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Halogen-bond-based cooperative ion-pair recognition by a crown-ether-embedded 5-iodo-1,2,3-triazole†

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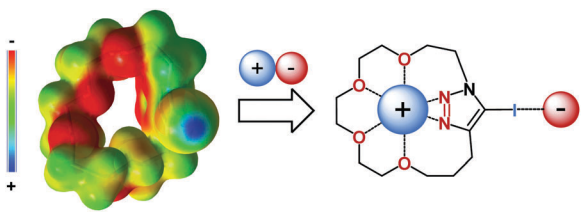
A crown-ether containing the iodo-triazole moiety for simultaneous cation–anion binding through Lewis-basic nitrogen atoms and C–I···I halogen-bond-donating iodine atoms was prepared. The complexation of the heteroditopic receptor was illustrated by X-ray and DFT analysis. The cooperative effect boosting the anion affinity was quantified by $^{1}H/^{13}C$ NMR titration experiments.

The selective recognition and sensing of ions has attracted enormous interest in supramolecular chemistry; however, the design of ditopic receptors capable of the simultaneous binding of both cation and anion is still an underexplored area.[1–3] Nevertheless, the combination of allosteric and electrostatic cooperative effects offer the opportunity to fine tune the affinity as well as selectivity of these ion-pair receptors, which enables a better control over the binding event in potential applications like, *e.g.*, salt extraction/solubilization, membrane transport, or sensing.[3]

While the cation binding sites in these ditopic systems usually take advantage of crown-ether or calixarene derivatives, the anion binding sites typically involve Lewis-acidic sites, electrostatic interactions or, most frequently, use hydrogen bond (HB) interactions.[1] Beside the commonly used urea, amide, or hydroxyl groups, also 1,2,3-triazoles have been employed recently as HB donors for ion-pair receptors[4,5] due to their good accessibility *via* facile and modular copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions as well as due to their CH-acidic and highly polar character.[6,7] Additionally, the Lewis-basic part of this heterocycle offers the opportunity to simultaneously coordinate metal cations and, thus, the possibility for a concurrent recognition of both cation and anion guest species through the triazole motif is given.[5,8,9]

While the usage of HBs in solution has already been well established, the application of halogen bond (XB) interactions in solution has attracted enormous interest over the last years.[10,11] In general, an XB is a highly directional supramolecular interaction between a Lewis-acidic region of a covalently bound halogen (σ-hole)[12] and a Lewis base. When compared to HB, the XB features a higher preference for linearity as well as a higher bond strength,[13] which constitutes the basis for applications of XBs in selective anion detection,[14–16] organocatalysis,[17,18] and anion-templated construction of interlocked structures.[19] Nevertheless, their application in the field of ion-pair recognition is very sparse,[20,21] which might be due to a combination of synthetic challenges and experimental complexities associated with the simultaneous as well as reliable quantification of different binding affinities.

In this communication, we report a macrocyclic ion-pair receptor comprising an iodo-triazole moiety for XB-based anion recognition and a Lewis-basic cavity consisting of a triethylene glycol chain and the nitrogen atoms of the triazole motif for cation binding. The heteroditopic character of the receptor is demonstrated by the calculated electrostatic potential surface (Scheme 1 and Fig. S51, ESI†). Accordingly, a possible ion-pair



Scheme 1 Calculated molecular electrostatic potential surface (red: 0.00 to blue: 0.15) mapped on total density (isovalue 0.01) for the studied ion pair system (left); schematic representation of ion pair recognition by an iodo-triazole containing crown-ether. Red color indicates Lewis-basic regions, blue color Lewis-acidic regions (right).

