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Enhanced anion recognition by ammonium [2]catenane functionalisation of a halogen bonding acyclic receptor†

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Ammonium-dibenzo[24]crown-8 [2]catenane functionalisation of a 3,5-bis-iodotriazole-pyridine motif produces a potent halogen bonding (XB) receptor capable of binding anions in aqueous-acetone solvent mixtures of up to 20% water. Exploiting the kinetically inert nature of the mechanically bonded cationic ammonium [2]catenane substituents, the XB receptor is demonstrated to exhibit superior anion recognition behaviour in comparison to labile sodium cation complexed bis-benzo[15]crown-5 XB and HB triazole-pyridine heteroditopic receptor analogues.

The continued interest in developing host systems for the molecular recognition of charged species is in no small part due to the pervasiveness of ions in a multitude of fundamental and essential chemical and biological processes.^{1,2} The characteristics of counterions have a significant impact on the cation and anion binding affinities of monotopic receptor systems. Consequently, the development of heteroditopic receptors for ion-pair recognition, where favourable proximal cation-anion electrostatic interactions and conformational allosteric cooperativity boost charged guest binding strength, has gained increasing attention in supramolecular host-guest chemistry research for the past few decades.³ Notably, heteroditopic hosts have demonstrated a plethora of potential applications including the extraction and recovery of transition and main-group metals, the solubilisation of inorganic salts in organic media, membrane transport and recognition of biologically-relevant zwitterions.⁴⁻⁶

Ion-pair recognition is associated with multiple complex equilibria. Strong ion-pairing, particularly in low polarity organic solvents, inhibits the complete dissociation of charged species, and only a fraction of free ions persists in solution.⁷

With heteroditopic receptors, the cation and anion are bound simultaneously, taking advantage of cooperativity between the proximal respective recognition sites. Commonly employed cation binding motifs in heteroditopic host design are crown ethers, and to achieve anion binding, hydrogen bond (HB) donors such as amide, urea and triazole are frequently used.⁸⁻¹¹ During the last decade, the emergence of sigma-hole interactions such as halogen bonding (XB) has demonstrated, in general, their superior anion guest binding capabilities compared to hydrogen bonding (HB) in host design.¹²⁻¹⁵

Recently, we reported a series of heteroditopic receptors containing XB donor groups covalently linked to benzo[15]crown-5 motifs, wherein co-bound sodium cation crown ether complexation cooperatively augmented bromide and iodide binding strength.¹⁶ Herein, we present an alternative novel post-mechanical bond synthesis strategy, where a positively charged ammonium [2]catenane motif replaces the crown ether complexed alkali metal cation. Stoddart's pioneering work demonstrating pseudorotaxane assembly between dibenzo[24]crown-8 and the dibenzyl ammonium group, stabilised by strong ion-dipole HB interactions,¹⁷ has led to its extensive employment in the mechanical interlocked molecule (MIM) synthesis of an enormous range of rotaxane and catenane supramolecular architectures.¹⁸⁻²⁰

A mechanically bonded dibenzo[24]crown-8 dibenzylammonium [2]catenane synthon was employed in the construction of a novel XB 3,5-bis-iodotriazole [2]catenane functionalised pyridyl receptor **1**·(PF₆)₂ for anion recognition in aqueous media (Fig. 1a). Extensive ¹H-NMR anion titration investigations demonstrate the superior anion recognition properties of **1**·(PF₆)₂ in comparison to bis-sodium cation complexed benzo[15]crown-5 functionalised XB and HB heteroditopic receptor analogues (**XB9-2NaPF₆** and **HB10-2NaPF₆**, respectively). These observations serve to highlight the importance of the kinetically inert nature of the cationic [2]catenane group in enhancing anion binding in competitive aqueous media, as an alternative to a kinetically labile alkali metal cation complexed crown ether.

