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Effects of the number and placement of positive charges on viologen–cucurbit[*n*]uril interactions

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Recent developments in the synthesis and applications of the cucurbit[*n*]uril family of synthetic hosts has led to an increasing interest in the detailed studies of their interactions with a wide variety of guests. This paper describes a quantitative study of the effects of the number and placement of positive charges on the binding of viologen guests to cucurbit[7]uril and cucurbit[8]uril. A series of viologen derivatives with one to four charges was characterised by isothermal titration calorimetry, ^{1}H NMR spectroscopy and mass spectrometry to determine the stoichiometry, affinity and mode of binding. These data show that stoichiometry can be controlled by the placement of charge, and that affinity can be increased by the addition of positive charges. This study should serve as a guide for the design of supramolecular structures built from viologens and cucurbit[*n*]urils.

Keywords: cucurbit[8]uril; cucurbit[7]uril; viologen; stoichiometry; dimerisation

1. Introduction

The precise construction of supramolecular assemblies and molecular devices requires a thorough understanding of the host–guest complexes from which they are built. Recent developments in the synthesis and applications of the cucurbit[*n*]uril (Q*n*) family of synthetic hosts (*1–3*) has led to an increasing interest in the detailed studies of their interactions with a wide variety of guests. This paper describes a quantitative study of the effects of the number and placement of positive charges on the binding of viologen guests to cucurbit[7]uril (Q7) and cucurbit[8]uril (Q8).

Q*n*s are pumpkin-shaped macrocycles built from repeating, methylene-bridged glycoluril units and featuring a hydrophobic cavity that is accessible via two constricted, carbonyl-lined portals (*1–3*). Organic cations bind to Q*n*s via non-specific hydrophobic and dispersion interactions and via specific electrostatic interactions between the cationic, e.g. ammonium, groups of the guest and the ureido carbonyl groups on the portal(s) of the Q*n* (Figure 1). Early work by Mock and Shih established the structure of cucurbit[6]uril (Q6) and the fundamental principles for the binding of its guests (*4–6*). In particular, they showed that the binding affinity of alkylammonium ions to Q6 is optimal when two ammonium groups are separated by five to six carbons, which approximates the length spanning the two carbonyl portals.

The discovery (*1*) and development of a synthetic methodology (*1*, *7*, *8*) for larger Q*n* homologues ($n = 7$, 8 and 10) led to rapid growth in the study of this class of compounds due to the broad array of guest structures, (*9–15*) and thus new opportunities for supramolecular chemistry (*2*), that became available. Q7 binds with equilibrium association constants (K_a) in the range 10^5–$10^9\,M^{-1}$ and 1:1 stoichiometry to aromatic cations such as viologens and diamino xylenes (*9*, *10*, *12*). The $10^{12}\,M^{-1}$ binding affinity of Q7 for ferrocene derivatives (*13*) has been studied and put to use for affinity capture (*16*). Q8 can bind larger guests, including adamantane derivatives, with affinities up to $10^{11}\,M^{-1}$ (*12*). Importantly, Q8 and larger hosts, including Q10 and *nor-seco*-Q10, can bind multiple guests simultaneously (*1*, *8*, *17*, *18*). This feature allows for an interesting dimension of control in the design of supramolecular architecture (*19*).

Due to its facile modification and its electronic and optical properties, methyl viologen (**V11**, Figures 1 and 2) has been studied extensively as a guest for Q7 and Q8 (*9*, *10*, *20*, *21*). Kaifer and co-workers have shown how to control the positioning of Q7 with respect to the bipyridinium (viologen) core based on the length and polarity of the alkyl chain attached to the pyridinium nitrogens (*21*). Specifically, they showed that Q7 will localise over the viologen core (pseudorotaxane structure) when the alkyl chain is shorter than three carbons or derivatised with polar groups such as amines or alcohols. **V11** binds in a 1:1 stoichiometric ratio to Q7 and to Q8, despite the fact that the latter has sufficient space to accommodate two equivalents of the guest. This result is

