CB[7] solutions <7) could give inconsistent NMR results. CB[7] batches giving neutral pH stock solutions were then used throughout this study. NaCl (99.5%) was from Prolabo. **V-P-I** was prepared according to a previously reported procedure.<sup>[2]</sup>

**2/ NMR Measurements.** NMR spectra were recorded on BRUKER Avance III nanobay – 300 or 400 spectrometers and a BRUKER Avance I – 500 spectrometer (<sup>1</sup>H-NMR 300.13, 400.13, and 500.13 MHz and <sup>13</sup>C-NMR 75.46, 100.60, and 125.75 MHz respectively) using D<sub>2</sub>O as the solvent (internal reference, 4.75 ppm, and a watergate sequence (water suppress) when necessary (potentially affecting signals and integrals near the signal suppressed). Acetone was also used when necessary as another reference. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

**3/ Mass spectrometry.** A stock solution of 0.02 mM **V-P-I** with 0.06 mM CB[7] was prepared and the pH adjusted to ~9 by a sodium hydroxide solution. The stock solution was diluted 4 times and filtrated through a 450 nm filter membrane before ElectroSpray Ionization Mass Spectrometry (ESI-MS). The ESI-MS analysis was performed with a Thermo LTQ OrbiTrap XL instrument equipped with an ESI/APCl multiprobe. The single injection mode was used. The syringe flow rate was set at 10 µL/min; the Sheath Gas (arb) was set at 12; the Auxiliary Gas (arb) was set at 3; the ISpray Voltage was set at 4.0 kV; the Capillary Temperature was set at 275°C.

**4/ DFT Calculations.** DFT calculations were performed with the Gaussian09 Rev.D01 package. All the structures were fully optimized at the B3LYP/6-31G(d) level of theory using a water continuum model (CPCM) and frequency checked for true minimas. Dispersion was taken into account using BJ-damping (additional keyword: empiricaldispersion=gd3bj).<sup>[3]</sup> Three positions of the host around the guest were considered (CB[7] on stations *V*, *P* or *I*). For **V-P-β<sup>+</sup>**•CB[7], the most stable complex has CB[7] on station *V*. For **V-P-β<sup>+</sup>**•CB[7], the most stable complex has the host on station *P*, in line with NMR results. For atomic coordinates of these two complexes, see the end of this document.

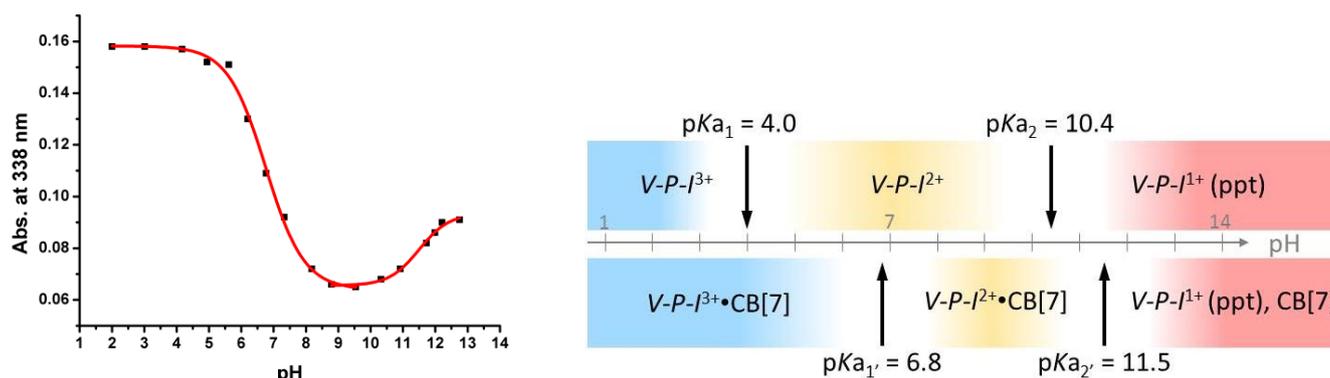
5/ UV-visible spectra of  $V-P-I^+$ ,  $V-P-I^+$ ,  $V-P-I^+ \cdot CB[7]$  and  $V-P-I^+ \cdot CB[7]$ .



**Figure S1.** UV-vis spectra of  $V-P-I^+$ ,  $V-P-I^+$ ,  $V-P-I^+ \cdot CB[7]$  and  $V-P-I^+ \cdot CB[7]$  and corresponding HOMO, LUMO, and energy levels.

The HOMO-LUMO gaps increase as a result of protonation, which is consistent with higher energy photons and so a shift toward more energetic wavelengths (UV) which is also observed experimentally and visually as the solutions' colors turn colorless with pH lowering.

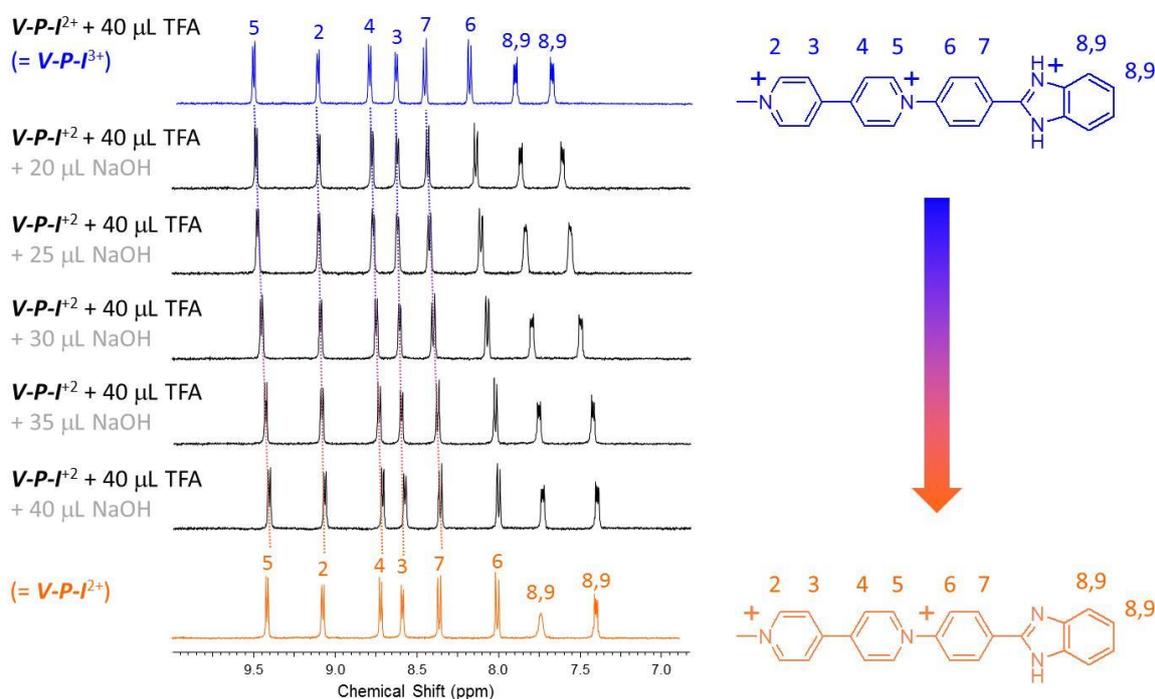
## 6/ pKa Measurements.



**Figure S2.** pKa Values determined by UV-vis spectroscopy in water/HCl/NaOH. ( $pK_{a1} = 6.76 \pm 0.05$ ,  $pK_{a2} = 11.50 \pm 0.10$ ;  $[V-P-I] = 0.01$  mM,  $[CB7]=0.04$  mM).

At these concentrations for **V-P-I** and CB[7], the proportion of 1:1 complex is ~95% while that of the 1:2 complex is only ~5% based on the binding constants reported in the paper. This allows for determining pKa values for 1:1 complexes while minimizing the effect of 1:2 complexes.

## 7/ <sup>1</sup>H NMR of V-P-I<sup>3+</sup> and titration toward V-P-I<sup>2+</sup> in D<sub>2</sub>O.



**Figure S3.** Excerpt of the aromatic region of the <sup>1</sup>H NMR spectra of **V-P-I** in acid conditions (**V-P-I<sup>3+</sup>**, top, addition of 40 μL of a 25 mM solution of TFA into 0.5 mL of a 1 mM solution of **V-P-I<sup>3+</sup>**) before gradual addition of NaOH (25 mM) toward formation of **V-P-I<sup>2+</sup>** (bottom) in D<sub>2</sub>O.

<sup>1</sup>H NMR titrations of **V-P-I<sup>3+</sup>** to **V-P-I<sup>2+</sup>** revealed signal changes in line with benzimidazole deprotonation (signals corresponding to protons number 8 and 9 are the most affected).

## 8/ Preparation and NMR spectra of $V-P-P^{2+}\cdot CB[7]$ and $V-P-P^{3+}\cdot CB[7]$ .

### Preparation and NMR spectra of $V-P-P^{2+}\cdot CB[7]$ :

A 1 mM solution of  $V-P-P^{2+}\cdot CB[7]$  was prepared from a stock solution of 5 mM of  $V-P-I$  (prepared by dissolution of 2.71 mg in 1.240 mL of  $D_2O$ ) and a stock solution of 5 mM of  $CB[7]$  (prepared by dissolution of 21.25 mg in 3.650 mL of  $D_2O$ ); 100  $\mu L$  of each solution and addition of 300  $\mu L$  of  $D_2O$ , leading to a yellow solution. 1D and 2D NMR spectra have already been reported (supporting information).<sup>[2]</sup>

$^1H$  NMR (500 MHz,  $D_2O$ )  $\delta$  9.30 (d,  $J = 6.5$  Hz, 2H, **H5**), 8.97 (d,  $J = 6.1$  Hz, 2H, **H2**), 8.45 (d,  $J = 8.0$  Hz, 2H, **H7**), 8.32 (d,  $J = 8.0$  Hz, 2H, **H6**), 7.75 (m, 2H, **H8** or **H9**), 7.40 (m, 2H, **H8** or **H9**), 7.16 (m, 2H, **H4**), 7.03 (m, 2H, **H3**), 5.67 (d,  $J = 14.2$  Hz, 7H, **CB[7]**), 5.62 (d,  $J = 13.7$  Hz, 7H, **CB[7]**), 5.45 (s, 14H, **CB[7]**), 4.62 (s, 3H, **-CH<sub>3</sub>**), 4.21 (d,  $J = 8.1$  Hz, 7H, **CB[7]**), 4.18 (d,  $J = 8.1$  Hz, 7H, **CB[7]**).

