JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01914 • Publication Date (Web): 05 Sep 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Electronic Substituent Effects of Guests on the Conformational Network and Binding Behaviour of Oxatub[4]arene

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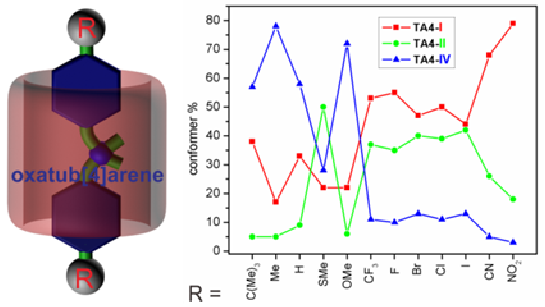


Abstract: A series of quaternary ammonium guests have been synthesized, and their binding behavior with oxatub[4]arene have been studied. In particular, remote electronic substituents of the guests can significantly affect the binding affinities mainly through a field/inductive effect by following a linear free energy relationship. More surprisingly, oxatub[4]arene, with a complex conformational network, shows a large amplitude of conformational change in response to the remote electronic substituents on the guests. This novel mode of synthetic molecular recognition may also have biological relevance.

Introduction

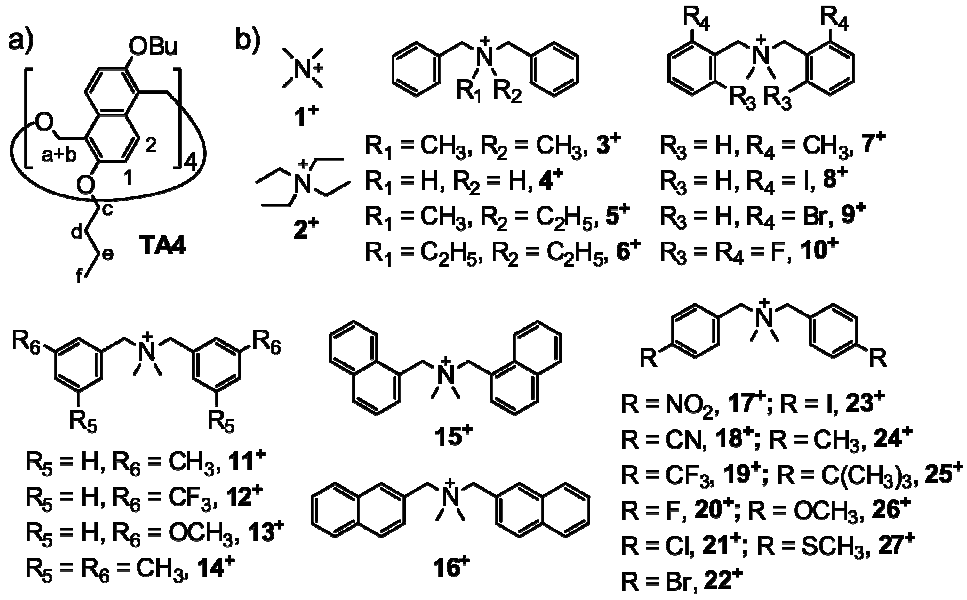
Large amplitude of conformational change during molecular recognition plays a pivotal role in biological behaviour and function, such as the allosteric effect,[1] signal transduction,[2] and biomolecular machines.[3] However, due to the complexity of biological systems, many aspects of the conformational properties of bioreceptors are still unclear.[4] Clarifying these aspects would help the understanding of biological behaviour and functions. Simplified macrocyclic receptors are often regarded as models for their natural counterparts. Numerous macrocyclic receptors with multiple conformations are known[5,6] but there are rare macrocyclic receptors which are qualified as models for studying the conformational complexity of bioreceptors,[7] either due to indistinguishable/ill-defined conformational states or because of poor/no binding abilities of some conformers.

Following our interest in biomimetic molecular recognition,[8] we have designed and synthesized several conformationally adaptive macrocycles,[9,10] one of which we named oxatub[4]arene (**TA4**, Scheme 1a).[10] This macrocycle possesses four well-defined conformations resulting from the naphthalene flipping (Figure 1). The four conformers have similar cavity sizes but are easily distinguished from each other. Each conformer can accommodate a guest. Consequently, this macrocycle consists of a rather complex conformational network. We envisaged it could be used to understand the influence of conformational complexity on molecular recognition. Herein, we report the influence of the structural modification of quaternary ammonium guests[11] (Scheme 1b) on the conformational network and molecular recognition of **TA4**, with an emphasis on the electronic substituent effect of the guests on the conformational complexity of the host.

Results and Discussion

In the previous report,[10b] we found tetraethyl ammonium $\mathbf{2}^+$ binds to **TA4** even more strongly than tetramethyl ammonium $\mathbf{1}^+$ does. This is presumably due to that tetraethyl ammonium $\mathbf{2}^+$ contributes more hydrogen atoms for C-H$\cdots\pi$ interactions than $\mathbf{1}^+$, as indicated by a more negative enthalpy term (Table 1). On this basis, we envisioned quaternary ammoniums with two benzyl substituents could also

be hosted by **TA4**. Thus, we designed and synthesized a series of quaternary ammonium guests (Scheme 1b), in particular the ones with different *para*-substituents on the phenyl groups, to explore the substituent effects of guests on the conformations and binding behaviour of **TA4**.



Scheme 1. Chemical structures of (a) *per*-butyl oxatub[4]arene (**TA4**) and (b) guests involved in this research. The counterions are PF_6^-. Numberings on the structure of **TA4** correspond to the assignments of NMR signals.