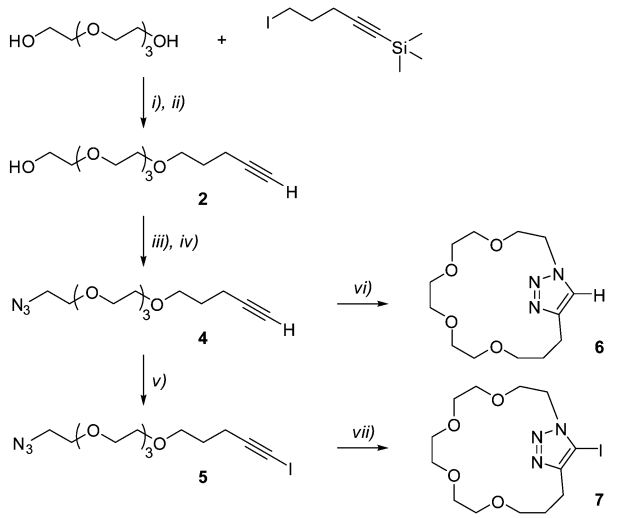
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† Electronic supplementary information (ESI) available: Experimental details, crystal structures, NMR spectra as well as detailed explanations towards NMR binding studies are included. See DOI: 10.1039/c6cc09749a

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Scheme 2 (i) NaH, THF, 0 °C, 30% (**1**); (ii) TBAF, THF/MeOH (2 : 3), room temperature (rt), 99% (**2**); (iii) TosCl, DMAP, Et_3N, CH_2Cl_2, 0 °C, 86% (**3**); (iv) NaN_3, DMSO, rt, 89% (**4**); (v) NIS, $AgNO_3$, acetone, rt, 87% (**5**); (vi) $CuSO_4$, NaAsc., $EtOH/H_2O/CH_2Cl_2$ (2 : 1 : 1), 50 °C, 74% (**6**); (vii) CuI, TBTA, THF, 40 °C, 75% (**7**).

binding mode that simultaneously employs the iodo-triazole's function as a Lewis base and as XB donor is illustrated in Scheme 1. The flexibility of the macrocyclic backbone should enable an adaption for the size of the cation, while the monodentate interaction simplifies the analysis of the binding affinity.

The HB- and XB-donating crown-ether-based macrocycles **6** and **7**, respectively, were accessible by taking advantage of highly efficient CuAAC-type reactions. For this purpose, unsymmetrically substituted triethylene glycols equipped with an azide as well as an alkyne (**4**)/iodo-alkyne (**5**) function were synthesised (Scheme 2). Subsequently, the fundamental synthetic challenge of forming well-defined monomeric macrocycles instead of larger macrocycles or linear oligomers was achieved using pseudo-high-dilution-conditions.[22] Hence, a solution of the linear precursor (**4** or **5**) was added dropwise to a heated solution containing the catalyst system ($CuSO_4$/NaAsc. for **4** or CuI/TBTA for **5**) required to initiate the intramolecular cyclization. Indeed, owing to the high efficiency of the cyclization reaction, the desired products were obtained in good yields and were characterized by NMR spectroscopy, mass spectrometry, and, ultimately, single-crystal X-ray diffraction (Fig. 1).

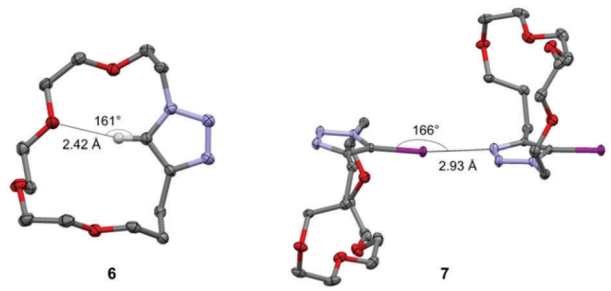


Fig. 1 Single crystal X-ray structures of **6** (left, with intramolecular HB) and **7** (right, with intermolecular XB) (thermal ellipsoids at 50% probability level, hydrogen atoms and solvent molecules are omitted for clarity).