### Preparation and NMR spectra of $V-P-P^{3+}\cdot CB[7]$ :

A 1 mM solution of  $V-P-P^{3+}\cdot CB[7]$  was prepared from a stock solution of 5 mM of  $V-P-I$  (prepared by dissolution of 2.71 mg in 1.240 mL of  $D_2O$ ) and a stock solution of 5 mM of  $CB[7]$  (prepared by dissolution of 21.25 mg in 3.650 mL of  $D_2O$ ); 100  $\mu L$  of each solution and addition of 300  $\mu L$  of  $D_2O$ . Then 2 equiv of TFA (40  $\mu L$  of a 50 mM solution) was added, leading to an colorless solution.

$^1H$  NMR (500 MHz,  $D_2O$ )  $\delta$  9.14 (d,  $J = 6.6$  Hz, 2H, **H2**), 8.78 (s, 4H, **H4** and **H5**), 8.66 (d,  $J = 6.1$  Hz, 2H, **H3**), 8.07 (d,  $J = 6.0$  Hz, 2H, **H8** or **H9**), 7.77 (d,  $J = 6.0$  Hz, 2H, **H8** or **H9**), 7.57 (d,  $J = 8.1$  Hz, 2H, **H7**), 7.26 (d,  $J = 8.2$  Hz, 2H, **H6**), 5.70 (d,  $J = 25.8$  Hz, 7H, **CB[7]**), 5.67 (d,  $J = 25.8$  Hz, 7H, **CB[7]**), 5.54 (s, 14H, **CB[7]**), 4.57 (s, 3H, **H1**), 4.26 (d,  $J = 10.2$  Hz, 7H, **CB[7]**), 4.23 (d,  $J = 10.2$  Hz, 7H, **CB[7]**).

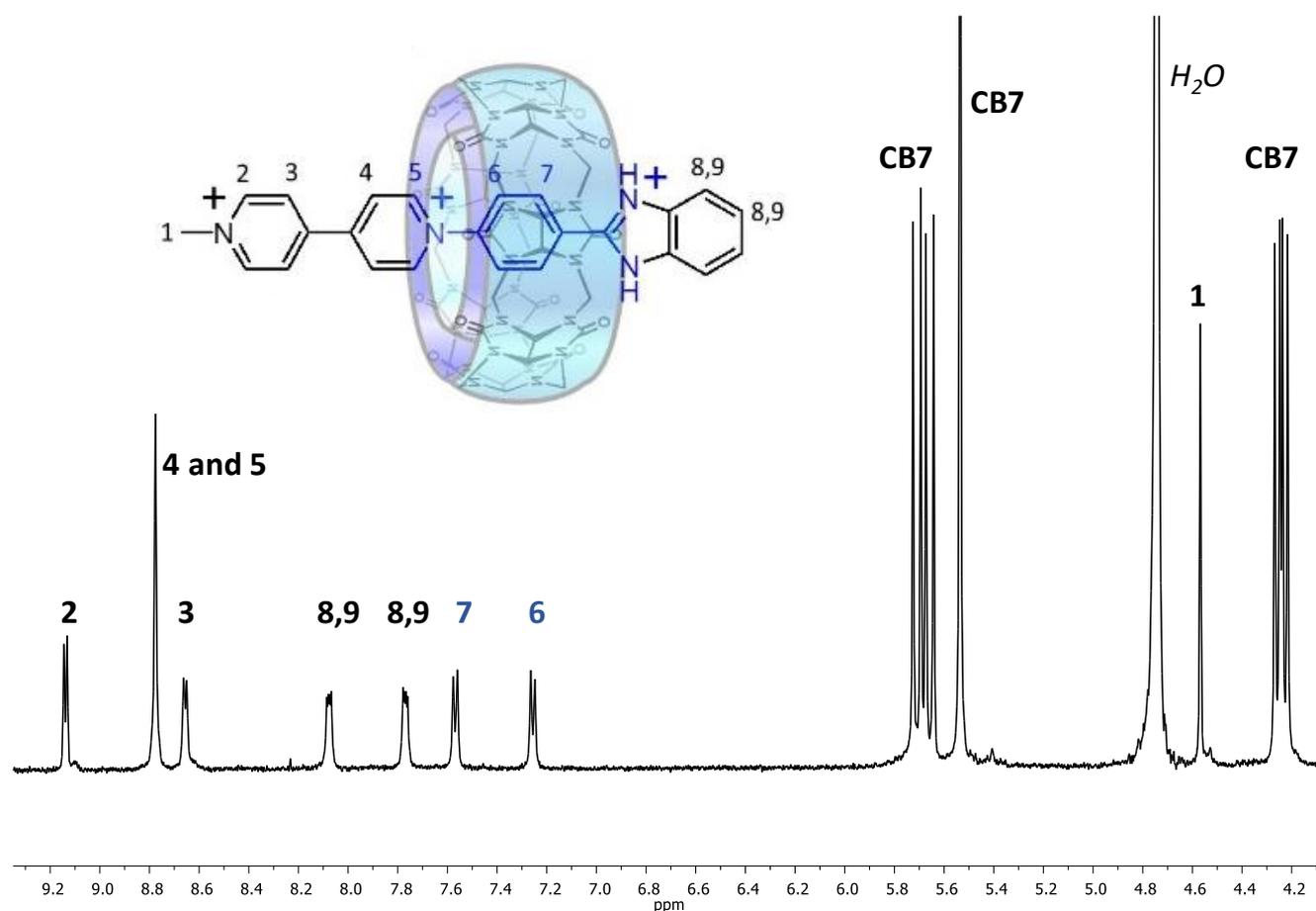
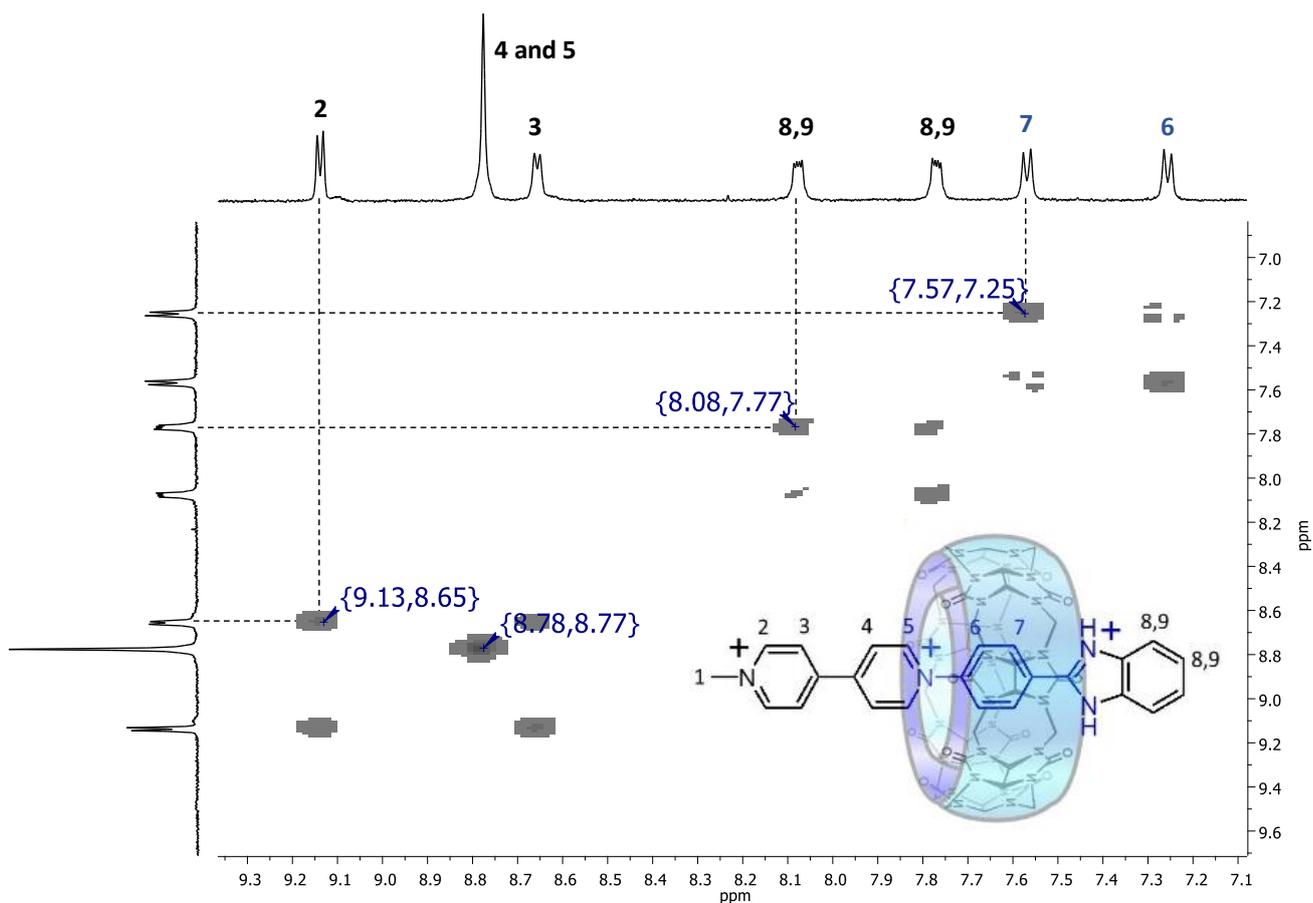
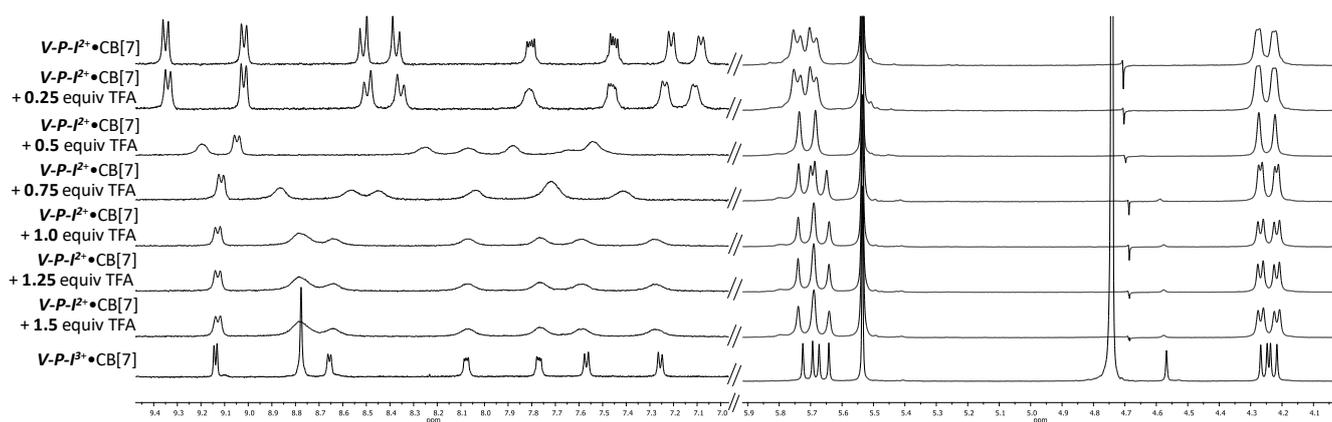


Figure S4.  $^1H$  NMR spectrum of the  $V-P-I\cdot CB[7]$  complex in  $D_2O$  (Bruker AV500, 1 mM).