The binding constants (Figure S1-S31) of **TA4** to these guests were determined either by isothermal titration calorimetry (ITC, for strong binding, $K_a > 1000\ M^{-1}$) or by NMR titrations (for weak binding, $K_a < 1000\ M^{-1}$). The data are shown in Table 1. Substituting two methyl groups in $\mathbf{1}^+$ with two benzyl groups affords guest $\mathbf{3}^+$. ^{1}H NMR experiment (Figure S32) showed that guest $\mathbf{3}^+$ was strongly bound by **TA4**, and the binding constant is $1.68\times10^5\ M^{-1}$. This binding constant is one order of magnitude larger than those for $\mathbf{1}^+$ and $\mathbf{2}^+$. ITC results show that the higher binding affinity is mainly contributed from entropic gain (Table 1). Replacing the two methyl groups in $\mathbf{3}^+$ with two protons completely shut down the binding, since no obvious complexation-induced shift was detected when mixing **TA4** with $\mathbf{4}^+$ in 1:1 ratio (Figure S33). This shows the important role of the core quaternary ammonium ions in the effective host-guest complexation. Changing the methyl groups of $\mathbf{3}^+$ to ethyl groups decreases the binding constants by 2 - 3 orders of magnitude, as seen for $\mathbf{5}^+$ and $\mathbf{6}^+$. This indicates that $\mathbf{5}^+$ and $\mathbf{6}^+$ are probably too bulky for the conformers of **TA4**.

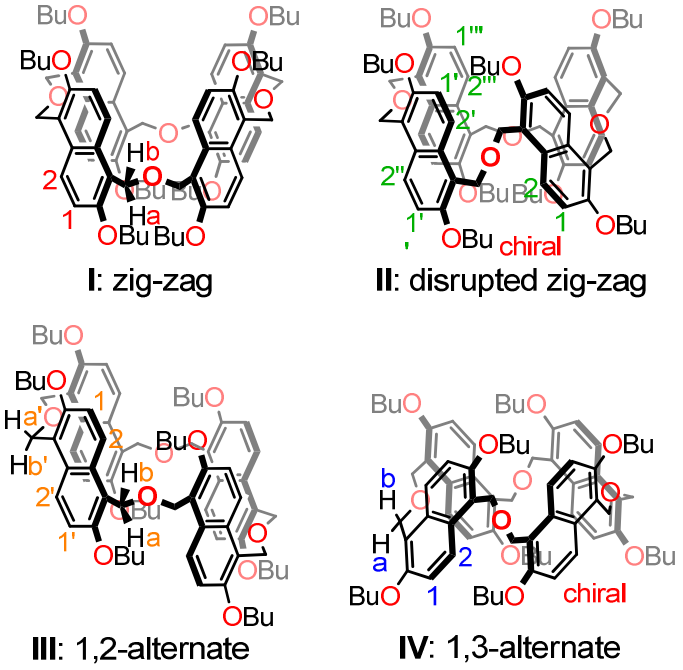


Figure 1. Chemical structures of the four conformers of **TA4**.[10a] Numberings on the structures and their colors correspond to the assignments of NMR signals.

To further test the substituent effect, substituent groups were installed on the phenyl groups of $\mathbf{3}^+$. *Ortho*-substitution ($\mathbf{7}^+$-$\mathbf{10}^+$) significantly weakens the binding, probably because the substituent groups are too bulky and disturbing the effective complexation. Introduction of *meta*-substituting groups ($\mathbf{11}^+$-$\mathbf{14}^+$) only slightly decrease the binding affinities when compared to the ones with *ortho*-substituent. *Ortho*-substitution obviously creates more serious steric hindrance for the effective binding than *meta*-substitution. This is more clearly evident when one compares the binding affinities between $\mathbf{15}^+$ and $\mathbf{16}^+$. The *ortho*/*meta*-substitution generally leads to weaker bindings, either through unfavourable entropy or due to unfavourable enthalpy. Nevertheless, *para*-substitution ($\mathbf{17}^+$-$\mathbf{27}^+$) generally increases the binding affinities with only one exception ($\mathbf{25}^+$). This suggests that *para*-substituent does not sterically disturb the effective binding site with **TA4**.

The *para*-substitution does not cause steric effect on the binding with **TA4** and only affects the binding through electronic substituent effects. Therefore, we can use the guests $\mathbf{3}^+$ and $\mathbf{17}^+$ – $\mathbf{27}^+$ to study the electronic substituent effect of guests on the binding behaviour of oxatub[4]arene for which Hammett's linear free energy relationship can be applied.[12] The logarithm of the relative binding

constants of $\mathbf{17}^+$ – $\mathbf{27}^+$ over $\mathbf{3}^+$ was plotted against the Hammett parameters, such as σ_p, σ_m and σ^+ (Figure 2, S34, and S35). However, only σ_m gave a relatively good linear relationship. Although R^2 is only 0.80, most of data are located near the line. σ_m is known to represent field/inductive effects. Thus, this suggests that the binding affinities of **TA4** to $\mathbf{17}^+$ – $\mathbf{27}^+$ were affected by the substituents through the field/inductive effect.[13] Presumably, the substituents affect the $\pi\cdots\pi$ stacking between the host and the guest through the field/inductive effects.[14]

Table 1. Binding constants (M^{-1}) as determined by ITC in the 1:1 mixture of 1,2-dichloroethane and MeCN at 25 °C or by ^{1}H NMR titration (400 MHz, CD_2Cl_2 : CD_3CN = 1:1, 25 °C).