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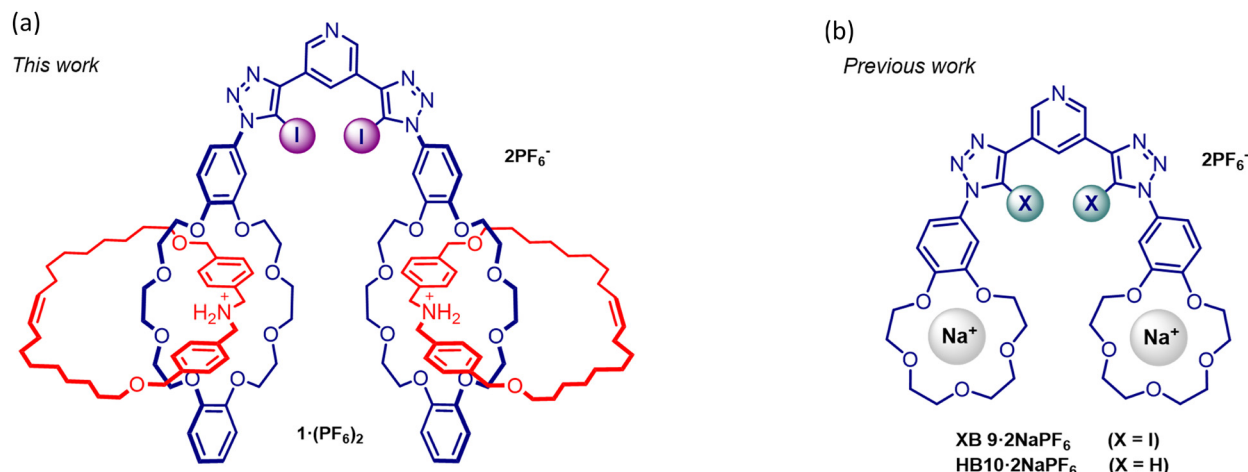


Fig. 1 Chemical structures of (a) ammonium-dibenzo[24]crown-8 [2]catenane functionalised XB receptor, **1·(PF₆)₂** and (b) XB and HB heteroditopic benzo-15-crown appended analogous receptors containing sodium ion complexed benzo[15]crown-5, **XB9·2NaPF₆** and **HB10·2NaPF₆**, respectively.

In order to prepare azide functionalised ammonium-crown ether [2]catenane synthon **8·PF₆** for subsequent CuAAC click XB reaction, the initial syntheses of azido-dibenzo[24]crown-8 **5** and the appropriate bis-alkene ammonium thread **6·PF₆**,^{21–23} were undertaken using modified procedures (Scheme S1, ESI†). To prepare the macrocycle **5**, the bis-tosylate precursor **2** was first prepared from an alkylation reaction of catechol, followed by tosylation. Subsequent macrocyclization was achieved *via* a potassium cation template ring closing reaction using a modified literature procedure.²⁴ An equimolar solution of the bis-tosylate **2** and 2-nitrocatechol in dry MeCN was refluxed in the presence of KPF₆ and K₂CO₃ to give nitro-functionalised dibenzo[24]crown-8 **3** in 87% yield. Reduction of **3** followed by diazotization and a nucleophilic aromatic substitution reaction with NaN₃ gave azido-dibenzo[24]crown-8 **5** in 90% yield (Scheme 1).

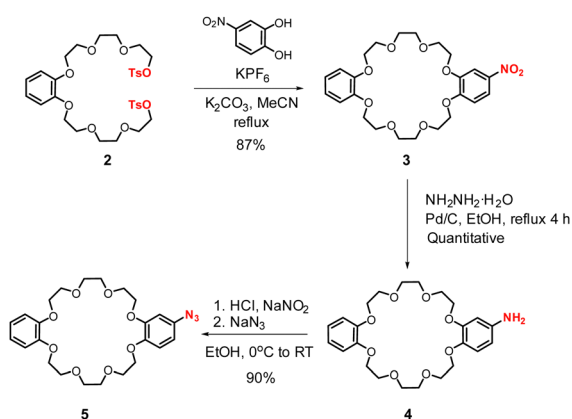
Qualitative ¹H-NMR spectroscopic studies of pseudorotaxane-complex formation between thread **6·PF₆** and macrocycle **5** were conducted by mixing an equimolar solution of each component in *d*₂-dichloromethane at room temperature. The ¹H-NMR spectrum of the resulting homogeneous solution showed well resolved signals of

both complexed and uncomplexed states, indicating the pseudorotaxane equilibrium was in slow exchange on the NMR timescale (Fig. S17, ESI†). The aromatic proton signals from the threading component **6·PF₆** (H_c and H_b) displayed an upfield shift upon interpenetration, concomitantly with the observation of substantial chemical shift changes of proton signals associated with the macrocyclic component. These evidences all indicate the formation of pseudorotaxane **7·PF₆**, in which hydrogen bonding and ammonium cation-dipole (NH⁺-O) interactions, along with π-π interactions stabilise the complexed assembly in *d*₂-dichloromethane.