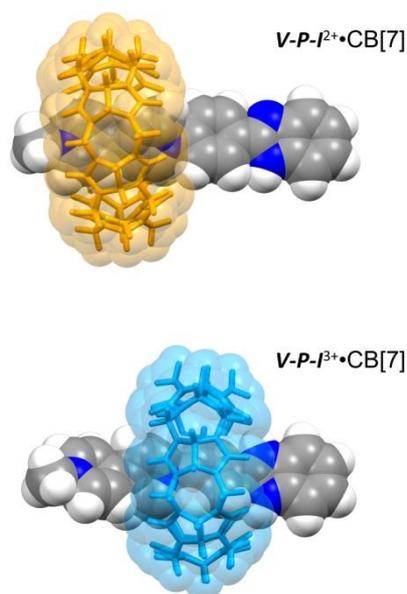
**Figure S5.** COSY H-H NMR spectrum of the  $V-P-\beta^+\bullet CB[7]$  complex in  $D_2O$  (Bruker AV300, 1mM).

### 9/ Amount of proton stimulus required for total ring translocation.



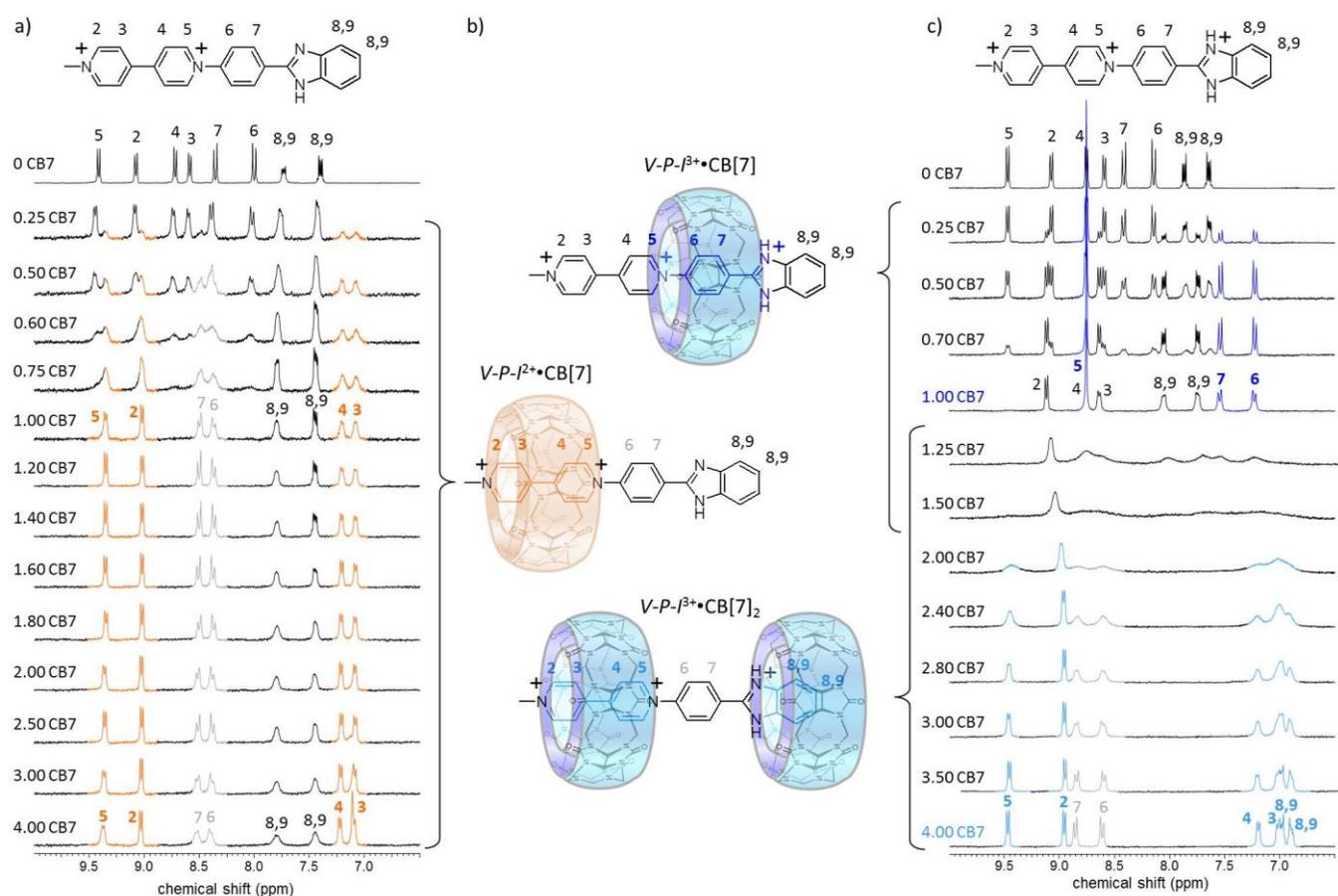
**Figure S6.**  $^1H$  NMR spectra (300MHz-NMR, 96 scans) of  $V-P-\beta^+\bullet CB[7]$  (top, concentration: 1 mM in  $D_2O$ , 300MHz-NMR) with gradual addition of trifluoroacetic acid TFA-D (concentration: 12.5 mM in  $D_2O$ ) toward formation of  $V-P-\beta\bullet CB[7]$  (bottom, concentration: 1 mM in  $D_2O$ , Bruker AV500) in  $D_2O$ .

## 10/ DFT calculations.



**Figure S7.** DFT minimized structures compatible with NMR data for the included complexes of (top)  $V-P-\beta^{2+}\cdot CB[7]$  and (bottom)  $V-P-\beta^{3+}\cdot CB[7]$ .

## 11/ $^1H$ NMR titrations of $V-P-I$ with $CB[7]$ in basic and acid conditions.

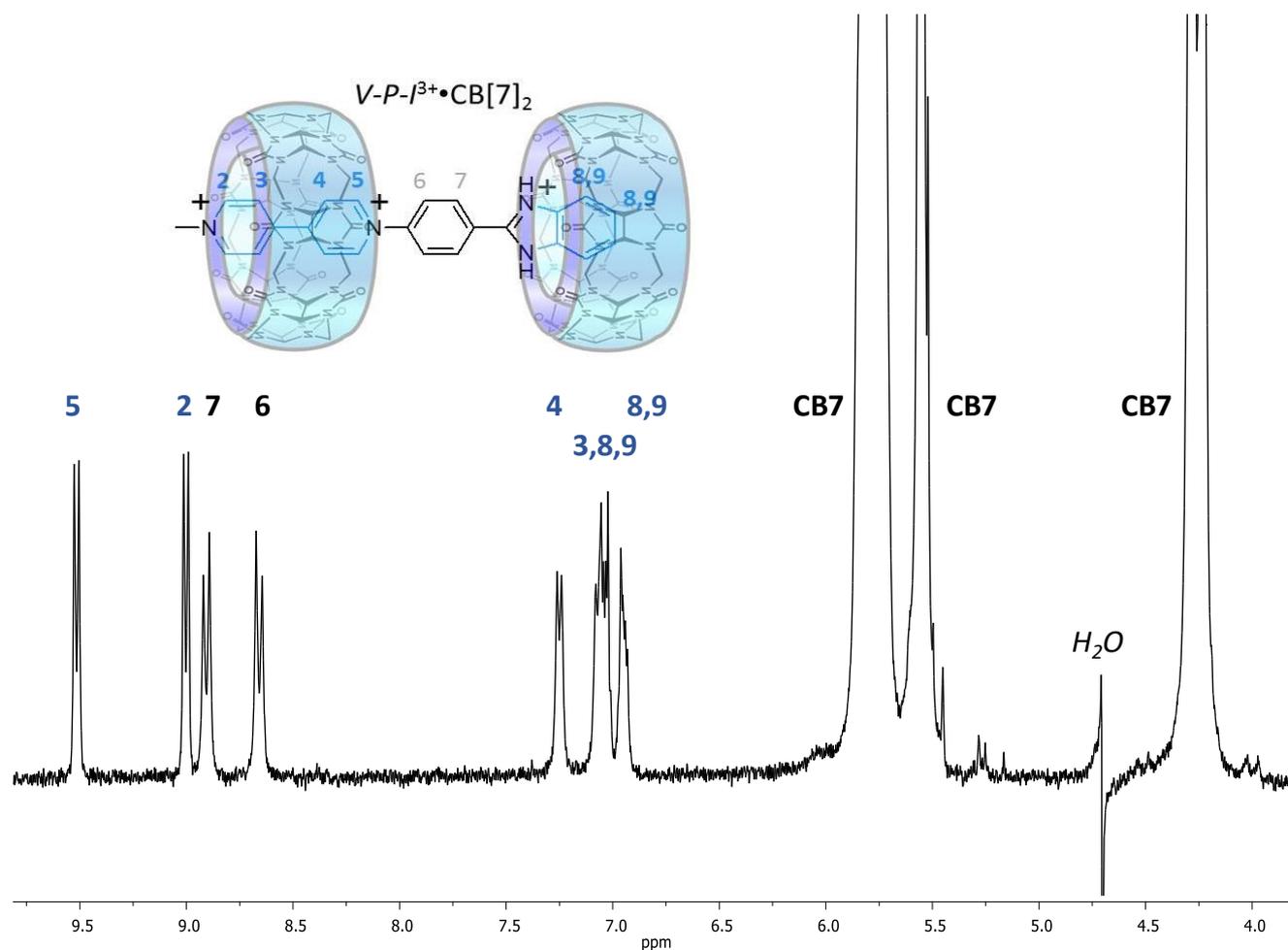


**Figure S8.** Excerpts of the aromatic region of  $V-P-\beta^{2+}$  (a) and  $V-P-\beta^{3+}$  (c) for the  $^1H$  NMR titration with  $CB[7]$  in  $D_2O$  ( $[V-P-\beta^{2+}] = 556 \mu M$  and  $[V-P-\beta^{3+}] = 1 mM$  ( $[TFA] = 3 mM$  for c)). Proposed structures are shown in (b).