guests [a]	K_a (M^{-1})	$\Delta G°$ (kJ·mol^{-1})	$\Delta H°$ (kJ·mol^{-1})	$-T\Delta S°$ (kJ·mol^{-1})
$\mathbf{1}^{+b}$	$(6.39 \pm 0.60) \times 10^3$	-21.8 ± 0.6	-16.6	-5.2
$\mathbf{2}^{+b}$	$(9.90 \pm 0.80) \times 10^3$	-22.9 ± 0.8	-23.8	-0.9
$\mathbf{3}^+$	$(1.68 \pm 0.30) \times 10^5$	-29.8 ± 0.2	-19.8	-10.0
$\mathbf{7}^+$	$(5.07 \pm 0.55) \times 10^3$	-20.6 ± 0.2	-20.9	0.3
$\mathbf{11}^+$	$(4.75 \pm 0.52) \times 10^4$	-26.7 ± 0.3	-12.2	-14.5
$\mathbf{12}^+$	$(1.28 \pm 0.22) \times 10^4$	-23.4 ± 0.2	-14.7	-8.7
$\mathbf{13}^+$	$(3.98 \pm 0.41) \times 10^4$	-26.3 ± 0.4	-13.2	-13.1
$\mathbf{14}^+$	$(3.55 \pm 0.25) \times 10^3$	-20.3 ± 0.2	-25.8	5.5
$\mathbf{15}^+$	$(3.19 \pm 0.30) \times 10^4$	-25.7 ± 0.4	-18.1	-7.6
$\mathbf{16}^+$	$(2.63 \pm 0.36) \times 10^5$	-30.9 ± 0.5	-16.9	-14.0
$\mathbf{17}^+$	$(1.58 \pm 0.80) \times 10^6$	-35.4 ± 0.5	-22.0	-13.4
$\mathbf{18}^+$	$(1.06 \pm 0.30) \times 10^6$	-34.4 ± 0.4	-24.8	-9.6
$\mathbf{19}^+$	$(4.86 \pm 0.65) \times 10^5$	-32.4 ± 0.3	-20.2	-12.2
$\mathbf{20}^+$	$(5.05 \pm 0.12) \times 10^5$	-32.5 ± 0.2	-25.1	-7.4
$\mathbf{21}^+$	$(6.59 \pm 0.54) \times 10^5$	-33.2 ± 0.3	-25.6	-7.6
$\mathbf{22}^+$	$(8.43 \pm 0.25) \times 10^5$	-33.9 ± 0.4	-27.2	-6.7
$\mathbf{23}^+$	$(1.54 \pm 0.35) \times 10^6$	-35.3 ± 0.5	-26.4	-8.9
$\mathbf{24}^+$	$(2.02 \pm 0.18) \times 10^5$	-30.2 ± 0.4	-17.5	-12.7
$\mathbf{25}^+$	$(1.21 \pm 0.35) \times 10^5$	-29.0 ± 0.2	-12.9	-16.1
$\mathbf{26}^+$	$(1.67 \pm 0.23) \times 10^5$	-29.8 ± 0.4	-19.7	-10.1
$\mathbf{27}^+$	$(3.01 \pm 0.30) \times 10^5$	-31.3 ± 0.2	-25.9	-5.4

guests [c]	K_a (M^{-1})	guests [c]	K_a (M^{-1})
$\mathbf{5}^+$	$(3.45 \pm 0.47) \times 10^2$	$\mathbf{9}^+$	$(1.05 \pm 0.08) \times 10^2$
$\mathbf{6}^+$	$(3.46 \pm 0.11) \times 10^2$	$\mathbf{10}^+$	$(4.10 \pm 0.3) \times 10^1$
$\mathbf{8}^+$	$(3.90 \pm 0.20) \times 10^1$		

[a] These binding constants were determined by ITC (Figure S1-S19); [b] the binding parameters of these two guests were reported (see ref 9b); [c] these binding constants were determined by NMR titrations (Figure S20-S31).

How would the conformational network of **TA4** respond to the substituents of the guests? First, we have to distinguish the conformers of **TA4** in the complexes. As reported earlier,[10] the four conformers

have different symmetries (Figure 1). Conformers **II** and **III** can be readily distinguished from each other and the other two conformers based on ^{1}H NMR peak pattern: there are eight doublets and four doublets for the aromatic peaks of the host, respectively. Nevertheless, conformers **I** and **IV** cannot be easily differentiated from each other, because the symmetries of conformers **I** and **IV** result in similar peak patterns in ^{1}H NMR spectra: two doublets for the aromatic protons. But the 2-dimensional arrangement of protons *2*, *a*, and *b* is different for conformers **I** and **IV** and causes different Nuclear Overhauser Effect (NOE) effects: in conformer **I**, proton *2* has NOE contact with proton *b* but not with proton *a*; while in conformer **IV**, proton *2* is in close proximity to both protons *a* and *b*. This has been used to distinguish the two conformers.[10]

For free **TA4**, the interconversion among the four conformers is relatively quick at the NMR timescale.[10a] When a guest is encapsulated by **TA4**, the cavity is thus occupied. Consequently, the conformational interconversion is stopped since the cavity is blocked. In order to allow the flipping of naphthalene, the guest has to be released and then naphthalene can flip. This means that the rate of conformational interconversion is determined by guest exchange rate. When the guest exchange is slow at the NMR timescale, the conformers in the complexes could be well differentiated according to their ^{1}H NMR spectra.

Luckily, most of the guests (**3**$^+$ and **5**$^+$ – **27**$^+$) in their complexes with **TA4** exchange slowly at the NMR timescale at 25 °C (the exceptions are **6**$^+$, **8**$^+$ and **9**$^+$). Thus, the conformations can be assigned (Figure 3 and S36) according to ^{1}H ^{1}H,-NOESY NMR spectra (Figure S37-S41), the peaks patterns and integrals of the host and the guests (the methyl groups on the quaternary ammonium groups appear in the region of 0.0 - 1.2 ppm), and extensive comparison. Among guests **5**$^+$ – **16**$^+$, more bulky guests (**5**$^+$, **7**$^+$, **10**$^+$ and **15**$^+$) prefer conformer **IV**, since they require a larger cavity to be accommodated and conformer **IV** has the largest cavity among the four conformers (Figure 1). For other guests (**11**$^+$ – **14**$^+$ and **16**$^+$), conformer **II** appear together with conformer **IV** to maximize the binding.

