CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201605092

Link to VoR: http://dx.doi.org/10.1002/chem.201605092

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10.1002/chem.201605092

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The delicate balance of preorganisation and adaptability in multiply bonded host–guest complexes

Larissa K. S. von Krbek,[a] Andreas J. Achazi,[b] Stefan Schoder,[a] Marius Gaedke,[a] Tobias Biberger,[a] Beate Paulus,*[b] and Christoph A. Schalley*[a]

Abstract: Rigidity and preorganisation are believed to be required for high affinity in multiply bonded supramolecular complexes as they help reducing the entropic penalty of the binding event. This comes at the price that such rigid complexes are sensitive to small geometric mismatches. In marked contrast, nature uses more flexible building blocks. Thus, one might consider putting the rigidity-high affinity notion to the test. Multivalent crown/ammonium complexes are ideal for this purpose as the monovalent interaction is well understood. A series of divalent complexes with different spacer lengths and rigidities has thus been analysed to correlate chelate cooperativities and spacer properties. Too long spacers reduce chelate cooperativity compared to exactly matching ones. However, in contrast to expectation, flexible guests bind with chelate cooperativities clearly exceeding those of rigid structures. Flexible spacers adapt to small geometric host/guest mismatches. Spacer-spacer interactions help overcoming the entropic penalty of conformational fixation during binding and a delicate balance of preorganisation and adaptability is at play in multivalent complexes.

Introduction

Preorganisation and complementarity are paradigmatic concepts in supramolecular chemistry, which are believed to be the key to exceptionally strong multiply bonded[1-9] structures. Cram[10-11] introduced the concept of preorganisation to supramolecular chemistry and Whitesides and co-workers[2, 12] extended this principle to multivalent biological systems. Preorganised, rigid systems supposedly suffer from a lower entropic penalty upon binding compared to more flexible, less preorganised systems.[13-14] Indeed, there are intriguing examples of highly cooperative multivalent binding in rigid supramolecular systems;[1-8] for example Anderson's[8] huge zinc porphyrin wheels that are synthesised around multivalent templates. The preorganisation and linker rigidity in these systems leads to a four orders of magnitude increase of binding affinity compared to noncyclic porphyrin oligomers. However, such rigid structures are very sensitive towards geometric mismatches between the binding partners. Even a slight structural discrepancy can lead to a drastic drop in binding affinity.[12, 15] This is likely an important reason, why many natural multivalent complexes do not exhibit such a high degree of preorganisation, but exhibit at least some flexibility allowing for adaptability. DNA for example has a highly flexible backbone, yet it is very stable when doubly stranded (due to multivalent binding enhancement). This concept is also used in foldamers[16-19] and Hunter and co-workers[20-21] recently reported a synthetic DNA analogue binding with high chelate cooperativities despite of its flexible backbone. Sufficient adaptability to small geometric mismatches between the multiply bonded interaction partners may thus be advantageous for strong multiple host–guest interactions.

Here, we address this question systematically by investigating several series of divalent crown ether/ammonium complexes and quantify the effects of spacer length and spacer flexibility on the chelate cooperativity of the complex. Chelate cooperativity[7-8, 22-24] is a term that accounts for the likeliness of a multiply bonded, i.e. multivalent, structure to form a fully bonded 1:1 complex instead of oligomers. Fundamental studies of this type will provide quantitative design rules to guide the construction of supramolecular assemblies and receptors. Recently, we demonstrated[25-26] the well-studied crown ether/ammonium binding motif[10-11, 27-30] to be especially suitable for our purpose as the monovalent interaction is a reliable, well understood binding motif.[31-33] Furthermore, these systems exhibit a limited molecular size suitable for computational analysis by density functional theory.[25-26, 31, 34] In our previous studies, we investigated[25-26] the cooperativities in two virtually identical divalent complexes with flexible linkers that exhibited significantly different, but very high chelate cooperativities. The present study aims at a more general view on multivalent interactions in such host-guest complexes. We expected to find the highest cooperativities for rigid linkers. However, the opposite was the case. Maximum chelate cooperativity was observed for the flexible structures. This indicates that there is a delicate balance between preorganisation and adaptability of a system.

Results and Discussion

Conceptual approach

Before discussing the results obtained, we briefly describe the general conceptual approach that was taken in this work. This approach has been described previously[26] and details can be found in the SI. Briefly, to quantify the multivalent binding enhancement compared to the corresponding monovalent counterparts, two different chelate cooperativity factors β and β' were defined by Hunter and Anderson[22] as well as Ercolani and Schiaffino,[23] respectively (eqs. 1 and 2, respectively, for a

[a] L. K. S. von Krbek, M. Sc.; A. J. Achazi, M. Sc., S. Schoder, M. Sc.; M. Gaedke, M. Sc.; T. Biberger, Prof. Dr. B. Paulus, Prof. Dr. C. A. Schalley
Institut für Chemie und Biochemie, Freie Universität Berlin
Takustraße 3, 14195 Berlin, Germany
E-mail: c.schalley@fu-berlin.de

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divalent complex **a**, Figure 1, middle). The cooperativity factor β quantifies the likeliness of an open singly bound divalent complex to close to the doubly bound form. Factor β' describes how prone the open complex is to oligomerisation, if an additional host is offered. This is why the cooperativity factor β' is normalised by the host concentration.