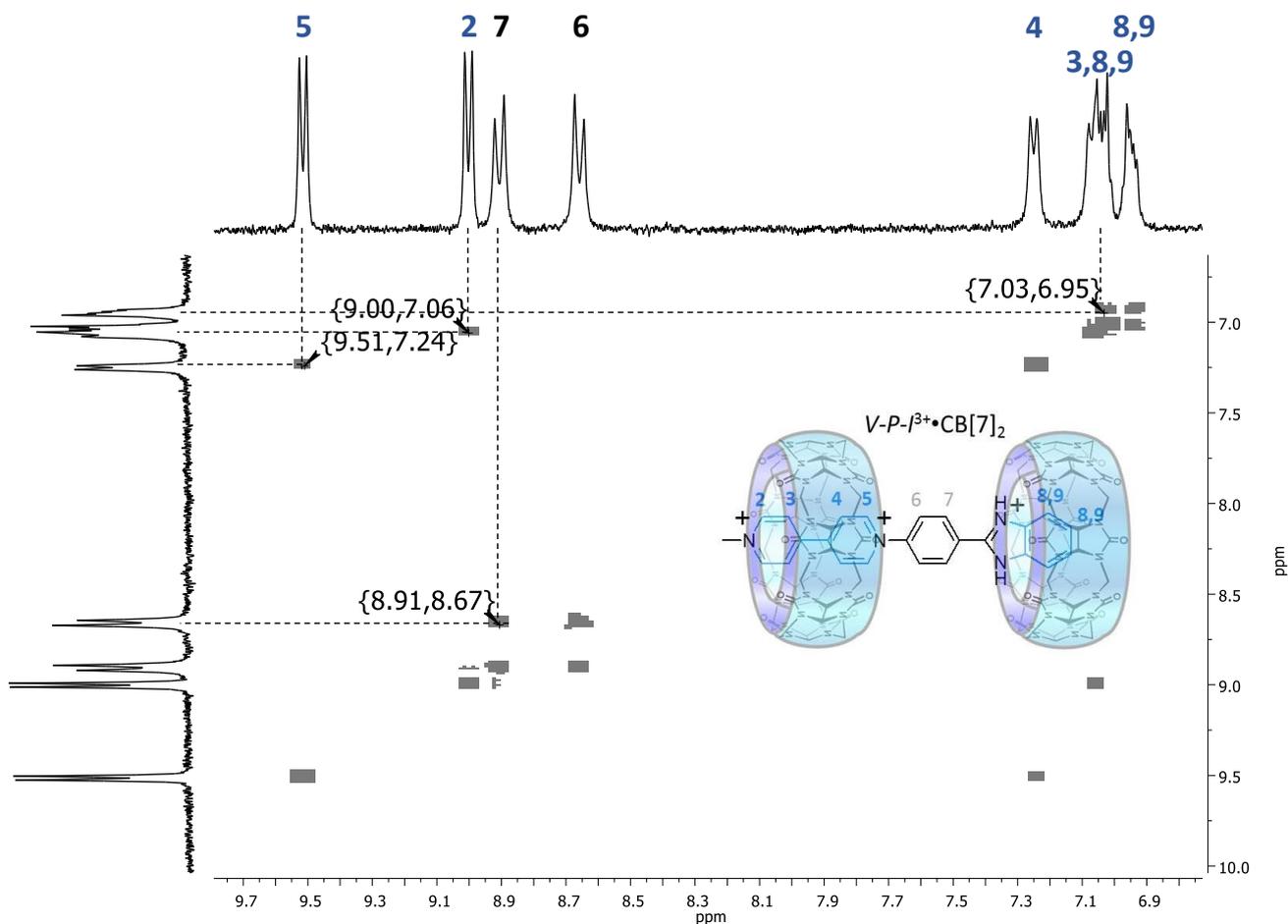
## 12/ Preparation and NMR spectra of $V-P-\beta^+\cdot CB[7]_2$ .

A 1 mM solution of  $V-P-\beta^+\cdot CB[7]$  was prepared from a stock solution of 5 mM of  $V-P-I$  (prepared by dissolution of 2.71 mg in 1.240 mL of  $D_2O$ ) and a stock solution of 5 mM of  $CB[7]$  (prepared by dissolution of 21.25 mg in 3.650 mL of  $D_2O$ ); 100  $\mu L$  of  $V-P-I$  solution and 400  $\mu L$  of  $CB[7]$  solution (4 equiv of  $CB[7]$ ). Then 2 equiv of TFA (40  $\mu L$  of a 50 mM solution) was added, leading to a colorless solution.

$^1H$  NMR (300 MHz,  $D_2O$ )  $\delta$  9.52 (d,  $J = 6.7$  Hz, 2H, **H5**), 9.00 (d,  $J = 6.7$  Hz, 2H, **H2**), 8.91 (d,  $J = 8.6$  Hz, 2H, **H7**), 8.66 (d,  $J = 8.7$  Hz, 2H, **H6**), 7.25 (d,  $J = 6.3$  Hz, 2H, **H4**), 7.04 (m, 4H, overlapped of **H3** and **H8** or **H9**), 6.96 (m, 2H, **H8** or **H9**), 5.76 (br m, 56H, **CB[7]**), 5.54 (s, 56H, **CB[7]**), 4.26 (d,  $J = 15.5$  Hz, 56H, **CB[7]**).

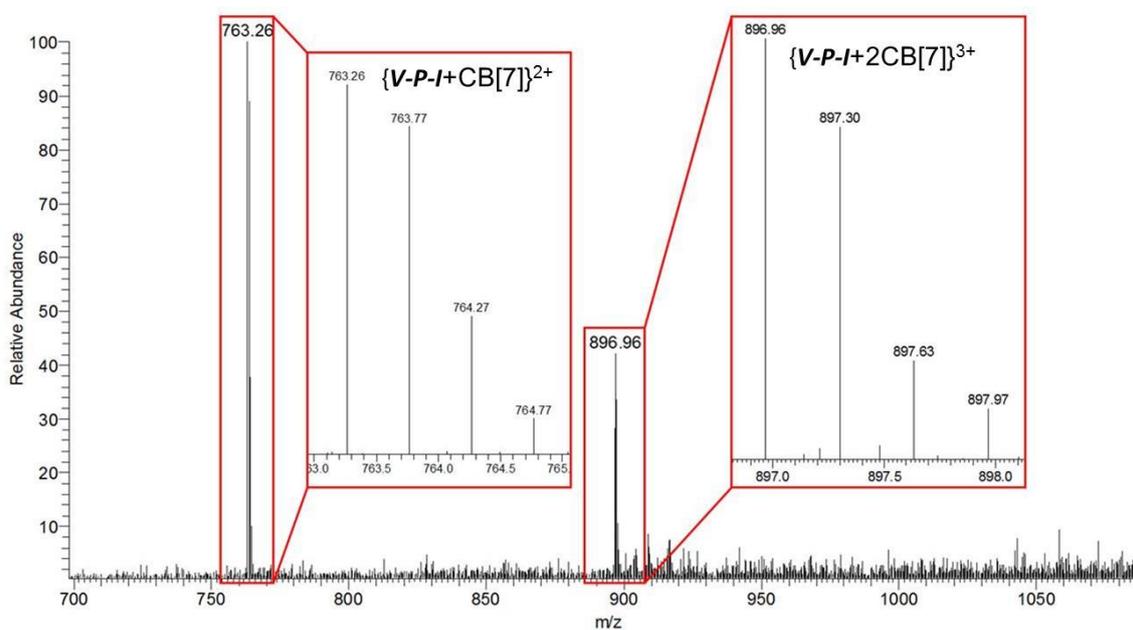


**Figure S9.**  $^1H$  NMR spectrum of the  $V-P-\beta^+\cdot CB[7]_2$  complex in  $D_2O$  (Bruker AV300, 1mM, 4 equiv of  $CB[7]$ ).



**Figure S10.** COSY H-H NMR spectrum of the  $V-P-\beta^3+\cdot CB[7]_2$  complex in  $D_2O$  (Bruker AV300, 1mM, 4 equiv of  $CB[7]$ ).

### 13/ Mass spectrometry of $V-P-I$ with $CB[7]$ .



**Figure S11.** MS spectrum of  $V-P-I$  and  $CB[7]$  showing the presence of 1:1 and 1:2 complexes.

14/ Job plots of V-P-I with CB[7].

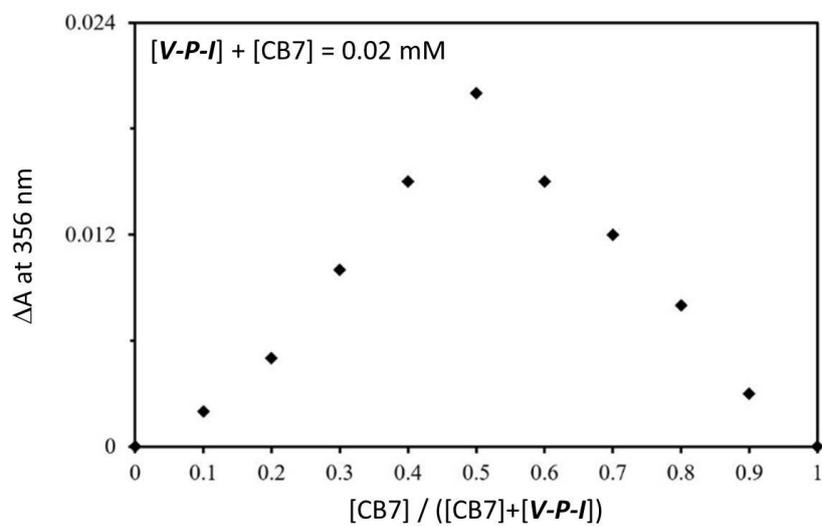


Figure S12. Job plot for V-P-I and CB[7] in basic conditions (pH ≈ 9).