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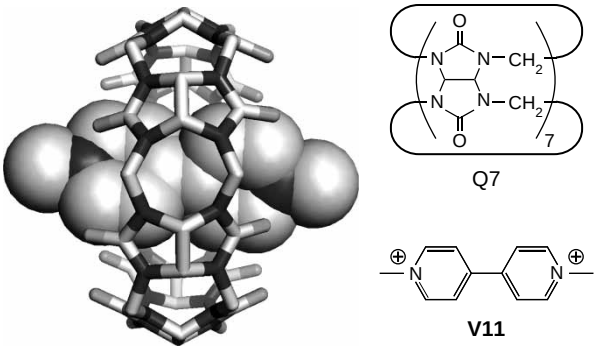

Figure 1. A model of the **V11**–Q7 complex showing the proximity of the quaternary ammonium nitrogens of **V11** to the ureido carbonyls of Q7.

believed to be due to repulsion between the localised ammonium charges based on two key results: (1) *bis*-imidazolyl derivatives of naphthalene, with diffuse cationic charges, bind Q8 in a 2:1 (guest:host) ratio (*1*); and (2) Single electron reduction of **V11** to the radical cation induces a change from 1:1 to 2:1 (guest:host) stoichiometry (*22–25*). These principles have been of key importance in the use of viologen–Q*n* interactions for the construction of molecular assemblies and devices (*19*, *22–28*).

Inspired by the examples described above and motivated to further establish design parameters for viologen guests, we describe here a study of the effects of the number and placement of positive charges on the stoichiometry and thermodynamics of binding to Q7 and Q8. A series of viologen derivatives with one to four charges (Figure 2) was designed and synthesised by alkylating 4,4′-bipyridine with methyl or 3-aminopropyl groups at one or both bipyridine nitrogens. In the nomenclature scheme used here, *V* denotes viologen, and the two numbers denote the number of ammonium groups (and thus positive charges) on the two sides of the viologen. We were reasonably certain, based on the works of Mock (*5*) and Kaifer (*21*), that Q7 and Q8 would not localise over the propylammonium tail, and so this tail should serve simply to add charge to the viologen while maintaining a consistent mode of binding. We expected to control the stoichiometry of binding through placement of charges on the same or opposite side of the viologen core, thereby directing charge localisation to opposite portals. We also expected a direct correlation between the number of charges and the affinity and exothermicity of binding due to the change in the number of ion–dipole interactions. To assess these affects, this series of viologens was characterised in complex with Q7 and Q8 by isothermal titration calorimetry (ITC), ^{1}H NMR spectroscopy and mass spectrometry to determine the stoichiometry, affinity and mode of binding of these viologens to Q7 and Q8. We find that stoichiometry can indeed be controlled by the placement of charge, and that the influence of charge on the thermodynamics of binding is significant for Q8 and less so for Q7.

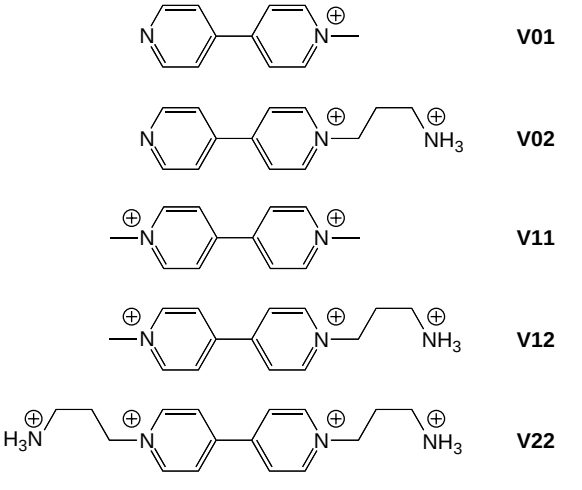

Figure 2. Chemical structures of the series of viologens studied here. In this nomenclature scheme, *V* denotes viologen and the two numbers denote the number of ammonium groups (and thus positive charges) on the two sides of the viologen.

2. Results

2.1 Isothermal titration calorimetry

The binding of each viologen compound to Q7 and Q8 was measured by ITC to determine the stoichiometry, K_a, ΔH and ΔS of binding (Tables 1 and 2). The K_a value for **V11** with Q8 is from Bush et al. (*29*) because it is under identical experimental conditions. All experiments were carried out at 27°C in 10 mM sodium phosphate, pH 7.0 (see Supporting Information). All viologens bind Q7 in a 1:1 stoichiometric ratio. **V01** and **V02** bind Q8 in a 2:1 ratio (Figure 3). **V11**, **V12** and **V22** bind Q8 in a 1:1 ratio. The presence of complexes in these stoichiometric ratios was confirmed by mass spectrometry (see Supporting Information). Calorimetric data for complexes with 1:1 (V:Q*n*) stoichiometry were analysed using the single set of sites model in Origin software. Data for 2:1 complexes were analysed using the sequential sites model; the overall ternary equilibrium constant, K_{ter}, was obtained as the product of the individual stepwise K_a values as described previously (*30*) and based on the work of Tochtrop et al. (*31*).