The stability of the pseudorotaxane complex assembly allowed for the preparation of the azide appended [2]catenane **8·PF₆** *via* a ring closing metathesis reaction using Grubbs' 1st-generation catalyst.^{25,26} The crude product was purified by preparative silica gel thin-layer chromatography, followed by size exclusion chromatography and anion exchange to afford the azido [2]catenane **8·PF₆** product in 30% yield (Scheme 2). The interlocked nature of catenane **8·PF₆** was confirmed by ¹H-¹H ROESY NMR spectroscopy (Fig. S12, ESI†).

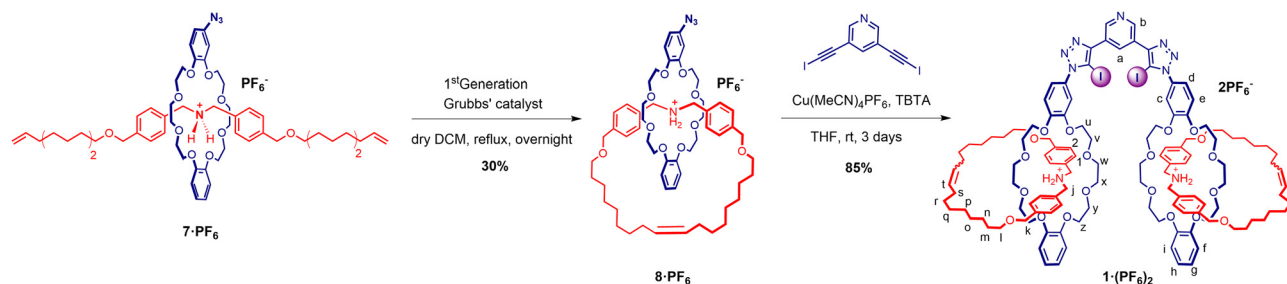
The CuAAC reaction of two equivalents of **8·PF₆** with 3,5-bis-iodoethynylpyridine²⁷ gave the target product **1·(PF₆)₂** in an excellent 85% yield after purification (Scheme 2). The ¹H-NMR spectrum of **1·(PF₆)₂** shows broad proton signals from the pyridyl ring (H_a and H_b) hidden under signals of aromatic crown ether protons with a significant downfield perturbation of aryl protons (H_c, H_d, and H_e) compared to those in the starting material **8·PF₆** (Fig. 2a). Additionally, the methylene proton (H_j, H_k, and H_{u-z}) resonances of **1·(PF₆)₂** are split into multiple signals whilst the alkyl proton (H_{i-s}) resonances remain unchanged. Moreover, the HRMS of **1·(PF₆)₂** revealed a signal of *m/z* = 1185.02467, corresponding to [M-2PF₆]²⁺, in agreement with the theoretical mass spectrum (Fig. 2b and ESI†).

The anion recognition properties of **1·(PF₆)₂** were initially investigated by ¹H-NMR spectroscopic titration experiments in the organic solvent mixture 10% *d*₆-DMSO/CDCl₃. Upon addition of iodide as tetrabutylammonium iodide (TBAI), the chemical shift of the internal pyridyl proton (H_a) displayed

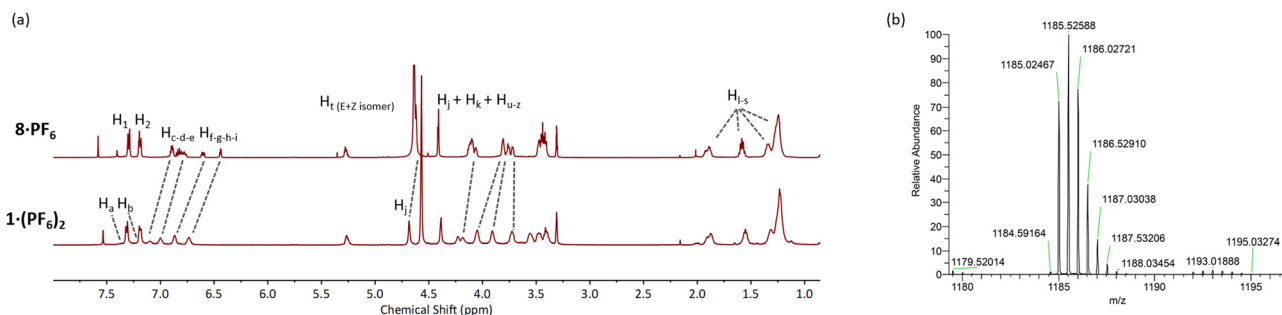


Scheme 1 Synthesis of azide functionalised dibenzo[24]crown-8, **5**.