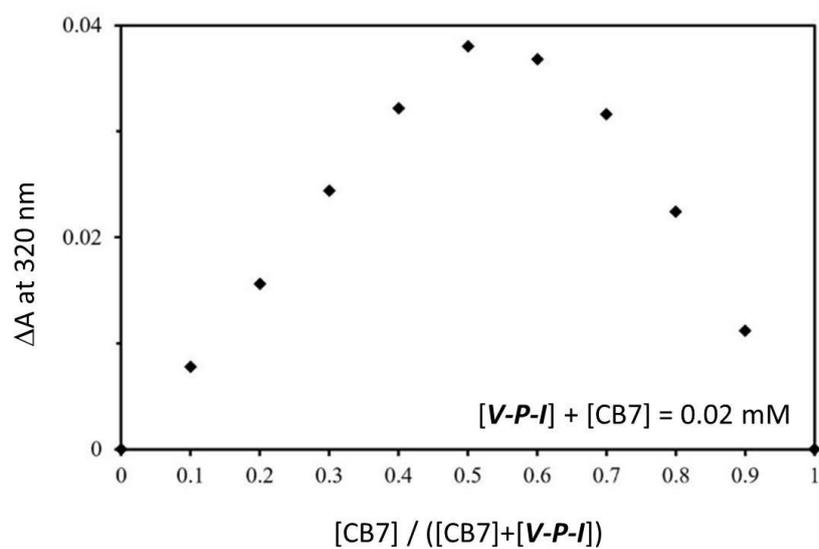


Figure S13. Job plot for V-P-I and CB[7] in acid conditions (pH ≈ 2).

## 15/ Determination of binding constants by competition NMR.

The binding constants of  $V-P-I^{3+}$  and  $V-P-I^{3+}\cdot CB[7]$  toward CB[7] were determined via  $^1H$  NMR using competitors, following the procedures of Isaacs et al.<sup>[4]</sup> and Macartney et al.<sup>[5]</sup>

### Determination of the binding constant of 1-butyl-3-methylimidazolium chloride (BMIC) toward CB[7] using $V-P-I^{3+}$ as competitor.

Solutions of BMIC or BMIC $\cdot$ CB[7] (Eq 1) were prepared (1 mM in D<sub>2</sub>O) and the NMR spectra were recorded at 298 K on a Bruker AV300 spectrometer (120 scans). The  $^1H$  NMR spectra permitted to determine the values of the observed chemical shifts  $\delta_{obs}$  of the  $CH_3$ -protons of the butyl group for free BMIC ( $\delta_{obs\_BMIC} = 0.916$  ppm, Figure S13a) and BMIC $\cdot$ CB[7] ( $\delta_{obs\_BMIC\cdot CB[7]} = 136$  ppm, Figure S13b and Table S1). We evaluated the chemical shift difference of the  $CH_3$ -protons between free BMIC and complexed BMIC :  $\Delta\delta_{obs\_CH_3} = \delta_{obs\_BMIC} - \delta_{obs\_BMIC\cdot CB[7]} = 0.780$  ppm (Table S1).

Competitive solutions (Eq 2) were prepared via mixing BMIC, CB[7] and  $V-P-I^{3+}$  in D<sub>2</sub>O (volume: 0.500 mL, traces of acetone as internal reference) and their  $^1H$  NMR spectra (Figure S13c) permitted to evaluate the values of the  $\delta_{obs\_CH_3}$  (observed chemical shifts  $CH_3$ -protons of the butyl group in competition) of BMIC (Table S1). The equilibrium constant of the competition  $K^{comp}$  is represented in Eq 4. The values of  $\Delta\delta_{obs\_CH_3}$  and  $\delta_{obs\_CH_3}$  are used to calculate the concentrations of the different species (Eq 6-9) and, eventually, Eq 5 gives the binding constant of BMIC  $K^{1:1\_BMIC}$  (Table S1) using the binding constant of  $V-P-I^{3+}$  toward CB[7] of  $7.25 \times 10^5 M^{-1}$ .<sup>[2]</sup> the binding constant of BMIC was  $151000 \pm 5000 M^{-1}$ .



$$\text{Eq 3} \quad K^{1:1} = \frac{[\{\text{BMIC}\cdot\text{CB}[7]\}]}{[\text{CB}[7]] \cdot [\text{BMIC}]} \quad \text{and} \quad [\text{BMIC}]_{total} = [\text{BMIC}]_{free} + [\{\text{BMIC}\cdot\text{CB}[7]\}]$$

$$\text{Eq 4} \quad K^{comp} = \frac{[\text{BMIC}] \cdot [\{V-P-I\cdot\text{CB}[7]\}]}{[\{\text{BMIC}\cdot\text{CB}[7]\}] \cdot [V-P-I]} = \frac{K^{1:1\_VPI}}{K^{1:1\_BMIC}}$$

and  $[V-P-I^{3+}]_{total} = [V-P-I^{3+}]_{free} + [\{V-P-I^{3+}\cdot\text{CB}[7]\}]$ ,  $[\text{CB}[7]]_{total} = [\{\text{BMIC}\cdot\text{CB}[7]\}] + [\{V-P-I^{3+}\cdot\text{CB}[7]\}] + [\text{CB}[7]]_{free}$  ( $[\text{CB}[7]]_{free}$  is negligible).

$$\text{Eq 5} \quad K^{1:1\_BMIC} = \frac{[\{\text{BMIC}\cdot\text{CB}[7]\}] \cdot [V-P-I] \cdot K^{1:1\_VPI}}{[\text{BMIC}] \cdot [\{V-P-I\cdot\text{CB}[7]\}]}$$

$$\text{Eq 6} \quad [\text{BMIC}] = \frac{(\delta_{obs\_CH_3}) - (\delta_{obs\_BMIC\cdot CB[7]})}{(\Delta\delta_{obs\_CH_3})} \cdot [\text{BMIC}]_{total} = \frac{(\delta_{obs\_CH_3}) - 0.136}{0.780} \cdot [\text{BMIC}]_{total}$$

$$\text{Eq 7} \quad [\{\text{BMIC}\cdot\text{CB}[7]\}] = \frac{(\delta_{obs\_BMIC}) - (\delta_{obs\_CH_3})}{(\Delta\delta_{obs\_CH_3})} \cdot [\text{BMIC}]_{total} = \frac{0.916 - (\delta_{obs\_CH_3})}{0.780} \cdot [\text{BMIC}]_{total}$$

$$\text{Eq 8} \quad [\{V-P-I\cdot\text{CB}[7]\}] = [\text{CB}[7]]_{total} - [\{\text{BMIC}\cdot\text{CB}[7]\}] \quad ([\text{CB}[7]]_{free} \text{ is negligible}).^{[5]}$$

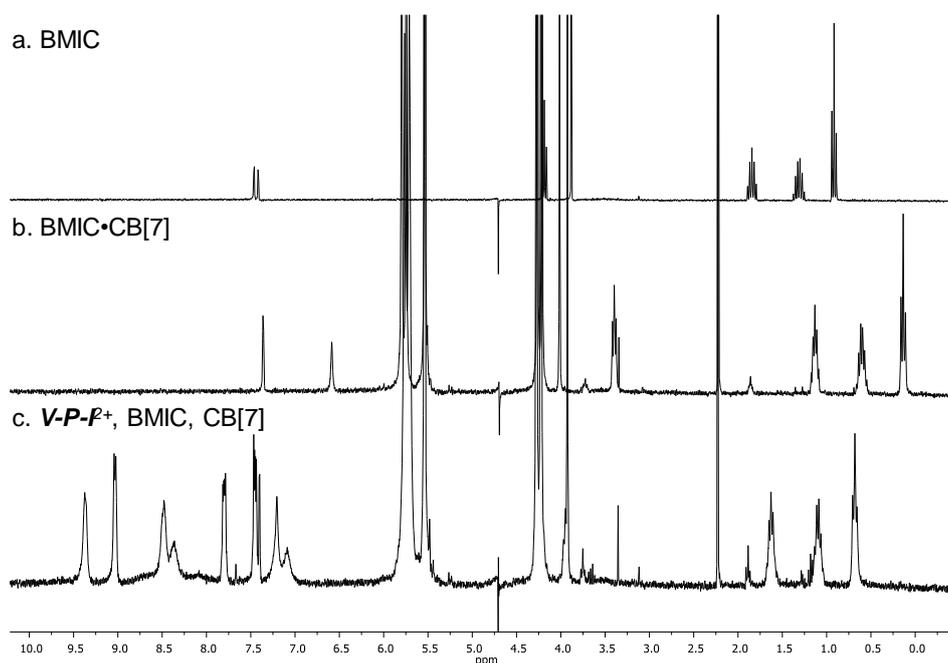
$$\text{Eq 9} \quad [V-P-I] = [V-P-I]_{total} - [\{V-P-I\cdot\text{CB}[7]\}]$$

**Table S1.** Calculation of binding constants from  $^1\text{H}$  NMR data.<sup>a</sup>

Ratios of BMIC/ <i>V-P-β</i> <sup>+</sup> /CB[7]	$\delta_{\text{obs\_CH}_3}$ (average) <sup>b</sup>	% of free BMIC <sup>c</sup>	Calculated binding constant of BMIC <sup>d</sup>
1/0/0	0.916 ppm	100	-
1/0/1	0.136 ppm	0	-
1/1/1	0.670 ppm	68.5	153000 M <sup>-1</sup>
2/1/1 <sup>e</sup>	0.749 ppm	78.6	148000 M <sup>-1</sup>

**binding constant of BMIC<sup>f</sup> = 151000 ± 5000 M<sup>-1</sup>**

<sup>a</sup>Conditions: [*V-P-β*<sup>+</sup>]<sub>total</sub> = [CB[7]]<sub>total</sub> = 1 mM in D<sub>2</sub>O, Bruker AV300 spectrometer, 80-120 scans, 298 K; <sup>b</sup>chemical shift of CH<sub>3</sub>-group of butyl of BMIC  $\delta_{\text{obs\_CH}_3}$ , the presented values are the averages, the NMR experiments were repeated 3 times; <sup>c</sup>calculated from Eq 6; <sup>d</sup>calculated from Eq 5; <sup>e</sup>[BMIC] = 2 mM, [*V-P-β*<sup>+</sup>]<sub>total</sub> = [CB[7]]<sub>total</sub> = 1 mM; <sup>f</sup>average value and standard deviation.