In the Q7 series (Table 1), K_a values increase steadily with each additional positive charge, from $1.2 \times 10^6\,M^{-1}$ for **V01** to $1.4 \times 10^7\,M^{-1}$ for **V12**. K_a values increase three- to five-fold for an increase from one to two charges and two- to three-fold for an increase from two to three charges. A lower limit value of K_a of $1.2 \times 10^7\,M^{-1}$ was

Table 1. Thermodynamic binding data for Q7.

Guest	V:Q7	$K_a/(M^{-1})$[a]	ΔG (kcal/mol)[b]	ΔH (kcal/mol)[c]	$-T\Delta S$ (kcal/mol)[d]
V01	(1:1)	$1.2 (\pm 0.1) \times 10^6$	$-8.4 (\pm 0.1)$	$-5.5 (\pm 0.1)$	$-2.8 (\pm 0.2)$
V02	(1:1)	$4.3 (\pm 0.2) \times 10^6$	$-9.1 (\pm 0.1)$	$-4.8 (\pm 0.1)$	$-4.4 (\pm 0.1)$
V11	(1:1)	$6.6 (\pm 0.1) \times 10^6$	$-9.4 (\pm 0.1)$	$-4.0 (\pm 0.1)$	$-5.3 (\pm 0.1)$
V12	(1:1)	$1.4 (\pm 0.1) \times 10^7$	$-9.8 (\pm 0.1)$	$-4.2 (\pm 0.2)$	$-5.6 (\pm 0.2)$
V22	(1:1)	$\geqq 1.2 \times 10^7$	≤ -9.7	$-4.0 (\pm 0.1)$	≤ -5.7

[a] Mean values measured from at least three ITC experiments at 27°C in 10 mM sodium phosphate, pH 7.0. Standard deviations are given in parentheses.
[b] Gibbs free energy values calculated from K_a values. Standard deviations for ΔG values were calculated as the relative error observed in K_a, due to their relationship by a natural logarithm.
[c] Enthalpy values measured by ITC.
[d] Entropic contributions to ΔG calculated from K_a and ΔH values.

measured for **V22** and thus the effect of increasing from three to four positive charges is unclear. In the Q8 series (Table 2), only complexes with the same stoichiometry (1:1 or 2:1) can be compared directly. For 2:1 (V:Q8) complexes, there is a seven-fold increase in affinity when increasing from one to two charges. For 1:1 complexes, there is a nine-fold increase in affinity when increasing from two to three charges. There is no change in affinity between three and four charges.

There are some general trends in the thermodynamics of binding. In all cases, binding is exothermic. All 1:1 complexes are both enthalpically and entropically driven, whereas all 2:1 complexes are driven predominantly by enthalpy.

In the Q7 series, binding becomes less enthalpically favourable from **V01** to **V02** (0.7 kcal/mol) and from **V02** to **V11** (0.8 kcal/mol), but stays constant between **V11**, **V12** and **V22**. Binding to Q7 is always entropically favourable and becomes more favourable from **V01** to **V02** ($T\Delta S$, 1.6 kcal/mol), **V02** to **V11** ($T\Delta S$, 0.9 kcal/mol) and **V11** to **V12** ($T\Delta S$, 0.3 kcal/mol).

In the Q8 series, there is no significant change in the enthalpy of binding between **V01** and **V02**. Binding becomes substantially more exothermic (1.9 kcal/mol) in moving from **V11** to **V12** and there is no difference between **V12** and **V22**. Binding to Q8 is slightly entropically unfavourable (0.0–0.7 kcal/mol) for **V01** and **V02**. The entropy of binding to Q8 becomes less favourable between **V11** and **V12** ($T\Delta S$, 0.7 kcal/mol) and does not change between **V12** and **V22**.