Both cooperativity factors indicate positive chelate cooperativity, i.e. predominant formation of closed complex, if β > 1 and β' > 1 (ln β > 0 and ln β' > 0, respectively). In case of factors smaller than 1, the divalent complex predominantly exists in its open form which is prone to oligomerisation, thus exhibiting negative chelate cooperativity. The absence of chelate cooperativity is indicated by β = 1 and β'= 1.

$$\beta = K_{\text{mono}} EM \quad \text{or} \quad \ln\beta = \ln(K_{\text{mono}} EM) \qquad (1)$$

$$\beta' = \frac{EM}{4[\mathbf{host}]} \quad \text{or} \quad \ln\beta' = \ln\left(\frac{EM}{4[\mathbf{host}]}\right) \qquad (2)$$

The effective molarity *EM* is the key variable in both cooperativity factors. In the two-step association process of a divalent complex **a** (Figure 1), *EM* accounts for the intramolecular ring closure in the second binding step. *EM* cannot be measured directly, but can be quantified by double mutant cycle analyses (DMC; Figure 1, top).[5, 26, 31-33, 35-37] The DMC connects a divalent complex **a** to two monovalent complexes **d** via two pathways of two consecutive mutations. By comparison of the four complexes **a** – **d** derived from the mutations, all secondary allosteric effects cancel and the chelate cooperativity remains. This DMC can also be described as the **b** + **c** → **a** + 2 **d** equilibrium (Figure 1, bottom). As all components appear on both sides of the equilibrium, the equilibrium constant *K* is only affected by chelate cooperativity. *EM* can be calculated from the set of all four binding constants K^{a} – K^{d} (eq. 3). These binding constants can be expressed as products of the intrinsic monovalent binding constant K_{mono} and the statistical factors[38-40] derived by the direct count method[38-39] or—with the same result—Benson's symmetry number method.[38, 40] If these products are inserted into the definition of *K* (eq. 3), it becomes clear that *K* is only dependent on *EM* in these cases.

$$K = \frac{K^{\text{a}}\,(K^{\text{d}})^2}{K^{\text{b}}\,K^{\text{c}}} = \frac{4\,(K_{\text{mono}})^2\,EM \cdot (2\,K_{\text{mono}})^2}{4\,(K_{\text{mono}})^2 \cdot 4\,(K_{\text{mono}})^2} = EM \qquad (3)$$

$$\Delta\Delta G^0 = \Delta G^0_{\text{a}} - \Delta G^0_{\text{b}} - \Delta G^0_{\text{c}} + 2\,\Delta G^0_{\text{d}} \qquad (4)$$

$$\Delta\Delta G^0 = -RT\ln(EM) = \Delta\Delta H^0 - \Delta(T\,\Delta S^0) \qquad (5)$$

The four individual binding constants K^{a} – K^{d} are experimentally accessible in four separate isothermal titration calorimetry (ITC) experiments. The advantage of ITC is that it measures the association constant *K*, the association enthalpy Δ*H* and the association entropy Δ*S* in the same experiment. Hence, the DMC can also be applied to Δ*H* and Δ*S* (eqs. 4, 5). This provides detailed insight into residual enthalpies ΔΔ*H* and entropies Δ(*T* Δ*S*) of divalent complexes. These values exhibit larger errors due to error propagation and their discussion later on will focus on trends rather than precise values.