**Figure S14.**  $^1\text{H}$  NMR of BMIC (a), {BMIC<sup>+</sup>·CB[7]} (b) and a mixture of BMIC, *V-P-β*<sup>+</sup> and CB[7] (c, ratio 1/1/1, 1 mM in D<sub>2</sub>O), data collected at 298 K on a Bruker AV300 spectrometer, the spectra were calibrated using traces of acetone as internal reference ( $\delta = 2.220$  ppm).<sup>[6]</sup>

### **Determination of the binding constant of *V-P-β*<sup>+</sup> toward CB[7] using 1-butyl-3-methylimidazolium chloride (BMIC) as competitor.**

Since the binding constant of BMIC was evaluated ( $151000 \pm 5000 \text{ M}^{-1}$ , Table S1) via a competitive  $^1\text{H}$  NMR method in D<sub>2</sub>O using the procedures reported by Isaacs *et al.*<sup>[4]</sup> and Macartney *et al.*<sup>[5]</sup> we applied the same method to evaluate the binding constant of *V-P-β*<sup>+</sup> toward CB[7], using BMIC as competitor.

Solutions of the competitor (Eq 2) were prepared by mixing BMIC, CB[7], *V-P-β*<sup>+</sup> and 2 equiv of TFA (10  $\mu\text{L}$  of 0.1 M solution in D<sub>2</sub>O) in D<sub>2</sub>O (volume: 0.500 mL, traces of acetone as internal reference) and their  $^1\text{H}$  NMR spectra (Figure S14c) allowed to evaluate the values of the  $\delta_{\text{obs\_CH}_3}$  (observed chemical shifts of CH<sub>3</sub>-protons of the butyl group in competition) of BMIC (Table S2).

The chemical shift difference  $\Delta\delta_{\text{obs\_CH}_3}$  of the CH<sub>3</sub>-protons (between free BMIC and complexed BMIC,  $\Delta\delta_{\text{obs\_CH}_3} = \delta_{\text{obs\_BMIC}} - \delta_{\text{obs\_BMIC}\cdot\text{CB}[7]}$ ) of 0.780 ppm, the binding constant of BMIC toward CB[7] ( $151000 \text{ M}^{-1}$ ) and equations Eq 5-10 were utilized for calculations (Table S2).

The binding constant of *V-P-β*<sup>+</sup> toward CB[7] was  $1.04 \pm 0.07 \times 10^7 \text{ M}^{-1}$ .

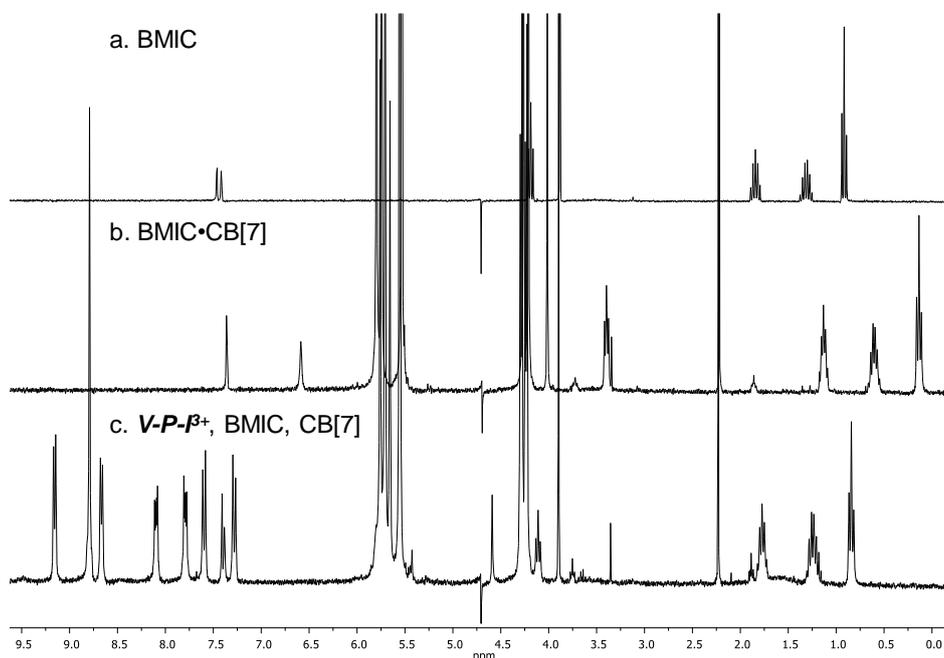
$$\text{Eq 10 } K^{1:1 VPI} = \frac{[BMIC] \cdot [V-P-I \cdot CB[7]] \cdot K^{1:1 BMIC}}{[BMIC \cdot CB[7]] \cdot [V-P-I]}$$

**Table S2.** Calculation of binding constants from  $^1\text{H}$  NMR data.<sup>a</sup>

Ratios of BMIC/ $V-P-\beta^+$ /CB[7]	$\delta_{\text{obs-CH}_3}$ (average)	% of free BMIC <sup>c</sup>	Calculated binding constant of $V-P-\beta^+$ <sup>d</sup>
1/0/0	0.916 ppm	100	-
1/0/1	0.136 ppm	0	-
1/1/1	0.830 ppm <sup>b</sup>	89.0	$9.9 \times 10^6 \text{ M}^{-1}$
2/1/1 <sup>e</sup>	0.859 ppm	92.7	$11.3 \times 10^6 \text{ M}^{-1}$

**binding constant of  $V-P-\beta^+ = 10.4 \pm 0.7 \times 10^6 \text{ M}^{-1}$ .**<sup>f</sup>

<sup>a</sup>Conditions:  $[V-P-\beta^+]_{\text{total}} = [CB[7]]_{\text{total}} = 1 \text{ mM}$  in  $\text{D}_2\text{O}$ , Bruker AV300 spectrometer, 80-120 scans, 298 K; <sup>b</sup>chemical shift of  $\text{CH}_3$ -group of butyl of BMIC  $\delta_{\text{obs-CH}_3}$ , the presented values are the averages, the NMR experiments were repeated 2 times; <sup>c</sup>calculated from **Eq 6**; <sup>d</sup>calculated from **Eq 5**; <sup>e</sup> $[BMIC] = 2 \text{ mM}$ ,  $[V-P-\beta^+]_{\text{total}} = [CB[7]]_{\text{total}} = 1 \text{ mM}$ ; <sup>f</sup>average value and standard deviation.



**Figure S15.**  $^1\text{H}$  NMR of BMIC (a),  $\{BMIC+CB[7]\}$  (b) and a mixture of BMIC,  $V-P-\beta^+$ , CB[7] (c, ratio 1/1/1, 1 mM in  $\text{D}_2\text{O}$ ) and 2 equiv of TFA (10  $\mu\text{L}$  of 0.1 M solution in  $\text{D}_2\text{O}$ ), data collected at 298 K on a Bruker AV300 spectrometer, the spectra were calibrated using traces of acetone as internal reference ( $\delta = 2.220 \text{ ppm}$ ).<sup>[6]</sup>

### **Determination of the binding constant of $\{V-P-\beta^+ \cdot CB[7]\}$ toward CB[7] using 1-Butyl-3-methylimidazolium chloride (BMIC) as competitor.**

Following the method of Macartney et al.<sup>[5]</sup> and considering the high binding constant of  $V-P-\beta^+$  toward CB[7] ( $10.4 \pm 0.7 \times 10^6 \text{ M}^{-1}$ ), we approximated that the main equilibrium for a solution containing  $V-P-\beta^+$  and 2 equiv of CB[7] was between  $\{V-P-\beta^+ \cdot CB[7]\}$  and  $\{V-P-\beta^+ \cdot (CB[7])_2\}$  (**Eq 11**). Solutions of the competitor (**Eq 2**) were prepared via mixing BMIC, CB[7],  $V-P-\beta^+$  (**Eq 12**) and 2 equiv of TFA (10  $\mu\text{L}$  of 0.1 M solution) in  $\text{D}_2\text{O}$  (volume: 0.500 mL, traces of acetone as internal reference) and their  $^1\text{H}$  NMR spectra (Figure S15c) allowed to determine the values of the  $\delta_{\text{obs-CH}_3}$  (observed chemical shifts  $\text{CH}_3$ -protons of the butyl group in competition) of BMIC (Table S3). The chemical shift difference  $\Delta\delta_{\text{obs-CH}_3}$  of the  $\text{CH}_3$ -protons (0.780 ppm) and the binding constant of BMIC toward CB[7] ( $151000 \text{ M}^{-1}$ ) were used for calculations via equations **Eq 6**, **7** and **13**.



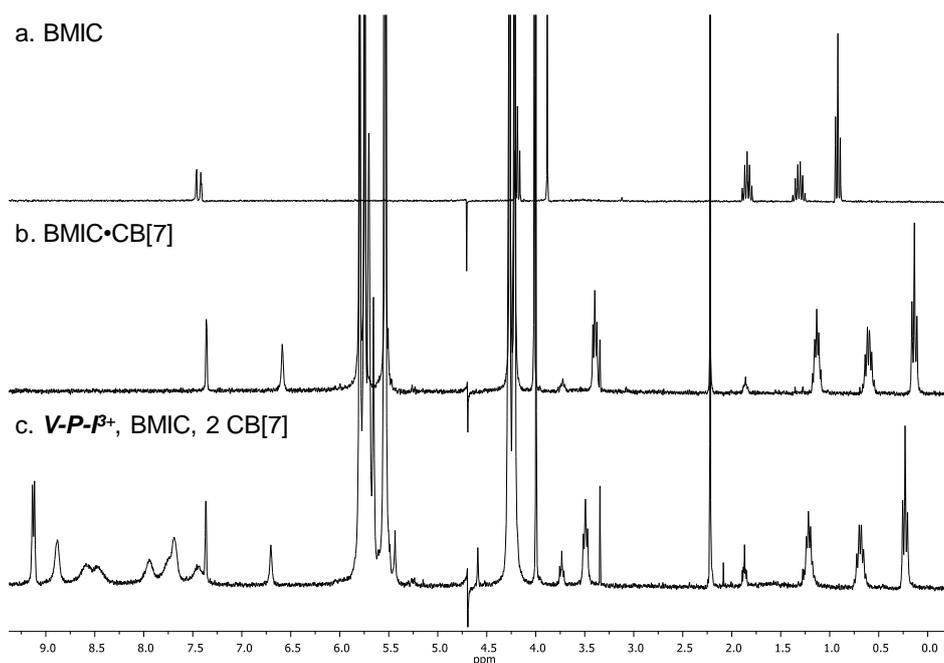
$$\text{Eq 13} \quad K^{1:2:VPI} = \frac{[\text{BMIC}]\cdot\{[\mathbf{V-P-I}\cdot(\text{CB}[7])_2]\}\cdot K^{1:1 \text{ BMIC}}}{\{[\text{BMIC}\cdot\text{CB}[7]]\}\cdot\{[\mathbf{V-P-I}\cdot\text{CB}[7]]\}}$$