Scheme 2 Synthetic scheme for azide functionalised [2]catenane **8-PF₆** via a ring closing metathesis and [2]catenane functionalised XB receptor **1-(PF₆)₂**.



water content where the host maintained sufficient solubility for $^1\text{H-NMR}$ spectroscopic titration, **1**(PF_6)₂ was still able to bind iodide strongly ($K_a = 860 \text{ M}^{-1}$). This observation clearly demonstrates that the combination of mechanically interlocked ammonium cation dibenzo[24]crown-8 containing substituents appended to a XB anion binding scaffold is as an effective novel methodology to achieve anion recognition in highly competitive aqueous solvent mixtures. It is also noteworthy that the superbase property of such ammonium MIM substituents potentially enables the positive charge to be retained even under basic aqueous solvent medium conditions.³⁰

In an effort to compare the halide anion binding properties of the kinetically inert positively charged catenane **1**(PF_6)₂ receptor with a labile ion-pair receptor analogue, the heteroditopic XB bis-dibenzo-24-crown-8 functionalised 3,5-bis-iodopyridyl receptor **XB11** was prepared for dibenzyl ammonium (**DBA**) cation-halide anion ion-pair binding investigation (see ESI† for synthetic details). Unfortunately, the poor solubility of **XB11** in common organic solvents, including acetone and acetone/ D_2O mixtures, necessitated the $^1\text{H-NMR}$ titration experiments being undertaken in 1 : 1 $\text{CD}_3\text{CN}/\text{CDCl}_3$. Monitoring perturbations of the receptor's aryl proton H_a in the vicinity of the XB recognition site, Bindfit analysis of the titration data (see ESI,† Table S1) determined the free **XB11** receptor binds Br^- ($K_a = 3640 \text{ M}^{-1}$) much more strongly than I^- ($K_a = 853 \text{ M}^{-1}$). In the presence of two equivalents of **DBA-PF**₆ resulting in pseudorotaxane assembly in each of the receptor's dibenzo-24-crown-8 substituents, TBA halide addition caused significant proton shifts, in particular in the aryl proton H_a of the XB recognition site and also induced chemical shift changes of proton signals of aryl protons of **DBA**⁺. Monitoring the aryl proton H_a proton, Bindfit analysis of the titration data (see ESI,† Table S1) determined 1 : 1 stoichiometric host-guest apparent association constant values for Br^- and I^- of 779 M^{-1} and 1752 M^{-1} , respectively, indicating that co-bound secondary ammonium crown ether pseudorotaxane complexation enhances I^- binding capability, and by stark contrast attenuates the strength of Br^- binding. Tentatively, this may be a consequence of competitive **DBA**⁺ cation-bromide ion-pairing, which appears to be more significant than **DBA**⁺ cation-iodide ion-pair association in the mixed organic solvent medium.‡

In conclusion, a novel XB 3,5-bis-iodotriazole-pyridine receptor functionalised with secondary ammonium-dibenzo[24]crown-8 [2]catenane motifs (**1**(PF_6)₂), was prepared in high yield *via* a post-synthetic MIM procedure. The kinetically inert nature of the mechanically interlocked ammonium cations facilitated XB-anion recognition in competitive aqueous-organic solvent mixtures of up to 20% $\text{D}_2\text{O}/d_6$ -acetone with iodide. Importantly, **1**(PF_6)₂ displayed superior strong and selective anion binding affinity in comparison to labile sodium cation complexed bis-benzo[15]crown-5 XB and HB triazole-pyridine heteroditopic receptor analogues. These observations highlight the potential of exploiting secondary ammonium cation MIM crown ether encapsulation for augmenting anion recognition in competitive aqueous media.

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Conflicts of interest

There are no conflicts to declare.

References

‡ Quantitative binding data could not be determined from Bindfit analysis of the TBACl titration isotherms.