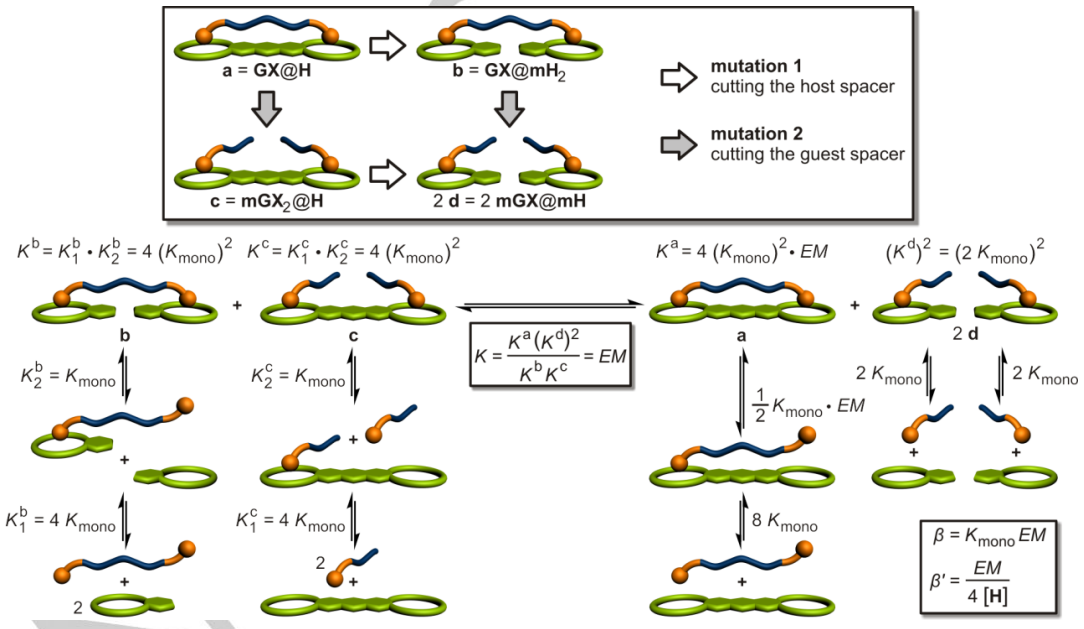

Figure 1. Top: Double mutant cycle for the thermodynamic analysis of chelate cooperativity of a divalent complex. Bottom: Evaluation of the effective molarity *EM*. The individual binding constants for each of the four complexes, K^{a} – K^{d} can be independently measured in four titration experiments. Each of them can be expressed in a term using the monovalent binding constant K_{mono}. As the crown ether can be approached by the ammonium ion from both sides, K_{mono} is the intrinsic monovalent binding constant after correction of the apparent one by a statistical factor of 2 to be consistent with the statistical factors of the other complexes. From the four binding constants, the equilibrium constant *K* for the **b** + **c** → **a** + 2**d** equilibrium can be calculated and is equivalent to *EM* in the cases under study here as all statistical factors cancel. Adapted with permission from Ref. [26] (© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim).

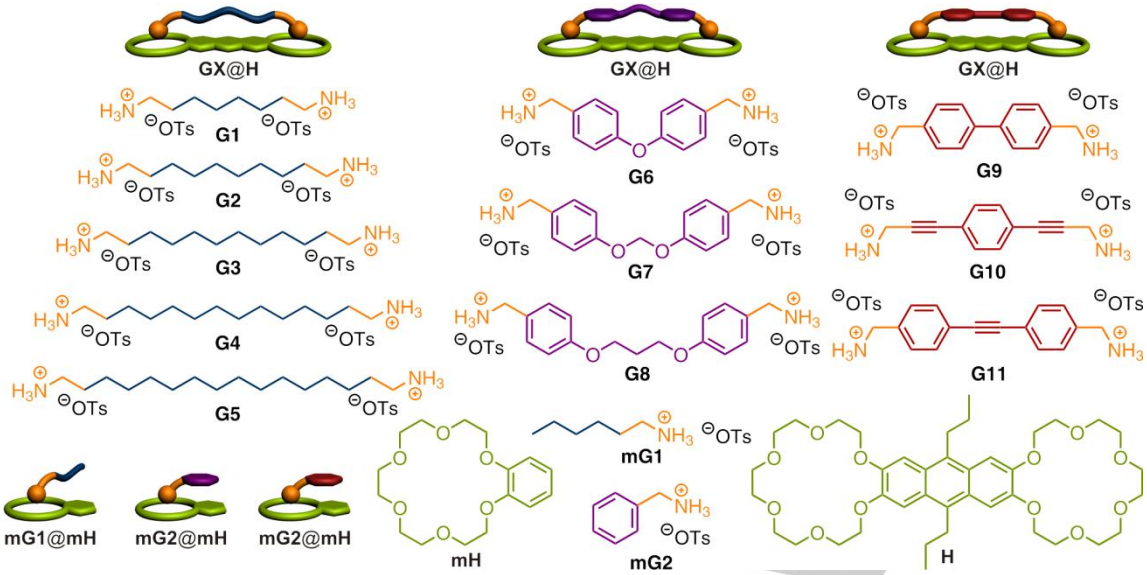

Chart 1. Divalent guests **GX**, divalent host **H** and their complexes **GX@H** as well as monovalent reference compounds **mG1**, **mG2**, **mH** and their complexes **mG1@mH** and **mG2@mH**. Divalent guests GX exhibit spacers of different lengths and degrees of flexibility between their ammonium binding sites. The different degrees of flexibility are colour coded: flexible = blue, "semi-rigid" = violet, rigid = red. Three more flexible guests bearing ether chains instead of alkyl were investigated as well. Results of those are reported in the SI. Note that there is only one monovalent reference system for **G6**–**G11**.