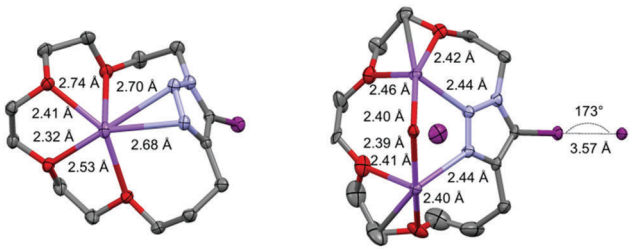


Fig. 2 Single crystal X-ray structure of **7** interacting with Na^+ forming a 1 : 1 complex (left) as well as the structure of **7** interacting with NaI forming a 1 : 2 complex (right); (sodium added as $NaBPh_4$, thermal ellipsoids at 50% probability level, hydrogen atoms, BPh_4^- counter ions, and solvent molecules are omitted for clarity).

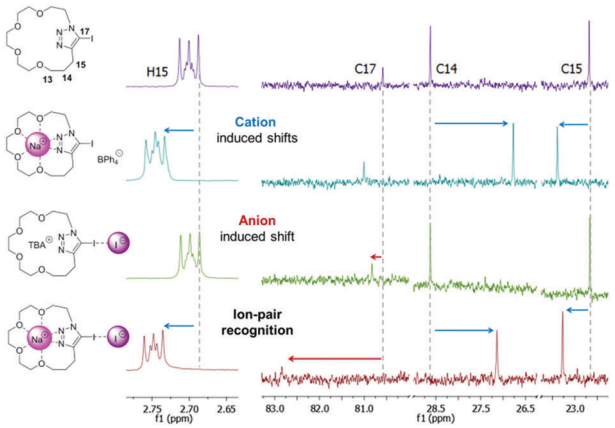
The participation of the Lewis-basic nitrogen atoms of the iodo-triazole moiety in the cation complexation was confirmed by single-crystal X-ray diffraction of the macrocycles **6** and **7** interacting with sodium and a non-coordinating anion (see Fig. 2 for **7** and Fig. S48 for **6**, ESI†).[23] The expected simultaneous interaction of the four oxygen atoms and the two triazole nitrogen atoms with the cation was observed. Nonetheless, sodium is apparently not an ideal guest for the binding cavity, which is indicated by several observations: (1) the $Na^+\cdots O$ distances in the 1 : 1 complex range from 2.32 Å to 2.74 Å indicating a slightly strained binding pocket and (2) depending on the added amount of sodium salt, the stoichiometry can adapt to a 1 : 1 as well as a 1 : 2 complex.

Nevertheless, the capability of the iodo-triazole moiety to coordinate simultaneously cationic and anionic guests was proven by the molecular structure of **7** interacting with sodium iodide in a 1 : 2 complex (Fig. 2). In this case, the nitrogen atoms still contribute towards the cation binding while the anion is complexed through the formation of a nearly linear (173°) XB, which is significantly shorter than the sum of the van der Waals radii ($d(I\cdots I)$ = 3.96 Å).[24] Additionally, both iodides are stabilized by HBs formed between the anion and bridging water molecules (Fig. S50C, ESI†). The close contact distances between Na^+ and I^- range from 4.6 Å to 5.1 Å, which falls between the $Na^+\cdots I^-$ contact ion pair distance (3.2 Å)[4] and the completely host-separated ion pair distance (5.6 Å)[20] observed for other sodium iodide complexes with organic receptor molecules.

After this proof of principle, the cooperative effect of the cation complexation on the anion-binding affinity was quantified by detailed binding studies in solution. For this purpose, the cation and anion binding of the macrocyclic receptors were investigated by ^1H NMR and ^{13}C NMR spectroscopy (Scheme 3). A mixture of CD_2Cl_2 and CD_3CN (3 : 1) was found to offer good solubility for both the receptor and all titrated salts, in particular sodium iodide (Table 1).