**Table S3.** Calculation of binding constants from  $^1\text{H}$  NMR data.<sup>a</sup>

Ratios of BMIC/ $\mathbf{V-P-I}^{3+}$ /CB[7]	$\delta_{\text{obs\_CH3}}$ (average) <sup>b</sup>	% of free BMIC <sup>c</sup>	Calculated constant of $\mathbf{V-P-I}^{3+}\cdot\text{CB}[7]$ <sup>d</sup>	binding
1/0/0	0.916 ppm	100	-	
1/0/1	0.136 ppm	0	-	
1/1/2 <sup>e</sup>	0.221 ppm	10.9	2300 M <sup>-1</sup>	

**binding constant for  $\mathbf{V-P-I}^{3+}\cdot\text{CB}[7]_2 = 2300 \pm 700 \text{ M}^{-1}$ .**

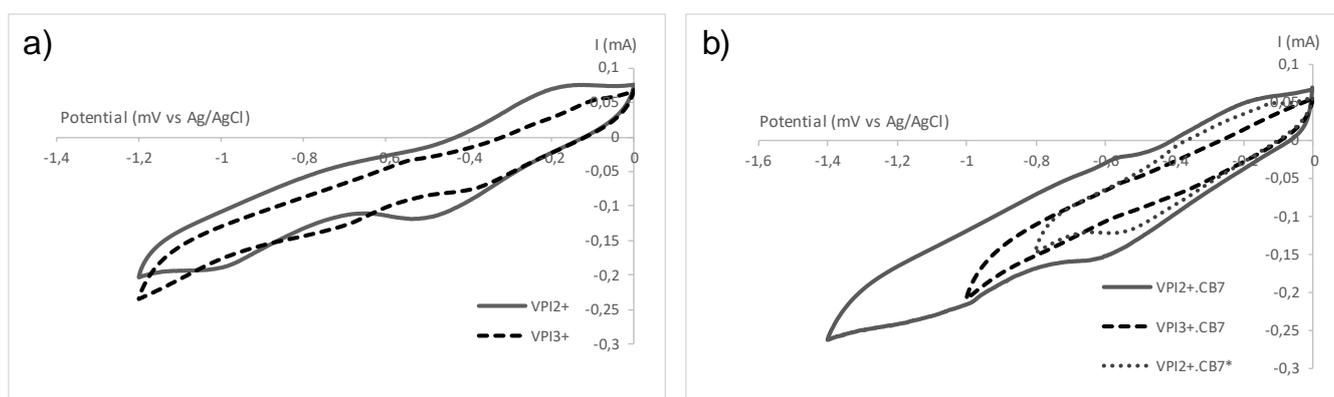
<sup>a</sup>Conditions:  $[\mathbf{V-P-I}^{3+}]_{\text{total}} = [\text{CB}[7]]_{\text{total}} = 1 \text{ mM}$  in  $\text{D}_2\text{O}$ , Bruker AV300 spectrometer, 80-120 scans, 298 K; <sup>b</sup>chemical shift of  $\text{CH}_3$ -group of butyl of BMIC  $\delta_{\text{obs\_CH3}}$ , the presented values are the averages, the NMR experiments were repeated 3 times; <sup>c</sup>calculated from **Eq 6**; <sup>d</sup>calculated from **Eq 5**; <sup>e</sup> $[\text{BMIC}] = 1 \text{ mM}$ ,  $[\mathbf{V-P-I}^{3+}]_{\text{total}} = 1 \text{ mM}$ ,  $[\text{CB}[7]]_{\text{total}} = 1 \text{ mM}$ ; <sup>f</sup>average value and standard deviation.



**Figure S16.**  $^1\text{H}$  NMR of BMIC (a),  $\{\text{BMIC}\cdot\text{CB}[7]\}$  (b) and a mixture of BMIC,  $\mathbf{V-P-I}^{3+}$  and CB[7] (c,  $\text{D}_2\text{O}$ , ratio 1/1/2, 1 mM of BMIC or  $\mathbf{V-P-I}^{3+}$ , 2 mM of CB[7]), data collected at 298 K on a Bruker AV300 spectrometer, the spectra were calibrated using traces of acetone as internal reference ( $\delta = 2.220 \text{ ppm}$ ).<sup>[6]</sup>

## 16/ Cyclic voltammetry of $V-P-\beta^+$ , $V-P-\beta^+$ , $V-P-\beta^+\cdot CB[7]$ and $V-P-\beta^+\cdot CB[7]$

Cyclic voltammetry experiments were performed with a Versastat potentiostat (AMETEK), an Ag/AgCl reference electrode and a glassy carbon electrode (0.071 cm<sup>2</sup>). The data were analyzed using EC-Lab10.40® software. A solution containing 0.80 mM of  $V-P-\beta^+$  (15.7 mg in a total volume of 45 mL of distilled water) and 0.2 M of NaCl (0.525 g in a total volume of 45 mL of distilled water) was analyzed with a scan rate of 50 mV s<sup>-1</sup> in the range of 0.0/-1.2/0.0 V and then was acidified with 0.072 mL of a 1 M HCl solution (3 equiv.) to permit the analysis of a  $V-P-\beta^+$  solution. The redox potentials of  $V-P-\beta^+\cdot CB[7]$  were measured from a solution containing 0.80 mM of  $V-P-\beta^+$ , 0.2 M of NaCl and 0.90 mM of CB[7] (41.8 mg, 1.1 equiv.) with a scan rate of 50 mV s<sup>-1</sup> in the range of 0/-1.4/0 V. The same solution was acidified with 0.072 mL of 1 M HCl solution (3 equiv.) with a scan rate of 50 mV s<sup>-1</sup> in the range of 0.0/-1.0/0.0 V. Addition of NaHCO<sub>3</sub> permitted to neutralize HCl and to observe the  $E^1_{1/2}$  redox waves of  $V-P-\beta^+\cdot CB[7]$  from the resulting solution (range of 0.0/-0.8/0.0 V), showing the reversible redox properties of the  $V-P-\beta^+\cdot CB[7]$ /  $V-P-\beta^+\cdot CB[7]$  system in neutral or acidic conditions, respectively.



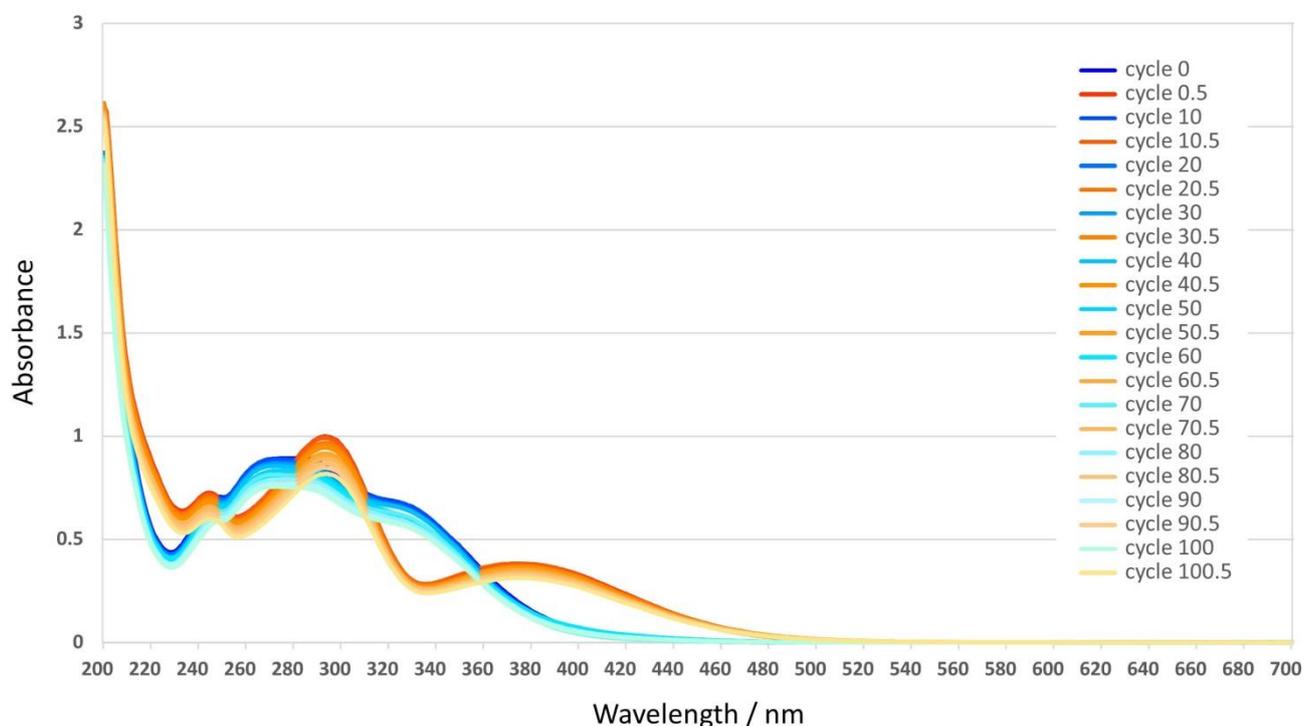
**Figure S17.** Cyclic voltammograms of  $V-P-\beta^+$  and  $V-P-\beta^+$  (a, left) and  $V-P-\beta^+\cdot CB[7]$  and  $V-P-\beta^+\cdot CB[7]$  (b, right,  $V-P-\beta^+\cdot CB[7]^*$  regenerated via addition of NaHCO<sub>3</sub>) on a glassy carbon electrode (0.071 cm<sup>2</sup>) and Ag/AgCl reference electrode. Conditions: concentration 0.80 mM, NaCl concentration of 0.2 M, scan rate of 50 mV s<sup>-1</sup>.

**Table S4.** Redox potentials of  $V-P-\beta^+$ ,  $V-P-\beta^+$ ,  $V-P-\beta^+\cdot CB[7]$  and  $V-P-\beta^+\cdot CB[7]$  determined from the corresponding cyclic voltammograms (potential expressed in volts (V) vs. a Ag/AgCl electrode). Potential of  $V-P-\beta^+\cdot CB[7]^*$  determined after addition of NaHCO<sub>3</sub> onto an acidic solution of  $V-P-\beta^+\cdot CB[7]$ .