For a correlation of linker length and flexibility with chelate cooperativity, DFT-optimised structures were used. DFT structure optimisation is done here with a dispersion corrected meta-GGA functional and a triple-zeta basis set (TPSS-D3(BJ)/def2-TZVP).[41-50] This method provided good geometric structures in previous studies[25-26, 43] (for a detailed description of the computational methods see SI).

This approach was established in earlier studies.[26] In this work, we took a known divalent [18]crown-6 host with a rigid linker scaffold (**H**) and investigated its association to different divalent primary ammonium ions (Chart 1). We systematically altered the linker length and flexibility in the ammonium guests to quantify the effect of both on the chelate cooperativity of the complex. Three different groups of guest spacer flexibilities were taken into account: flexible alkyl spacers (blue), less flexible, "semi-rigid" aryl ether spacers (violet) and rigid aryl/alkynyl spacers (red). We did not alter the host structure to have a reliable benchmark in all systems.

To test, whether the guest spacer lengths selected for this study cover the whole range from too short to longer-than-necessary spacers, the calculated N–N distances of the host-guest complexes **GX@H**−2OTs were compared to those of the unbound, relaxed guests **GX**−2OTs (Figure 2). The $(NH_4^+)_2$**@H** 2:1 complex provides the N–N distance for an unstrained host-guest structure. The orange line in Figure 2 indicates the trend of relaxed N–N distances in the free divalent guests. As long as the guests are too short, the N–N distances for the host-guest complexes follow this line until a good length fit is achieved.

For guests that have too long spacers, the N–N distances in the divalent complexes is more or less constant and nicely matches the green line, which indicates the N–N distance in the $(NH_4^+)_2$**@H** 2:1 complex. Consequently, the selection of guests should be appropriate to get a more general view on the role of spacer length (and flexibility) on cooperativity.

The guests under investigation can be divided into four groups: (i) Too short guest **G1** which most likely cannot bridge the distance between the two crown ethers in **H** and, therefore, is mostly singly bound. (ii) Short guests **G2**, **G6**,

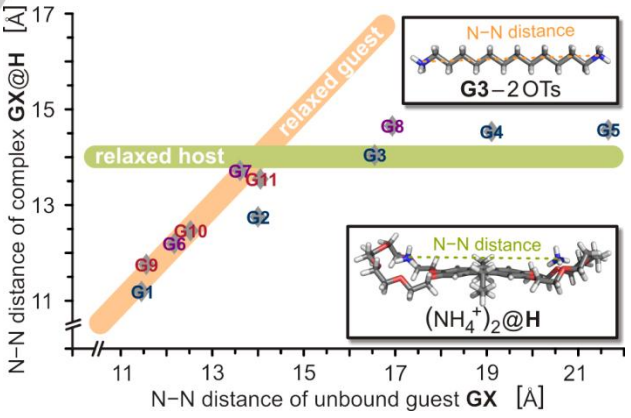

Figure 2. Comparison of N–N distances in unbound guests **GX**−2OTs (one representative structure in top right corner) and in complexes **GX@H**−2OTs. The orange line corresponds to N–N(unbound guest) = N–N(complex). The green line corresponds to the N–N distance in $(NH_4^+)_2$**@H** (structure in bottom right corner). Guest with N–N distances shorter than that of the host benchmark (14.0 Å) show linear behaviour along the orange trendline, while longer guests show asymptotic behaviour towards the green line. According to this correlation, **G7** and **G11** are expected to exhibit the highest chelate cooperativities.

G9 and **G10** to which **H** can adapt by changing the crown conformations to accommodate shorter guests. (iii) Guests **G7** and **G11** with (almost) optimal N–N distances. (iv) Guests **G3**, **G4**, **G5** and **G8** with too long spacers which have to contract to bind to **H**. Hence, complexes **G7@H** and **G11@H** with optimal spacer lengths are expected to exhibit the highest chelate cooperativities. They furthermore exhibit more rigid spacer scaffolds that are expected to be preferable for high-affinity divalent binding and high chelate cooperativity. Shorter guests spacers (ii) should exhibit reduced chelate cooperativities as the complexes can be expected to be strained with unfavourable enthalpic effects. Longer spacers (iv) are expected to be entropically unfavourable due to a higher degree of conformational fixation in the complex. Also, there might be enthalpic penalties from unfavourable *gauche* conformations along the alkyl chain.