- Q. He, G. I. Vargas-Zúñiga, S. H. Kim, S. K. Kim and J. L. Sessler, *Chem. Rev.*, 2019, **119**, 9753–9835.
- S. K. Kim and J. L. Sessler, *Chem. Soc. Rev.*, 2010, **39**, 3784–3809.
- A. J. McConnell, A. Docker and P. D. Beer, *ChemPlusChem*, 2020, **85**, 1824–1841.
- J. M. Mahoney, A. M. Beatty and B. D. Smith, *Inorg. Chem.*, 2004, **43**, 7617–7621.
- Q. He, G. M. Peters, V. M. Lynch and J. L. Sessler, *Angew. Chem., Int. Ed.*, 2017, **56**, 13396–13400.
- M. Li, B. Hua and F. Huang, *Org. Chem. Front.*, 2021, **8**, 3675–3680.
- A. J. McConnell and P. D. Beer, *Angew. Chem., Int. Ed.*, 2012, **51**, 5052–5061.
- B. Qiao, A. Sengupta, Y. Liu, K. P. McDonald, M. Pink, J. R. Anderson, K. Raghavachari and A. H. Flood, *J. Am. Chem. Soc.*, 2015, **137**, 9746–9757.
- X.-L. Ni, J. Tahara, S. Rahman, X. Zeng, D. L. Hughes, C. Redshaw and T. Yamato, *Chem. – Asian J.*, 2012, **7**, 519–527.
- M. Zakrzewski, D. Załubiniak and P. Piątek, *Dalton Trans.*, 2018, **47**, 323–330.
- D.-H. Li and B. D. Smith, *J. Org. Chem.*, 2019, **84**, 2808–2816.
- J. Y. C. Lim, T. Bunchuay and P. D. Beer, *Chem. – Eur. J.*, 2017, **23**, 4700–4707.
- T. Bunchuay, A. Docker, A. J. Martinez-Martinez and P. D. Beer, *Angew. Chem., Int. Ed.*, 2019, **58**, 13823–13827.
- T. Bunchuay, K. Boonpalit, A. Docker, A. Ruengsak, J. Tantirungrotechai, M. Sukwattanasinitt, P. Surawatanawong and P. D. Beer, *Chem. Commun.*, 2021, **57**, 11976–11979.
- T. Bunchuay, A. Docker, N. G. White and P. D. Beer, *Polyhedron*, 2021, **209**, 115482.
- T. Bunchuay, A. Docker, U. Eiamprasert, P. Surawatanawong, A. Brown and P. D. Beer, *Angew. Chem., Int. Ed.*, 2020, **59**, 12007–12012.
- P. R. Ashton, P. J. Campbell, P. T. Glink, D. Philp, N. Spencer, J. F. Stoddart, E. J. T. Chrystal, S. Menzer, D. J. Williams and P. A. Tasker, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1865–1869.
- S.-J. Rao, Q. Zhang, J. Mei, X.-H. Ye, C. Gao, Q.-C. Wang, D.-H. Qu and H. Tian, *Chem. Sci.*, 2017, **8**, 6777–6783.
- H. V. Schröder, S. Sobottka, M. Nößler, H. Hupatz, M. Gaedke, B. Sarkar and C. A. Schalley, *Chem. Sci.*, 2017, **8**, 6300–6306.
- G. Gholami, K. Zhu, G. Baggi, E. Schott, X. Zarate and S. J. Loeb, *Chem. Sci.*, 2017, **8**, 7718–7723.
- H. Iwamoto, S. Tafuku, Y. Sato, W. Takizawa, W. Katagiri, E. Tayama, E. Hasegawa, Y. Fukazawa and T. Haino, *Chem. Commun.*, 2016, **52**, 319–322.
- H. Iwamoto, W. Takizawa, K. Itoh, T. Hagiwara, E. Tayama, E. Hasegawa and T. Haino, *J. Org. Chem.*, 2013, **78**, 5205–5217.
- P. R. Aston, P. T. Glink, J. F. Stoddart, P. A. Tasker, A. J. P. White and D. J. Williams, *Chem. – Eur. J.*, 1996, **2**, 729–736.
- H. R. Wessels and H. W. Gibson, *Tetrahedron*, 2016, **72**, 396–399.
- S. T. Nguyen, L. K. Johnson, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1992, **114**, 3974–3975.
- T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29.
- S. W. Robinson and P. D. Beer, *Org. Biomol. Chem.*, 2017, **15**, 153–159.
- M. J. Hynes, *J. Chem. Soc., Dalton Trans.*, 1993, 311–312.
- “BindFit v0.5|Supramolecular,” can be found under <https://app.supramolecular.org/bindfit/>.
- M. J. Power, D. T. J. Morris, I. J. Vitorica-Yrezabal and D. A. Leigh, *J. Am. Chem. Soc.*, 2023, **145**, 8593–8599.