2.2 ^{1}H NMR spectroscopy

NMR spectra were obtained for all viologen compounds in the presence and absence of Q7 or Q8 in deuterium oxide at 25°C. In all cases, the aromatic peaks exhibit a paratropic shift upon binding, consistent with inclusion of the aromatic group within the cavity of the Q*n* (Figure 4) (see Supporting Information) (*21*). Compounds that bind Q8 in a 2:1 stoichiometric ratio were also studied by ^{1}H NMR in 2:1 and 3:1 (V:Q*n*) mixtures. In all cases, the 3:1 mixture shows a combination of the 2:1 spectrum and the free viologen.

2.3 Charge regulation

At pH 7, the primary amino groups should be protonated and thus positively charged. The proximal pyridinium nitrogen, however, can lower the pK_a of the primary ammonium group. To control for this possibility, we studied **V02m**, a permethylated derivative of **V02** (Figure 5).

Table 2. Thermodynamic binding data for Q8.

Guest	V:Q8	K_a[a]	ΔG (kcal/mol)[b]	ΔH (kcal/mol)[c]	$-T\Delta S$ (kcal/mol)[d]
V01	(2:1)	$1.7 (\pm 0.4) \times 10^{10}$ M^{-2}	$-14.0 (\pm 0.1)$	$-14.7 (\pm 0.5)$	$0.7 (\pm 0.6)$
V02	(2:1)	$1.2 (\pm 0.2) \times 10^{11}$ M^{-2}	$-15.2 (\pm 0.9)$	$-15.2 (\pm 0.3)$	$0.0 (\pm 0.2)$
V11[e]	(1:1)	$8.5 (\pm 0.3) \times 10^5$ M^{-1e}	$-8.1 (\pm 0.1)$[e]	$-3.7 (\pm 0.3)$	$-4.5 (\pm 0.2)$
V12	(1:1)	$7.3 (\pm 1.3) \times 10^6$ M^{-1}	$-9.4 (\pm 0.1)$	$-5.6 (\pm 0.3)$	$-3.8 (\pm 0.3)$
V22	(1:1)	$7.2 (\pm 1.3) \times 10^6$ M^{-1}	$-9.4 (\pm 0.1)$	$-5.6 (\pm 0.1)$	$-3.8 (\pm 0.1)$

[a] Mean values measured from at least three ITC experiments at 27°C in 10 mM sodium phosphate, pH 7.0. Standard deviations are given in parentheses.
[b] Gibbs free energy values calculated from K_a values. Standard deviations for ΔG values were calculated as the relative error observed in K_a, due to their relationship by a natural logarithm.
[c] Enthalpy values measured by ITC.
[d] Entropic contributions to ΔG calculated from K_a and ΔH values.
[e] Values obtained from reference (*29*).

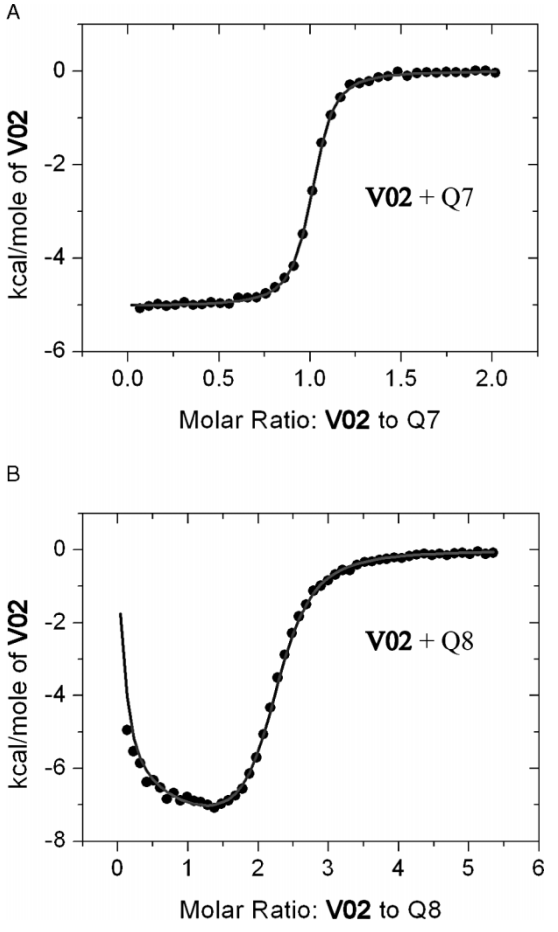

Figure 3. ITC data for the complexation of **V02** with Q7 (A) and Q8, (B) at 27°C in 10 mM sodium phosphate, pH 7.0. The stoichiometry of binding is derived from the inflection point of the sigmoidal curve.