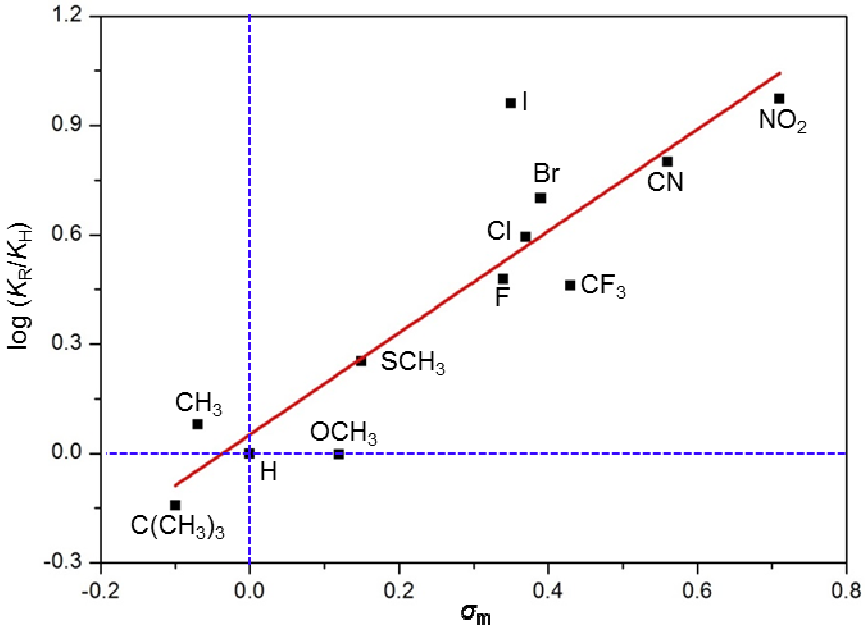


Figure 2. Binding affinities of guests $\mathbf{17}^+$-$\mathbf{27}^+$ (K_X) relative to guest $\mathbf{3}^+$ (K_H) as a function of Hammett parameter σ_m ($\rho = 1.4 \pm 0.2$).

The conformer distribution of **TA4** in the presence of guests $\mathbf{3}^+$ or $\mathbf{17}^+ - \mathbf{27}^+$ is summarized in Figure 4. The guests with electron-withdrawing substituents (NO_2 and CN) tend to induce conformer **I**. With decreasing the electron-withdrawing ability of the substituents, the percentages of conformers **II** and **IV** start to increase and that of conformer **I** decreases. With respect to the halogen substituents and the related (F, Cl, Br, I, CF_3), the conformer distribution is largely unchanged with conformers **I** and **II** as the major ones. In contrast, the guests with electron-donating substituents (OMe, Me, $C(Me)_3$) and $\mathbf{3}^+$ are in favour of conformer **IV**. The exception is the guest with methylthio (MeS) substituent ($\mathbf{27}^+$), for which conformer **II** is the major conformer for **TA4**. Steric effect can be ruled out because the bulkier substituents do not induce more conformer **IV** than less bulky substituents (for examples, *t*-butyl vs. methyl; MeS vs. MeO; CF_3/NO_2 vs. halogens/H). As a consequence, only slight change of the substituent group on the remote position of guest $\mathbf{3}^+$ significantly influenced the conformational states of **TA4** in the complexes.

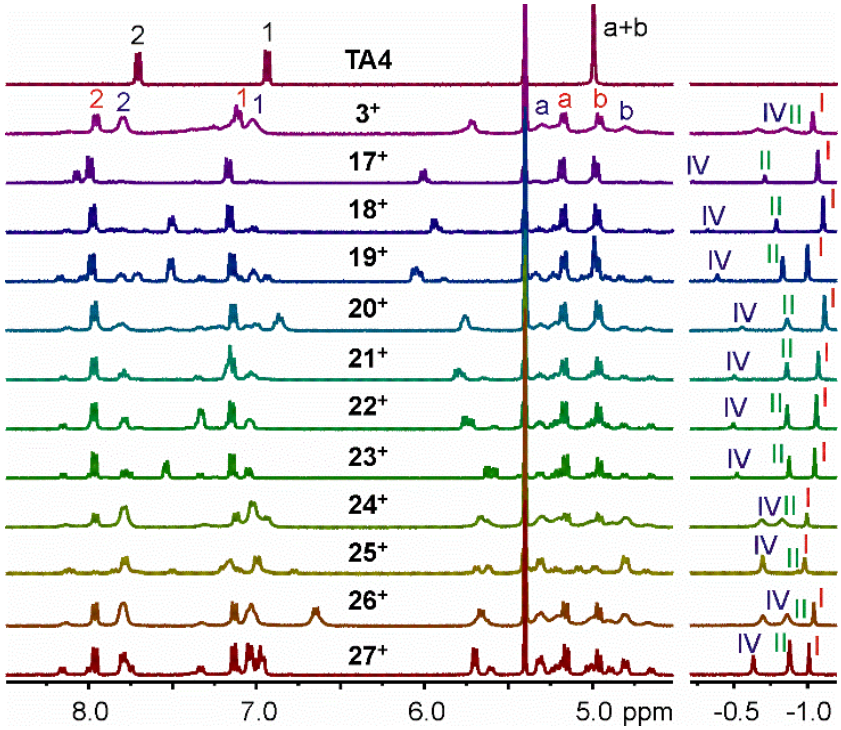


Figure 3. Partial ^{1}H NMR spectra (400 MHz, CD_2Cl_2:CD_3CN = 1:1, 2.0 mM, 25 ^{o}C) of **TA4** in the absence or the presence of one equiv of individual guest $\mathbf{3}^+$ or $\mathbf{17}^+$ - $\mathbf{27}^+$.

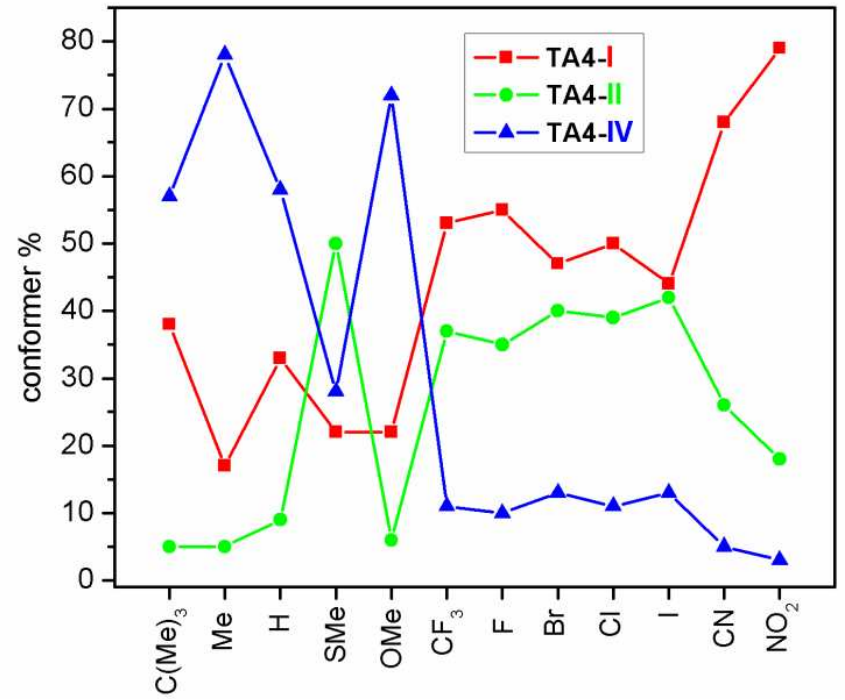


Figure 4. Conformer distribution of **TA4** in the presence of one equiv of quaternary ammonium guests with different electronic substituent groups ($\mathbf{3}^+$ and $\mathbf{17}^+$ - $\mathbf{27}^+$). [**I**] + [**II**] + [**IV**] = 100%.