Synthesis and complex characterisation

The synthesis of monovalent guests **mG1** and **mG2**,[25] divalent host **H**[26] as well as divalent guest **G3**[26] and their complexes was reported before. The other 10 divalent guests were obtained as described in the SI. Complex formation was achieved by mixing the two binding partners in a 1:1 molar ratio in 1:1 (v/v) mixtures of chloroform and methanol. Exclusive formation of doubly bound 1:1 complexes was demonstrated by ^{1}H NMR (see SI). As expected, the only exception is **G1@H**, which is at least partially open. ESI mass spectrometric experiments substantiate the 1:1 stoichiometry and exclude the formation of 2:2 complexes or larger oligomers (see SI).

Analysis of chelate cooperativities

The thermodynamic binding data of the complexes **GX@H** were determined by isothermal titration calorimetry (ITC) in 1:1 (v/v) mixtures of chloroform and methanol. [51] The data were fitted to a 1:1 binding isotherm. The resulting association constants are summarised in Table 1. Double mutant cycle analyses of the divalent complexes provide their effective molarities *EM* and their chelate cooperativity factors β and β' (Table 1). Figure 3a depicts the cooperativities plotted in logarithmic form (ln β and ln β') against the deviations of the N–N distances of the complexes against the corresponding relaxed distances. To facilitate the analysis, we roughly distinguish two cases (i) If the guest is more flexible than the host (**G1**–**G8**), one expects mainly the guest to adapt to the host. The host adapts to the guest as well, but with less pronounced geometrical changes. Energetically, the deformation of the host contributes however more to the strain (examples in Figure 3b). For these guests, the N–N distances of the relaxed complex ($(NH_4^+)_2$**@H**) are compared to the N–N distances of the complexes **GX@H**−2OTs. (ii) If the host structure is more flexible than the guest structure (**G9**–**G11**) it is more reasonable to compare the N–N distances of the complexes **GX@H**−2OTs with the N–N distances of the unbound guests **GX**−2OTs.

Several observations are made from the plots in Figure 3a. First of all, both cooperativity factors result in similar trends and we can conclude that it does not make a significant difference for the interpretation of chelate cooperatives in the present study, which of the two definitions of chelate cooperativity is used.

Table 1. Association constants of divalent complexes K^a and the corresponding normalised monovalent reference constants obtained from ITC titrations ($CHCl_3$/MeOH 1:1 (v/v), 298 K (for complete data sets including 1:2 and 2:1 complexes of two monovalent and one divalent component, see SI, Tables S2-S15). Effective molarities *EM*, chelate cooperativity factors β[22] and β'[23], as well as residual enthalpies ΔΔ*H* and entropies Δ(*T* Δ*S*) were obtained by complete DMC analysis (eqs. 1 - 5)

complex	K_{mono}[25] [10^3 M^{-1}]	K^a [10^3 M^{-1}]	*EM* [mM]	*β*	*β'* [a]	ΔΔ*H* [kJ mol^{-1}]	Δ(*T* Δ*S*) [kJ mol^{-1}]
G1@H	2.0 ± 0.2	14 ± 1.4	1.3 ± 0.3	2.5 ± 0.6	0.16 ± 0.04	3.0 ± 4.0	7.9 ± 3.9
G2@H	2.0 ± 0.2	700 ± 70	430 ± 100	860 ± 210	54 ± 12	−(4.1 ± 3.6)	−(6.4 ± 3.6)
G3@H[23]	2.0 ± 0.2	2,700 ± 270	880 ± 200	1,800 ± 430	110 ± 30	−(11.1 ± 4.0)	−(11.5 ± 4.1)
G4@H	2.0 ± 0.2	620 ± 62	200 ± 40	400 ± 100	25 ± 6	−(2.3 ± 3.6)	−(6.4 ± 3.7)
G5@H	2.0 ± 0.2	300 ± 30	96 ± 22	190 ± 50	12 ± 3	−(3.7 ± 3.5)	−(9.6 ± 3.5)
G6@H	4.3 ± 0.4	300 ± 30	20 ± 4	85 ± 21	2.5 ± 0.6	5.3 ± 4.3	−(4.4 ± 4.4)
G7@H	4.3 ± 0.4	1,400 ± 140	110 ± 20	460 ± 110	13 ± 3	1.8 ± 4.5	−(3.6 ± 4.5)
G8@H	4.3 ± 0.4	1,100 ± 110	51 ± 11	220 ± 50	6.4 ± 1.5	5.0 ± 3.7	−(2.5 ± 3.8)
G9@H	4.3 ± 0.4	220 ± 22	11 ± 5	45 ± 21	2.6 ± 1.2	11.0 ± 3.7	−(0.2 ± 3.9)
G10@H	4.3 ± 0.4	1,500 ± 150	120 ± 30	500 ± 120	15 ± 3	−(5.7 ± 3.7)	−(10.5 ± 3.8)
G11@H	4.3 ± 0.4	380 ± 38	28 ± 8	120 ± 36	1.94 ± 0.25	3.1 ± 3.8	−(5.8 ± 3.8)

[a] The concentration in the ITC vessel, by which the cooperativity factor β' is normalised, was 2 mM in all cases, except **G9** and **G11**, where it was 1 mM, because of solubility problems.