V02m was synthesised by treating bipyridine with (3-bromopropyl)-trimethylammonium bromide in refluxing acetonitrile. **V02m** binds to Q7 and to Q8 with similar stoichiometry and affinity as **V02**, as confirmed by ITC (Table 3) and mass spectrometry (see Supporting Information). NMR confirms the inclusion of the viologen portion of **V02m** inside the Q*n* cavity, as well as the 2:1 stoichiometry of the **V02m**–Q8 complex. These results strongly suggest that the primary amino group of V02 is protonated when bound.

3. Discussion

The goal of this study is to understand the importance of the placement and number of positive charges on the binding of a guest to Q7 and Q8. Methyl viologen (**V11**) is an excellent parent compound for this study because it is well characterised and easily modifiable synthetically. The data presented here show how simple modifications of **V11** affect its binding properties.

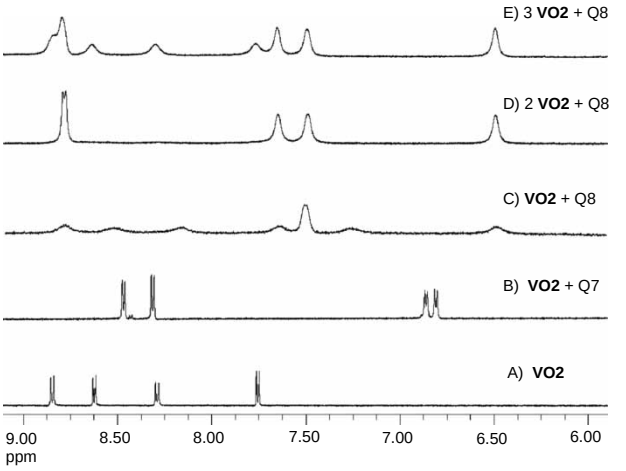

Figure 4. Aromatic region of ^{1}H NMR spectra at 25°C in deuterium oxide for **V02** by itself (A) and in complex with Q7 (B) and Q8 (C–E) at different molar ratios. There is a clear paratropic shift upon binding. It is also clear that the 3:1 (**V02**:Q8) mixture shows a combination of the spectra from the 2:1 mixture and the free **V02** guest.

3.1 Stoichiometry

Prior work has shown that the larger cavity of Q8 can accommodate two aromatic guests, that Q8 binds only one equivalent of the dicationic **V11** and that Q8 binds two equivalents of the singly reduced, radical cation of **V11** (*22–25*). Based on these studies we predicted that **V01** should bind Q8 in a 2:1 ratio due to the ability to keep the two positive charges removed to opposite portals. The calorimetric and NMR titration data presented here support this prediction. The removal of a pyridinium charge from **V11**, e.g. **V01**, **V02** and **V02m**, results in a change in the stoichiometry of binding to Q8 from 1:1 to 2:1. Addition of charges to **V11** has no affect on the stoichiometry of binding. Furthermore, the NMR data show that Q8 binds over the bipyridine core in all cases, suggesting only two possible binding modes – one with all charges proximal to the same Q8 portal, and the other, more likely, with charges separated to each portal. The 2:1 (V:Q8) stoichiometry observed for **V02** and **V02m** shows that an additional charge can be added to one side of the viologen in order to increase the affinity of binding while maintaining a consistent 2:1 binding mode. This dramatic effect has clear implications for the design of supramolecular architecture, where homodimeric structures can be made by monoalkylating bipyridine and treating with Q8.

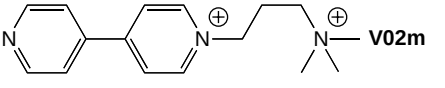

Figure 5. Chemical structure of **V02m**.

Table 3. Comparison of **V02** and **V02m**.

Guest	Q*n*	V:Q*n*	K_a[a]
V02	Q7	(1:1)	$4.3 (\pm 0.2) \times 10^6$ M^{-1}
V02m	Q7	(1:1)	$3.4 (\pm 0.1) \times 10^6$ M^{-1}
V02	Q8	(2:1)	$1.2 (\pm 0.2) \times 10^{11}$ M^{-2}
V02m	Q8	(2:1)	$9.1 (\pm 1.6) \times 10^{10}$ M^{-2}

[a] Mean values measured from at least three ITC experiments at 27°C in 10 mM sodium phosphate, pH 7.0. Standard deviations are given in parentheses.