17$^+$ and **26**$^+$ are two representative guests and prefer conformers **I** and **IV**, respectively. In order to rationalize the underlying reason, computation was performed on the complexes **17**$^+$**@TA4-I** and **26**$^+$**@TA4-IV.** Their energy-minimized structures were shown in Figure 5. As mentioned above, the core binding site is the quaternary ammoniums and the attached methyl or methylene groups. C-H···O, C-H···π, and cation···π interactions between the quaternary ammonium core and **TA4** are indeed observed for both **17**$^+$**@TA4-I** and **26**$^+$**@TA4-IV.** Differently, the phenylene groups of guest **17**$^+$ are more heavily involved in the interactions with **TA4** through C-H···O, C-H···π, and π ···π interactions than guest **26**$^+$. The cavity size of conformer **I** is smaller than that of conformer **IV**. Therefore, it is better for conformer **I** to interact with the phenylene groups on the guests. While the larger cavity allows conformer **IV** to better accommodate the quaternary ammonium core. This may explain why guests with electron-deficient and electron-rich substituents prefer conformer **I** and **IV**, respectively. Conformer **II** share very similar cavity size and structure with conformer **I**, and therefore shows similar preference to the substituents.

Although such large amplitudes of conformational changes were induced by the remote substituents, the binding constants still reasonably follow the linear free energy relationship, and the substituent groups affect the binding affinity mainly through the field/inductive effect. In other words, the conformational network of oxatub[4]arene shows response to the subtle changes on the field/inductive effect of the remote substituents.

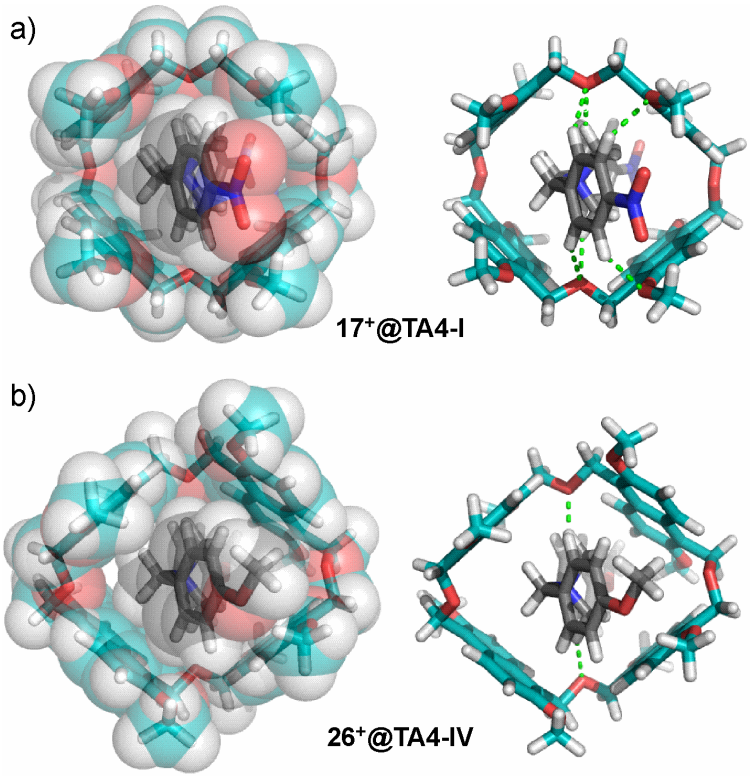


Figure 5. Energy-minimized structures of **17**$^{+}$**@TA4-I** and **26**$^{+}$**@TA4-IV** using the Semiempirical PM6 level of theory (Spartan '14, Wavefunction, Inc.). Butyl groups of **TA4** were shorted to methyl groups for viewing clarity.

Conclusions

In summary, we synthesized a series of quaternary ammonium ion guests with different substituent groups and studied the influence of substituent groups of the guests on the binding behaviour and conformational networks of oxatub[4]arene. The *para*-substitution can affect the binding affinities through a field/inductive effect by following a linear free energy relationship. Surprisingly, oxatub[4]arene undergoes a large amplitude of conformational changes in response to the remote substituents. To the best of our knowledge, this is the first time that such an effect was observed in synthetic molecular recognition. We believe this novel mode of synthetic molecular recognition may also have biological relevance.[1a,15]

Experimental Section

General Methods. All the reagents involved in this research were commercially available and used without further purification unless otherwise noted. Solvents were either employed as purchased or dried prior to use by standard laboratory procedures. Thin-layer chromatography (TLC) was carried out on 0.25 mm Yantai silica gel plates (60F-254). Column chromatography was performed on silica gel 60 (Tsingdao 40 – 63 nm, 200 – 300 mesh). ^{1}H, ^{13}C NMR, and ^{1}H-^{1}H ROESY NMR spectra were recorded on Bruker Avance-400/500 spectrometers. All chemical shifts are reported in *ppm* with residual solvents or TMS (tetramethylsilane) as the internal standards. The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t triplet; m, multiplet. Electrospray-ionization time-of-flight high-resolution mass spectrometry (ESI-TOF-HRMS) experiments were conducted on an applied Q EXACTIVE mass spectrometry system. Guests **3**$^{+}$, **4**$^{+}$, **6**$^{+}$, **7**$^{+}$, **19**$^{+}$, **20**$^{+}$, **24**$^{+}$ and **26**$^{+}$ were synthesized by following the literature procedures.[16]

Synthetic Procedures.