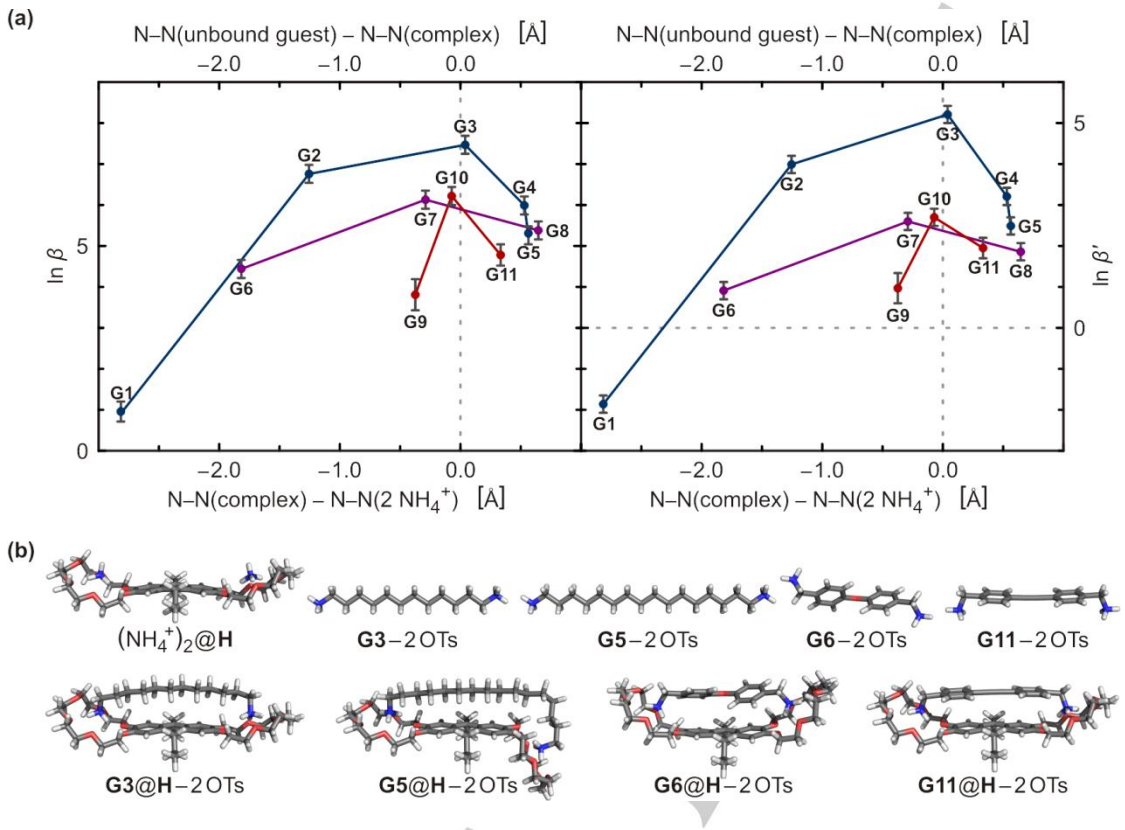

Figure 3. (a) Correlations of chelate cooperativity factors ln β (left) and ln β' (right) to (i) the differences in N–N distances of complex **GX@H**−2OTs and relaxed complex $(NH_4^+)_2$**@H** (N–N(complex) − N–N(2 NH_4^+)) for guests **G1**–**G8** (blue & purple lines) or to (ii) the differences in N–N distances of unbound guests **GX**−2OTs and complex **GX@H**−2OTs (N–N(unbound guest) − N–N(complex)) for guests **G9**–**G11** (red lines). Shorter guest spacers correspond to lower values on the x axis. Values below x = 0 correspond to a contracted conformation of host or rigid guest compared to their relaxed structures. Values of x > 0 correspond to a stretched conformation of host or rigid guest compared to their relaxed structures. For x =1, the more rigid component of the complex is in a relaxed structure, resulting in the highest chelate cooperativities. (b) Representative DFT calculated structures of relaxed host $(NH_4^+)_2$**@H**, unbound guests **G3**, **G5**, **G6** and **G11** as well as their complexes with **H** for an assessment of the impact of guest spacer length and flexibility on the chelate cooperativity of the whole complex.

The second finding is that a separate consideration of the series of flexible, semi-rigid and rigid guests is required to obtain a clearer picture: In each of the three series the highest chelate cooperativity is found for the guest with the best size match (**G3** among the flexible guests, **G7** in the semi-rigid and **G10** in the rigid series). Consequently, flexibility and spacer length are two factors that are intimately interdependent and can, thus, not be considered separately. To compare lengths is only reasonable for guests of similar rigidity.