3.2 Thermodynamics

Removing one charge from **V11** (to **V01**) results in a 1.0 kcal/mol decrease in affinity for Q7, a 1.5 kcal/mol enthalpic gain and a 2.5 kcal/mol entropic loss ($T\Delta S$, Table 1).[1] This modest (11%) decrease in affinity for **V01** suggests that ion–dipole interactions are not as crucial to binding as dispersion interactions and hydrophobic inclusion. The entropy/enthalpy compensation observed here suggests a strong solvation of the pyridinium cations, the binding of which leads to entropically favourable and enthalpically unfavourable release of tightly bound water molecules.

The effects of the *placement* of charges can be assessed by comparing **V11** with **V02**, where two charges are located on opposite sides or the same side of the bipyridine core, respectively. When compared with **V11**, **V02** binds Q7 with a 0.3 kcal/mol decrease in affinity, a 0.8 kcal/mol enthalpic gain and a 0.9 kcal/mol entropic loss. The entropy/enthalpy compensation observed here is similar to that observed for removal of a charge from **V11** to **V01**. These results suggest little importance of the placement of charges on the thermodynamics of binding.

Adding a propylammonium group to **V11** to make **V12** increases the affinity of binding to Q7 by a modest 0.4 kcal/mol and has little effect on the entropy or enthalpy of binding. In contrast, however, adding a propylammonium group to **V11** to make **V12** results in an increase in the binding affinity for Q8 by 1.3 kcal/mol, an enthalpic gain of 1.9 kcal/mol and an entropic loss of 0.7 kcal/mol. The greater increase in affinity and favourable enthalpy of binding observed for Q8 versus Q7 is likely due to the larger portal of Q8, which can accommodate a greater separation of the propylammonium and pyridinium charges while allowing both charges to interact with the portal of Q8.

There is essentially no difference in the thermodynamics of binding between **V12** and **V22** for Q8. For Q7, these two complexes appear identical, but experimental limitations preclude a more accurate comparison. From modelling, we believe this result to be due to the poor availability of conformations that allow both propylamine tails to be simultaneously proximal to carbonyl groups on Q8. A practical implication of this result is that one can maximise the affinity of interaction between viologen and Q8 while allowing the conjugation of viologens to other species by linking these species directly to one amino group of **V22**.

Overall, the modest increase in affinity observed upon adding three charges to **V01** suggests that hydrophobic inclusion and dispersion interactions contribute to the stability of viologen–Q*n* interactions to a greater extent than specific cation–dipole interactions.

3.3 Conclusions

This study serves as a guide for the control of stoichiometry and affinity of binding for Q*n*–viologen complexes (Figure 6). We demonstrate that placement of charges on a viologen governs the stoichiometry of binding to Q8, but has little effect on the affinity or stoichiometry of binding to Q7. We also show that while binding affinity correlates somewhat directly with the number of positive charges on the viologen, increasing K_a up to $\sim 10^7$ M^{-1}, the effect is greater for Q8 than for Q7 but overall is less than expected. Understanding these structure–activity relationships should help in the design of next-generation supramolecular structures.

4. Materials and methods

4.1 Materials

The following commercial reagents of analytical or higher purity grade were used without further purification: deuterium oxide (Cambridge Isotope Laboratories);

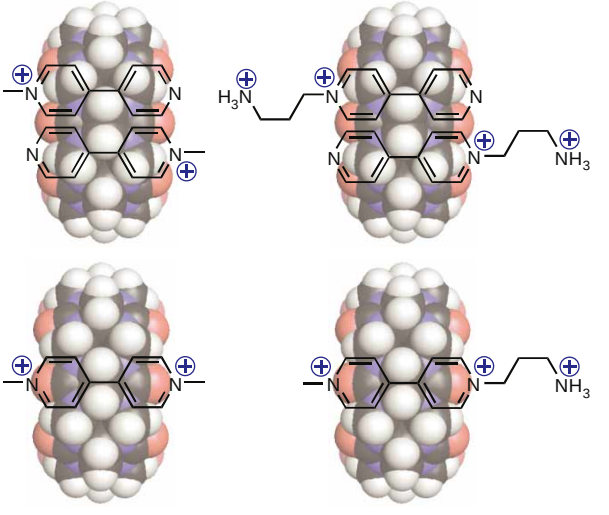

Figure 6. Schematic illustration of the effect of the placement and number of positive charges on the stoichiometry of binding to Q8.