Compound 5-PF_6. Benzyl bromide (1.0 g, 5.9 mmol) and *N*-Benzyl-*N*-Ethylmethyl amine (872.5 mg, 5.9 mmol) were mixed in acetonitrile (30 mL), and the resulting solution was stirred at 90°C for 12h. After cooling to room temperature, the reaction mixture was concentrated. A small amount of diethyl ether was added to the residual solution. The precipitate was filtered off to give **5-Br** as a white powder, which was used directly in the next step. The solution of **5-Br** in deionized water was added dropwise into the saturated aqueous solution of NH_4PF_6. After stirring for 1 h, the precipitate was collected through filtration, washed with deionized water and dried in vacuum to give **5-PF_6** as a white powder (250 mg, 25% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.63-7.50 (m, 10H), 4.50-4.37 (m, 4H), 3.24 (q, J =7.2Hz, 2H), 2.81 (s, 3H), 1.47 (ddd, J =7.3, 5.6, 1.8 Hz). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 133.1, 130.7, 129.2, 127.2, 65.2, 56.0, 45.8, 7.7. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{17}H_{22}N^+$, 240.1747; found 240.1744 (error = -1.2 ppm).

General synthetic procedure for compounds 8-PF_6, 9-PF_6, 10-PF_6, 11-PF_6, 12-PF_6, 13-PF_6, 14-PF_6, 15-PF_6, 16-PF_6, 21-PF_6, 22-PF_6 and 25-PF_6. Aromatic quaternary ammonium (**QA**) hexafluorophosphates were synthesized by using the procedure reported by Rissanen and coworkers.[16a] The corresponding benzyl bromide (200 mg) and DMF (10 mL) were mixed and the resulting solution was stirred at 80°C for 48h. After cooling to room temperature, the solution was concentrated. A small amount of diethyl ether was added to the residual solution. The resulting precipitate was filtered off to give the corresponding **QA** bromides as white powder, which was used directly in the next step. The solution of **QA** bromides in deionized water was added dropwise into the saturated aqueous NH_4PF_6. After stirring for 1 h, the precipitate was collected through filtration, washed with deionized water and dried in vacuum to give the corresponding **QA** hexafluorophosphates.

8-PF_6: white powder (160 mg, 40% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 8.06 (dd, J = 8.0, 1.2 Hz, 2H), 7.61 (dd, J = 7.8, 1.7 Hz, 2H), 7.53 (td, J = 7.6, 1.3 Hz, 2H), 7.28 – 7.22 (m, 2H), 4.75 (s, 4H), 3.04 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 141.5, 134.7, 132.7, 130.4, 129.3, 104.2, 71.7, 49.8. ESI-TOF-HRMS *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}I_2N^+$, 477.9523; found 477.9517 (error = -1.3 ppm).

9-PF_6: white powder (210 mg, 55% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.84 (dd, J = 7.9, 1.4 Hz, 2H), 7.70 (dd, J = 7.7, 1.8 Hz, 2H), 7.57 (td, J = 7.5, 1.5 Hz, 2H), 7.51 (td, J = 7.7, 1.8 Hz, 2H), 4.80 (s, 4H), 3.06 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 135.7, 134.4, 132.9, 128.6, 127.4, 127.1, 67.4, 49.4. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}Br_2N^+$, 381.9801; found 381.9800 (error = -0.3 ppm).

10-PF_6: white powder (200 mg, 54% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.42-7.34 (m, 6H), 4.57 (s, 4H), 2.98 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 159.7 (dd, J_{FC} = 8.4, 3.9 Hz), 157.3 (dd, J_{FC} = 12.3, 4.3 Hz), 121.2 (dd, J_{FC} = 24.2, 3.7 Hz), 120.3 (dd, J_{FC} = 23.7, 10.0 Hz), 118.1 (dd, J_{FC} = 25.2, 9.3 Hz), 116.0 (dd, J_{FC} = 16.6, 8.6 Hz), 61.6, 49.0. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{16}F_4N^+$, 298.1213; found 298.1209 (error = -1.3 ppm).

11-PF_6: white powder (205 mg, 54% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.43 (d, J = 6.5 Hz, 4H), 7.37 – 7.30 (m, 4H), 4.43 (s, 4H), 2.86 (s, 6H), 2.42 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 139.3, 133.7, 131.4, 130.1, 129.1, 127.2, 68.5, 48.7, 48.61, 48.57, 20.3. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{18}H_{24}N^+$, 254.1903; found 254.1895 (error = -3.1 ppm).

12-PF_6: white powder (87 mg, 24% yield). ^{1}H NMR (500 MHz, CD_3CN, 298 K) δ [ppm] = 7.93 (d, J = 7.8 Hz, 2H), 7.87 (s, 2H), 7.82 (d, J = 7.8 Hz, 2H), 7.77 (t, J = 7.8 Hz, 2H), 4.57 (s, 4H), 2.94 (s, 6H). ^{13}C NMR (125 MHz, CD_3CN, 298 K) δ [ppm] = 137.1, 130.9 (q, J_{FC} = 32.5 Hz), 129.7 (q, J_{FC} = 3.9 Hz), 127.6 (q, J_{FC} = 3.7 Hz), 123.9 (q, J_{FC} = 32.5 Hz), 67.6, 48.8. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{18}H_{18}F_6N^+$, 362.1338; found 362.1326 (error = -3.3 ppm).

13-PF_6: white powder (150 mg, 42% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.47 (t, J = 7.9 Hz, 2H), 7.17 – 7.09 (m, 4H), 7.07 (t, J = 2.2 Hz, 2H), 4.45 (s, 4H), 3.86 (s, 6H), 2.91 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] =160.1, 130.3, 128.6, 125.2, 118.5, 116.3, 68.5, 55.2, 49.0, 48.92, 48.88. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{18}H_{24}NO_2^+$, 286.1802; found 286.1793 (error = -3.0 ppm).