A third observation is that there appears to be no significant difference in the chelate cooperativity between the “semi-rigid” and the rigid guests as expressed in the almost identical chelate cooperativity factors of **G7** and **G10**. Clearly, however, a small deviation from the optimal length causes a sharper drop in chelate cooperativity for the rigid than the semi-rigid guests. High rigidity thus comes at the price of a higher sensitivity of the binding interactions to small geometric mismatches between host and guest. Slightly stretching or compressing the guests scaffold even by only 0.5 Å results in a decrease of the cooperativity factors by one order of magnitude.

Most strikingly and in marked contrast to the expectation discussed above, semi-rigid **G7** and rigid **G11** do *not* exhibit the highest chelate cooperativities, even though they are close to perfect in spacer length and require less conformational fixation upon divalent binding than the flexible guests. Instead, two flexible guests **G2** (slightly too short) and **G3** (slightly too long) exhibit the highest chelate cooperativities. Even flexible guest **G4**, with a spacer significantly longer than required to bridge between binding sites exhibits chelate cooperativities β similar to and β' higher than **G7** and **G10**. Although the semi-rigid guest **G8** fits better to the host in length, it can still not compete with **G4** neither in β nor in β'. Similarly, the chelate cooperativity drops somewhat below that of **G4** for the longest flexible guest **G5**, but is still in the same order of magnitude as compared to **G8** and **G11**. Unexpectedly, flexible guests thus clearly exceed the more rigid ones in chelate cooperativity over a broader length range, even when the latter ones are expected to fit better to the host geometrically. Generally, the complexes with flexible guests are less affected by variations of the spacer length than the complexes with more rigid guests (**G6**–**G11**, purple/red lines).

Analysis of residual enthalpies and entropies

These results contradict the widely accepted notion that flexible scaffolds are unfavorable for multivalent binding as they suffer from a higher entropic penalty upon ring closure than more rigid structures. To address this point, we investigated residual enthalpies $\Delta\Delta H$ and entropies $-\Delta(T\Delta S)$ of the divalent complexes under study with respect to spacer lengths and flexibilities. A correlation of residual enthalpies and entropies to the structural parameters used in Figure 3a elucidates the impact of both parameters on the chelate cooperativities of the complexes (Figure 4). In contrast to expectation, the impact of the residual enthalpy $\Delta\Delta H$ on the chelate cooperativity is generally larger than the impact of the residual entropy $-\Delta(T\Delta S)$. Within the series of "semi-rigid" guest scaffolds (**G6**–**G8**, purple lines), residual enthalpies and entropies do not change significantly. Within the other two series, the highest entropic penalties $-\Delta(T\,\Delta S)$ are surprisingly paid by the complexes exhibiting the highest chelate cooperativities, i.e. **G3**@**H** and **G10**@**H**. These unfavourable entropies are compensated by even more negative residual enthalpies $\Delta\Delta H$, which stabilise the complex. They are likely caused by secondary interactions between guest and host spacers, such as C–H···π and π···π interactions, and a low amount of strain in the matching doubly bound host-guest complex. This provides clear evidence, that the common notion that the entropic penalty of the ring closure step is the main drawback in multivalent binding needs to be regarded more carefully.

Conclusions

Three series of divalent crown ether/ammonium complexes have been investigated by isothermal titration calorimetry with respect to their chelate cooperativities including an analysis of enthalpy and entropy factors that contribute to chelate cooperativity. Density functional theory aided the analysis of the thermochemical data by providing the structural parameters required.

In complexes combining a host with a rigid scaffold with guests of different spacer lengths and flexibilities, the flexible guests are favoured over the more rigid ones, almost irrespective of their spacer length as long as the spacers are long enough to permit divalent binding. Our results therefore clearly underline the importance of a certain flexibility and adaptability for achieving strong divalent binding and high chelate cooperativities. The underlying reason is the much more pronounced effect that slight structural mismatches have on complexes of rigid host and guest components. They exhibit high chelate cooperativities only, when the geometries of host and guest exactly match each other.

Furthermore, the cyclisation into the divalent complexes under study is mainly driven by enthalpy, in particular favourable secondary spacer–spacer interactions between host and guest play a role. The entropic penalty for too long, but flexible spacers resulting from their conformational fixation in the doubly bound state is in contrast only a minor effect.