4,4′-dipyridyl (TCI); iodomethane (Acros); sodium phosphate (mono and dibasic), acetonitrile, 3-bromopropylamine hydrobromide, methyl viologen dichloride, dichloromethane and (3-bromopropyl)trimethylammonium bromide (Sigma Aldrich); Q8 and Q7 were synthesised by the group of Dr Anthony Day (University of New South Wales) and purchased from Unisearch. Water was obtained from a Barnstead Nanopure Infinity water system (18 MΩ cm^{-1}). **V01** (*32*), **V02** (*33*), **V12** (*32*) and **V22** (*21*) were synthesised by mono- or *bis*-alkylation of bipyridine, according to published protocols.

A stock solution of 1.0 M sodium phosphate was adjusted to pH 7.0 and sterile filtered. Phosphate buffer (10 mM) was made as needed by diluting the 1 M stock. Fresh analyte solutions were prepared every couple of days and were dissolved thoroughly by heating at 60°C and, if necessary, by ultrasonication. All analytes were massed to ±0.02 mg with an accuracy of at least three significant digits. Purities of hygroscopic reagents were determined by ^{1}H NMR using freshly distilled *t*-butyl alcohol as a standard.

4.2 Synthesis of 4-pyridin-4-yl-[3-(trimethylammonio)propyl]pyridinium bromide (V02m)

4,4′-Dipyridyl (2.06 g, 13.2 mmol) and (3-bromopropyl)-trimethylammonium bromide (0.348 g, 1.33 mmol) were combined in 30 mL acetonitrile and heated at mild reflux under N_2 for 20 h. The resulting cream coloured precipitate was collected by vacuum filtration and washed with dichloromethane to obtain the product as an off-white fine powder (0.27 g, 47% yield). ^{1}H NMR (D_2O) δ 8.87 (dd, 2H, $J = 1.6$, 7.2 Hz), 8.63 (dt, 2H, $J = 1.6$, 4.8 Hz), 8.31 (dd, 2H, $J = 1.6$, 7.2 Hz), 7.77 (dd, 2H, $J = 1.6$, 4.8 Hz), ~4.7 (occluded, 2H), 3.40 (t, 2H, $J = 8$ Hz), 3.03 (d, 9H, $J = 2$ Hz), 2.49 (quint, 2H, $J = 8.4$ Hz). ^{13}C NMR (D_2O) δ 154.73, 150.16, 145.06, 142.54, 126.60, 122.67, 62.59, 57.81, 53.33, 24.70. Hi-res FAB mass spec: $\mathbf{V02m}^{2+} - {}^{79}Br^-$ calc: 336.11, found: 336.11, $\mathbf{V02m}^{2+} - {}^{81}Br^-$ calc: 338.11, found: 338.10.

4.3 Isothermal titration calorimetry

Titration experiments were carried out in 10 mM sodium phosphate buffer (pH 7.0) at 27°C on a VP-ITC calorimeter from Microcal, Inc. Complexes with **V12** were analysed by the single injection method for ITC (*34*). In these cases, the syringe concentration was 20 times that of the cell. All other complexes were analysed by the standard injection method, wherein a typical titration schedule consisted of 29 or 57 consecutive injections of 2–10 μl with an interval of at least a 200 s between injections. Heats of dilution, measured by titration beyond saturation, were subtracted from each dataset. All samples were degassed prior to titration. Data were analysed with Origin software.

4.4 NMR spectroscopy

All NMR spectra were collected in deuterium oxide on a Varian Inova 400 MHz spectrometer at 25°C. For the ^{1}H NMR spectra, a presaturation pulse was used to suppress the signal from residual protiated solvent.

4.5 Mass spectrometry

Mass spectra in positive ion mode were obtained from aqueous solutions of ~10 μM analyte using a Thermo Finnigan Deca XP Plus with an electrospray source. **V02m** was also characterised by high-resolution fast-atom bombardment mass spectrometry at the University of Iowa High Resolution Mass Spectrometry Facility.

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Note

1. This comparison cannot be made directly with Q8 due to the difference in stoichiometry.

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