14-PF_6: white powder (180 mg, 48% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] =7.24 (s, 2H), 7.12 (s, 4H), 4.36 (s, 4H), 2.83 (s, 6H), 2.37 (s, 12H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 139.0, 132.1, 130.7, 127.1, 68.6, 68.59, 68.57, 48.70, 48.66, 48.6, 20.2. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{20}H_{28}N^+$, 282.2216; found 282.2213 (error = -1.1 ppm).

15-PF_6: white powder (180 mg, 48% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 8.29 (d, J =8.5 Hz, 2H), 8.17 (d, J =8.3 Hz, 2H), 8.08 (d, J =8.1 Hz, 2H), 7.81 (d, J =7.1 Hz, 2H), 7.77-7.60 (m, 6H), 5.16 (s, 4H), 2.92 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 134.24, 134.20, 133.03, 132.02, 129.4, 127.8, 126.5, 125.3, 123.4, 65.1, 49.4. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{24}H_{24}N^+$, 326.1903; found 326.1898 (error = -1.5 ppm).

16-PF_6: white powder (58 mg, 15% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 8.12-8.08 (m, 2H), 8.04 (d, J = 8.5 Hz, 2H), 8.02-7.97 (m, 4H), 7.68-7.61 (m, 4H), 7.59 (dd, J = 8.5, 1.9 Hz, 2H), 4.68 (s, 4H), 2.97 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 134.0, 133.8, 133.0, 129.3,

128.9, 128.5, 127.9, 127.7, 127.1, 124.8, 68.60, 68.57, 68.5, 48.82, 48.78, 48.7. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{24}H_{24}N^+$, 326.1903; found 326.1898 (error = -1.5 ppm).

21-PF$_6$: white powder (220 mg, 60% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.60-7.55 (m, 4H), 7.52 (d, J = 8.2 Hz, 4H), 4.45 (s, 4H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 136.6, 134.8, 129.3, 126.0, 67.4, 48.52, 48.48, 48.4. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}Cl_2N^+$, 294.0811; found 294.0807 (error = -1.4 ppm).

22-PF$_6$: white powder (260 mg, 70% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.73 (d, J = 8.4 Hz, 4H), 7.44 (d, J = 8.5 Hz, 4H), 4.43 (s, 4H), 2.86 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 135.0, 132.4, 126.4, 125.0, 67.5, 48.6. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}Br_2N^+$, 381.9801; found 381.9800 (error = -0.3 ppm).

25-PF$_6$: white powder (64 mg, 17% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.59 (d, J = 8.0 Hz, 4H), 7.45 (d, J = 8.0 Hz, 4H), 4.43 (s, 4H), 2.83 (s, 6H), 3.36 (s, 18H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 154.1, 132.8, 126.2, 124.3, 68.2, 68.1, 68.1, 48.4, 48.4, 48.3, 34.5, 30.4. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{24}H_{36}N^+$, 338.2842; found 338.2837 (error = -1.5 ppm).

General synthetic procedure for compounds 17-PF$_6$, 18-PF$_6$, 23-PF$_6$ and 27-PF$_6$. The mixture of the substituted benzyl bromide and dimethylamine (aqueous soluiton) in 1:8 in acetonitrile was stirred at room temperature for 48h. The solution was concentrated. A small amount of diethyl ether was added and the resulting precipitate was filtered to give the corresponding QA bromides as white powder, which was used directly in the next step. The solution of QA bromides in deionized water was added dropwise into the saturated aqueous solution of NH_4PF_6. After stirring for 1 h, the precipitate was collected through filtration, washed with deionized water and dried in vacuum to give the corresponding QA hexafluorophosphates.

17-PF$_6$: white powder (220 mg, 60% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 8.36 (d, J = 8.7 Hz, 4H), 7.79 (d, J = 8.7 Hz, 4H), 4.61 (s, 4H), 2.95 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 149.5, 134.6, 133.7, 124.1, 67.3, 49.1. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}N_3O_4^+$, 316.1292; found 316.1287 (error = -1.6 ppm).

18-PF$_6$: white powder (165 mg, 45% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.92 (d, J = 8.3 Hz, 4H), 7.69 (d, J = 8.3 Hz, 4H), 4.53 (s, 4H), 2.90 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 134.0, 133.0, 131.9, 117.9, 114.4, 67.6, 49.0. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{18}H_{18}N_3^+$, 276.1495; found 276.1491(error = -1.4 ppm).

23-PF_6: white powder (170 mg, 45% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.92 (d, J = 8.3 Hz, 4H), 7.29 (d, J = 8.4 Hz, 4H), 4.41 (s, 4H), 2.85 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 138.4, 134.9, 126.9, 97.1, 67.7, 48.6. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{16}H_{18}I_2N^+$, 477.9523; found 477.9514 (error = -1.9 ppm).

27-PF_6: white powder (320 mg, 87% yield). ^{1}H NMR (400 MHz, CD_3CN, 298 K) δ [ppm] = 7.44 (d, J = 8.6 Hz, 4H), 7.39 (d, J = 8.5 Hz, 4H), 4.41 (s, 4H), 2.84 (s, 6H), 2.54 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN, 298 K) δ [ppm] = 142.7, 133.4, 125.8, 123.2, 67.9, 48.3, 48.3, 48.2, 14.0. ESI-TOF-HRMS: *m/z* calcd for $[M\text{-}PF_6]^+$ $C_{18}H_{24}NS_2^+$, 318.1345; found 318.1340 (error = -1.6 ppm).

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Notes

The authors declare no competing financial interest.

Acknowledgements. This research was financially supported by the National Natural Science Foundation of China (No. 21572097), the Thousand Young Talents Program, and the Shenzhen special funds for the development of biomedicine, internet, new energy, and new material industries (No. JCYJ20160226192118056, JCYJ20170307105848463). Fei Jia is grateful to the China Scholarship Council (CSC) for a Ph.D. fellowship.

Supporting Information Available. Binding constants determinations, ^{1}H,^{1}H-ROESY NMR spectra, and Hammett plots. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Motlagh, H. N.; Wrabl, J. O.; Li, J.; Hilser, V. J. *Nature* **2014**, *508*, 331; (b) Yuan, Y.; Tam, M. F.; Simplaceanu, V.; Ho, C. *Chem. Rev.* **2015**, *115*, 1702; (c) Kremer C.; Lützen, A. *Chem. Eur. J.* **2013**, *19*, 6162; (d) Knipe, P. C.; Thompson, S.; Hamilton, A. D. *Chem. Sci.* **2015**, *6*, 1630.