In contrast to supramolecular paradigms such as the principle of preorganisation, a delicate balance between preorganisation and adaptability is at play, when multiply bonded structures are concerned. As it appears, flexible systems have been underestimated so far with respect to their ability to achieve high multivalent binding strengths and favourable chelate cooperativity. When developing multivalent complexes, these results encourage the supramolecular chemist to include less rigid spacers in the design of the building blocks. This is of interest also because solubility problems connected to the often well-packing and easily precipitating rigid molecules can more easily be circumvented and because the synthesis of more flexible chains is often easier to accomplish.

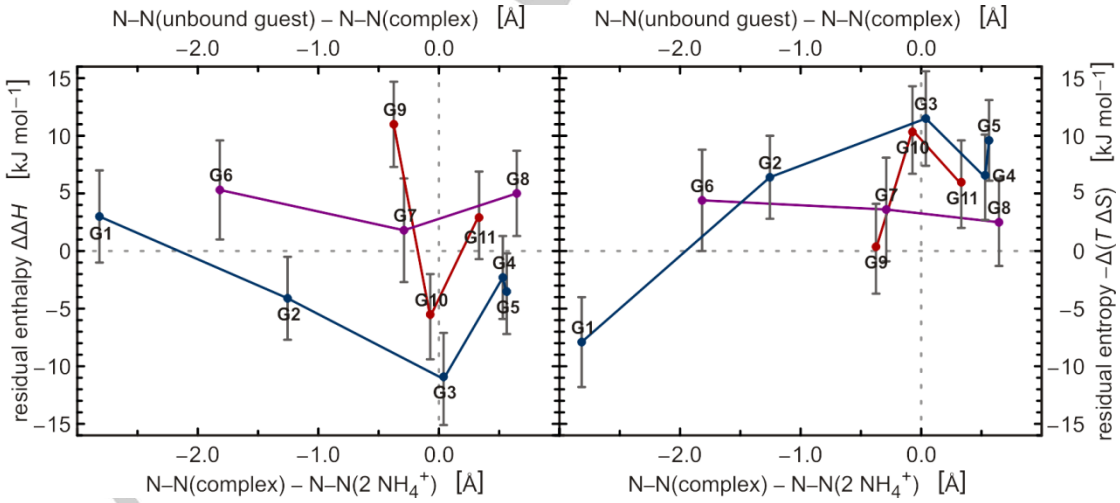

Figure 4. Correlations of residual enthalpies $\Delta\Delta H$ (left) and residual entropies $-\Delta(T\Delta S)$ (right) to (i) the differences in N–N distances of complex **GX**@**H**−2OTs and relaxed host $(NH_4^+)_2$@**H** (N–N(complex) − N–N(2 NH_4^+)) for guests **G1**–**G8** (blue & purple lines) or to (ii) the differences in N–N distances of unbound guests **GX**−2OTs and complex **GX**@**H**−2OTs (N–N(unbound guest) − N–N(complex)) for guests **G9**–**G11** (red lines).

Acknowledgements

The authors thank the *Deutsche Forschungsgemeinschaft* for generous financial support (SFB 765). Support by the High-Performance Computing facilities of the *Freie Universität Berlin* (ZEDAT) is acknowledged. Furthermore, the authors thank Florian Korinth and Tuğrul Kaynak for help in the synthesis. L.K.S.v.K. is grateful to the *Studienstiftung des Deutschen Volkes* for a PhD fellowship.

Keywords: multivalency • chelate cooperativity • preorganisation-adaptability dichotomy • isothermal titration calorimetry • density functional theory

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[51] The solvent mixture was optimized for the systems under study. Solvent dependent studies of cooperativity effects in **G3**@**H** and a similar system were previously reported.[26] Solubility issues prohibited the analysis of the other complexes in various solvent mixtures.

10.1002/chem.201605092

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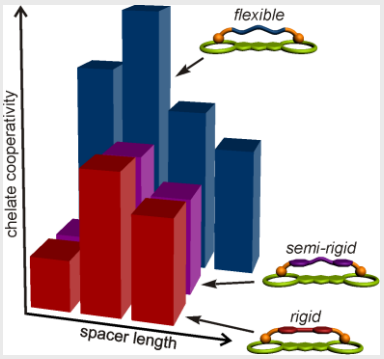
Entry for the Table of Contents

Layout 1:

FULL PAPER

Adaptability beats rigidity: Thermochemical (ITC) and computational (DFT) analyses on various crown/ammonium complexes with different guest-spacer lengths and flexibilities revealed a delicate interplay of preorganisation and adaptability. Flexible and rigid spacers equally suffer entropic penalty upon binding, but flexible spacers are able to compensate for mismatches between host and guest. Furthermore, spacer-spacer interactions render flexible spacers favourable.



Larissa K. S. von Krbek, Andreas J. Achazi, Stefan Schoder, Marius Gaedke, Tobias Biberger, Beate Paulus, and Christoph A. Schalley**

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The delicate balance of preorganisation and adaptability in multiply bonded host–guest complexes