	$E^1_{red}$ (V)	$E^1_{ox}$ (V)	$E^1_{1/2}$ (V)	$E^2_{red}$ (V)	$E^2_{ox}$ (V)	$E^2_{1/2}$ (V)
$V-P-\beta^+$	-0.51	-0.21	-0.36	-0.99	-0.52	-0.76
$V-P-\beta^+$	-0.36	-0.13	-0.25	-0.72	-0.54	-0.63
$V-P-\beta^+\cdot CB[7]$	-0.55	-0.19	-0.37	-0.99	-0.49	-0.74
$V-P-\beta^+\cdot CB[7]$	-0.35	-0.10	-0.23	-0.73	-0.49	-0.61
$V-P-\beta^+\cdot CB[7]^*$	-0.56	-0.13	-0.35	-	-	-

**17/ UV-visible spectra recorded in acid and basic conditions every 10 cycles and up to 100 cycles.**

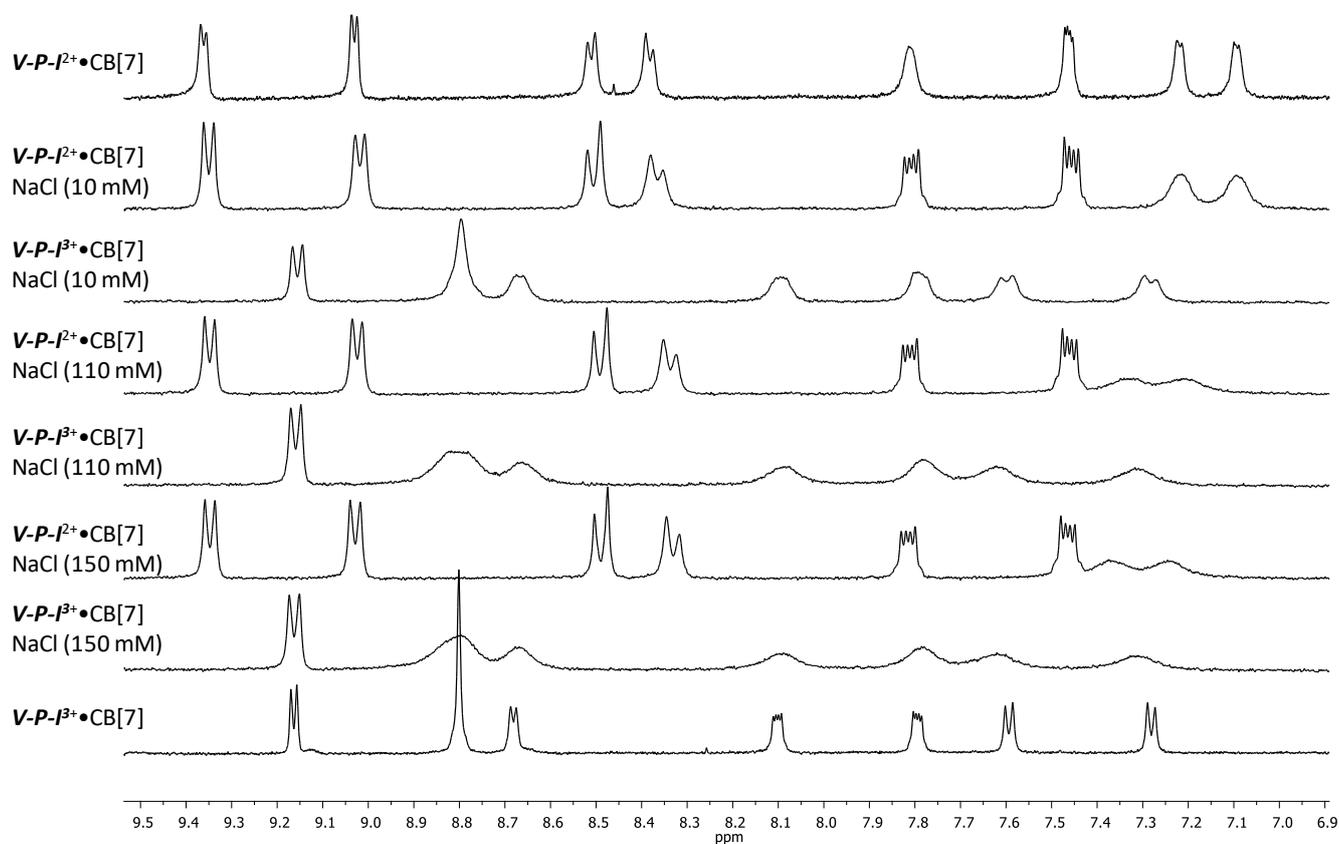
For the pH responsive fatigue resistance tests, a 100 mL stock solution (pH = 4.5) of 0.04 mM **V-P-I** with 1.1 equiv CB[7] was prepared adjusting the pH with an HCl solution. A volume of 3 mL from the stock solution was collected for UV-Vis measurements (UV-Vis reference spectrum of **V-P-I<sup>3+</sup>•CB[7]**). Then, an NaOH solution was added into the stock solution to adjust the pH to 9.5 before collecting a volume of 3 mL for UV-Vis measurements. Then, HCl and NaOH solutions were successively and alternatively introduced in the stock solution to adjust the pH to 4.5 or 9.5, respectively, repeating the alternative acid/base changes for 10 times (10 acid/base cycles). Volumes of 3 mL were collected from the stock solution for UV-vis measurements after each 10 cycles and pH adjustments were repeated until reaching 100 cycles. Measurements (acid and basic conditions) were so performed every 10 cycles. All the volume changes during the fatigue tests have been taken into account (dilution effects) for the calculations of the corrected absorbance intensities.



**Figure S18.** UV-vis spectra of a **V-P-I** solution containing CB[7] (1.1 equiv) over cycles of acid and basic pH changes.

## 18/ Effect of NaCl on the efficiency of cycling.

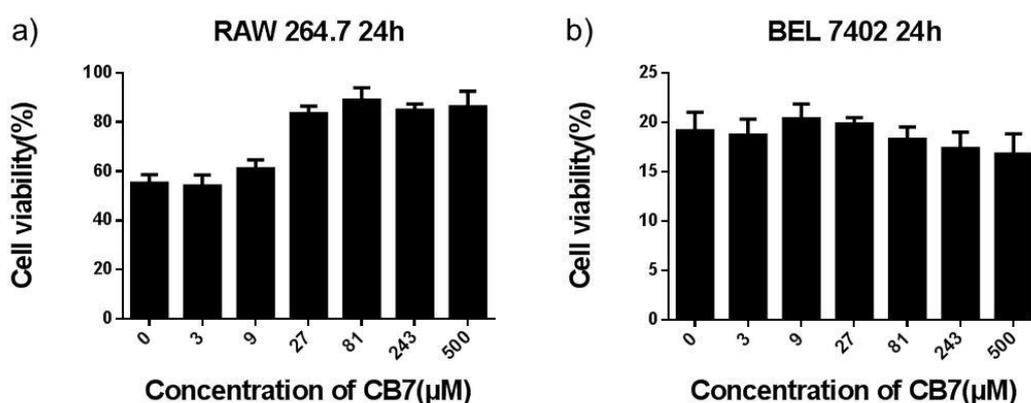
Switching tests for the ring translocation of CB[7] over  $V-P-\beta^+$  or  $V-P-\beta^+$  at various NaCl concentrations.



**Figure S19.** <sup>1</sup>H NMR spectra of  $V-P-\beta^+\cdot CB[7]$  and  $V-P-\beta^-\cdot CB[7]$  (1 mM) in D<sub>2</sub>O in the presence of NaCl (10, 110 or 150 mM in D<sub>2</sub>O).  $V-P-\beta^+\cdot CB[7]$  solutions were prepared via addition of 2 equiv of TFA (25  $\mu$ L, 12.5 mM in D<sub>2</sub>O) into the  $V-P-\beta^+\cdot CB[7]$  corresponding solutions (300 MHz, 160 scans).

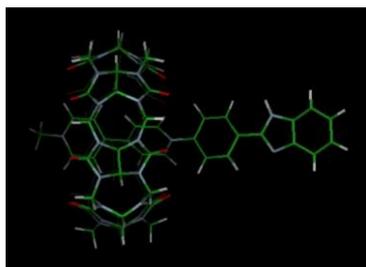
## 19/ Cytotoxicity assays.

BEL 7402 and RAW 264.7 cell lines were obtained from the Committee of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). BEL 7402 and RAW 264.7 cells were seeded in a 96-well plate at a density of  $8 \times 10^3$  cells per well in 100  $\mu$ L of DMEM medium containing 10 % FBS and 1 % PS and incubated in a humidified 5 % CO<sub>2</sub> atmosphere at 37 °C for 24 h. The cell culture medium was replaced with 100  $\mu$ L of a fresh one containing *V-P-I* and *V-P-I*-CB[7]. The cells were further incubated for additional 24 h, subsequently the medium was replaced with 100  $\mu$ L of a fresh medium containing 10  $\mu$ L of methylthiazolyldiphenyl-tetrazolium bromide (MTT) (5 mg/mL) for an additional 4 h at 37 °C. After gentle removal of the medium, the purple water-insoluble crystals formed by live cells remaining at the bottom of the wells were dissolved with 100  $\mu$ L of DMSO and the solution was gently shaken for 10 min. UV absorption of the resulting solution at 590 nm was measured by a multi-well plate reader. The same experiments were performed for 3 times to obtain a mean value and standard deviation.



**Figure S20.** Cell viability (%) of RAW 264.7 cell line (a) and BEL 7402 cell line (b) treated with the 9  $\mu$ M *V-P-I* and increasing concentrations of CB[7].

## 20/ Atomic coordinates of the minimized complexes.



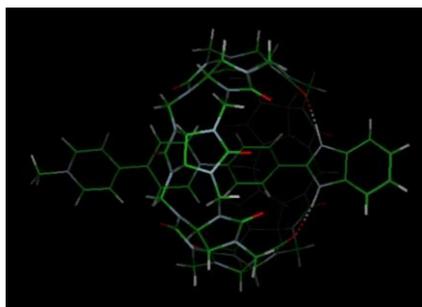
174

scf done: -5358.276814

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scf done: -5358.742702

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