(2) Changeux, J.-P.; Edelstein, S. J. *Science* **2005**, *308*, 1424.

(3) LeVine, M. V.; Cuendet, M. A.; Khelashvili, G.; Weinstein, H. *Chem. Rev*. **2016**, *116*, 6552.

(4) Changeux, J.-P.; Edelstein, S. *F1000 Biol. Rep.* **2011**, *3*, 19.

(5) Selected reviews: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713; (b) Ikeda, A. ; Shinkai, S.; *Chem. Rev*. **1997**, *97*, 1713; (c) Gale, P. A.; Anzenbacher, P. Jr.; Sessler, J. L. Coord. *Chem. Rev*. **2001**, *222*, 57; () Kim, S. K.; Sessler, J. L. *Acc. Chem. Res.* **2014**, *47*, 2525; (e) Xue, M.; Yang,Y.; Chi, X.-D.; Zhang, Z.-B.; Huang, F. *Acc. Chem. Res.* **2012**, *8*, 1294; (f) Ogoshi, T.; Yamagishi, T.-a.; Nakamoto, Y. *Chem. Rev*. **2016**, *116*, 7937;

(6) Selected examples: (a) Talotta, C.; Gaeta, C.; Qi, Z.; Schalley, C. A.; Neri, P. *Angew. Chem., Int. Ed.* **2013**, 52, 7437; (b) Galán, A.; Escudero-Adán, E. C.; Frontera, A.; Ballester, P. *J. Org. Chem.* **2014**, *79*, 5545; (c) Guo, Q.-H.; Zhao, L.; Wang, M.-X. *Angew. Chem. Int. Ed.* **2015**, *54*, 8386; (d) Zhang, G.-W.; Li, P.-F.; Meng, Z.; Wang, H.-X.; Han, Y.; Chen, C.-F. *Angew. Chem. Int. Ed.* **2016**, *55*, 5304; (e) Chen, H.; Fan, J.; Hu, X.; Ma, J.; Wang, S.; Li, J.; Yu, Y.; Jia, X.; Li, C. *Chem. Sci.* **2015**, *6*, 197.

(7) (a) Brown, R. A.; Diemer, V.; Webb, S. J.; Clayden, J.; *Nat. Chem.* **2013**, *5*, 853; (b) De Poli, M.; Zawodny, W.; Quinonero, O.; Lorch, M.; Webb, S. J.; Clayden, J. *Science* **2016**, *352*, 575; (c) Lister, F. G. A.; Le Bailly, B. A. F.; Webb, S. J.; Clayden, J. *Nat. Chem*. **2017**, *9*, 420; (d) Hong, C. M.; Kaphan, D. M.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 8013.

(8) (a) Huang, G.; He, Z.; Cai, C.-X.; Pan, F.; Yang, D.; Rissanen, K.; Jiang, W. *Chem. Commun.* **2015**, *51*, 15490; (b) Huang, G.; Valkonen, A.; Rissanen, K.; Jiang, W. *Chem. Commun.* **2016**, *52*, 9078; (c) Huang, G.-B.; Wang, S.-H.; Ke, H.; Yang, L.-P.; Jiang, W. *J. Am. Chem. Soc.* **2016**, *138*, 14550; (d) Yao, H.; Yang, L.-P.; He, Z.; Li, J.-R.; Jiang, W. *Chin. Chem. Lett.* **2017**, *28*, 782; (e) Wang, L.-L.; Chen, Z.; Liu, W.-E.; Ke, H.; Wang, S.-H.; Jiang, W. *J. Am. Chem. Soc.* **2017**, *139*, 8436.

(9) (a) Yang, L.-P.; Jia, F.; Zhou, Q.-H.; Pan, F.; Sun, J.-N.; Rissanen, K.; Chung, L. W.; Jiang, W. *Chem. Eur. J*. **2017**, *23*, 1516; (b) Tran, A. H.; Miller, D. O.; Georghiou, P. E. *J. Org. Chem*. **2005**, *70*, 1115.

(10) (a) Jia, F.; He, Z.; Yang, L.-P.; Pan, Z.-S.; Yi, M.; Jiang, R.-W.; Jiang, W. *Chem. Sci.* **2015**, *6*, 6731; (b) Jia, F.; Wang, H.-Y.; Li, D.-H. ; Yang, L.-P.; Jiang, W. *Chem. Comm.* **2016**, *52*, 5666; (c) Jia, F.; Li, D.-H.; Yang, T.-L.; Yang, L.-P.; Dang, L. ; Jiang, W. *Chem. Comm*. **2017**, *53*, 336; (d) Yang, L.-P.; Liu, H.; Lu, S.-B.; Jia, F.; Jiang, W. *Org. Lett*. **2017**, *19*, 1212.

(11) Späth, A.; König, B. *Beilstein J. Org. Chem.* **2010**, *6*, No. 32.

(12) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 165; (b) McGrath, J. M.; Pluth, M. D. *J. Org. Chem*. **2014**, *79*, 11797; (c) Ling, X.; Saretz, S.; Xiao, L.; Francecon, J.; Masson, E. *Chem. Sci*. **2016**, *7*, 3569.

(13) Dougherty, D. A. *Acc. Chem. Res.* **2013**, *46*, 885.

(14) Hwang, J. W.; Li, P.; Shimizu, K. D. *Org. Biomol. Chem.* **2017**, *15*, 1554.

(15) Wei, G.; Xi, W.; Nussinov, R.; Ma, B. *Chem. Rev*. **2016**, *116*, 6516.

(16) (a) Busi, S.; Lahtinen, M.; Karna, M.; Valkonen, J.; Kolehmainen, E.; Rissanen, K. *J. Mol. Struct.* **2006**, *787*, 18-30. (b) Zhang, C.; Li, S.; Zhang, J.; Zhu, K.; Li, N.; Huang, F. *Org. Lett.* **2007**, *9*, 5553-5556.