Initially, the individual cation and anion binding affinity of the receptor system was studied by using sodium tetraphenylborate ($NaBPh_4$) and tetra-*n*-butyl ammonium iodide (TBAI), respectively. Here, characteristic sodium- as well as iodide-induced chemical shift migrations in the ^1H NMR and ^{13}C NMR spectra were observed, while their respective bulky, non-coordinating counter

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Scheme 3 Schematic representation of the $^{1}H/^{13}C$ NMR (500/126 MHz, $CD_2Cl_2:CD_3CN$ 3 : 1) of host **7** [1 mM] with 8 eq. of different guests illustrating the chemical shifts used for the calculation of the cation or anion binding affinities.

ions did not show any significant influence on the chemical shifts in a control experiment (Fig. S22, ESI†).[23]

Noteworthy, the analysis of the anion affinity represents a basic experimental challenge in this study owing to a fundamental difference between HB- and XB-based receptors. While the binding analysis of the HB-based systems benefit from mostly large chemical shift migrations of the HB-forming protons, the distance between XB-based anion-binding sites and adjacent hydrogen atoms is often too large to see any significant chemical shift migrations in the ^{1}H NMR spectrum. Consequently, alternatives like *e.g.* UV/Vis, ^{19}F NMR, or ^{13}C NMR analysis have to be used.[25]

In this work, the anion binding could only be exemplified by the ^{13}C NMR chemical shift migration of the quaternary carbon atom (C_{17}) directly connected to the XB-donating iodine atom (Scheme 3). In combination with the very low concentrations of the host solutions ([1 mM]), which were dictated by the limited solubility of sodium iodide in organic solvents (Table S1, ESI†), very long ^{13}C NMR acquisition times and a cryogenic NMR probe were thus required.[23] Moreover, owing to the even worse organosolubility of other salts, *e.g.*, NaBr/NaCl (to study the influence of the basicity of the anion) or KI (to study the influence of the cavity size on the cation affinity), a more comprehensive binding study was prevented. Despite these limitations, the found characteristic cation- and anion-induced chemical shift migrations in the NMR data (Scheme 3) allowed the calculation of sodium- and iodide-binding affinities (K_{Na} and K_I, respectively) applying a 1 : 1 binding model (Table 1).[26]

The comparatively weak cation-binding affinity of the macrocycle ($K_{Na} < 10^3\ M^{-1}$ compared to $K_{Na} > 10^4\ M^{-1}$ for optimized crown-ether systems)[27] is in line with the non-ideal geometry of the cavity for the sodium ion as concluded from the X-ray analysis (Fig. 2). Furthermore, the binding affinity of **7** towards mere iodide (added as TBA salt) is very weak, which is caused by: (1) the charge-neutrality of the triazole moiety, *i.e.* the absence of charge-assistance; (2) the monodentate interaction; (3) the rather low charge density/basicity of iodide; (4) the absence of cooperative effects through cation complexation. Accordingly, the reliable quantification of the anion affinity was rather challenging; however, comparable monodentate iodo-triazole-based receptors gave very similar results.[28]

Table 1 Overview of the binding constants calculated from NMR titration data for **6** and **7** with different guests (sodium added as $NaBPh_4$ and iodide added as TBAI, measurements at 297 K in a $CD_2Cl_2:CD_3CN$ (3 : 1) solvent mixture)

Host	Guest	NMR	K_{Na} [M^{-1}]	K_I [M^{-1}]
7	Na^+	^{1}H	434 ± 6[a]	—
	I^-	^{13}C	—	4.7 ± 0.4[d]
	NaI	^{1}H	394 ± 14[a]	N/S
		^{13}C	406 ± 60[b]	135 ± 17[d]
6	Na^+	^{1}H	126 ± 6[c]	—
	I^-	^{13}C	—	N/D
	NaI	^{1}H	155 ± 19[c]	N/S
		^{13}C	174 ± 30[b]	N/D

Signal used for the calculation of the corresponding association constant: *a* = H_{15}, *b* = C_{14}, *c* = H_{13}, *d* = C_{17}; N/S = no shift; no anion induced shift observable in the ^{1}H NMR; N/D = not determined, no reliable quantification of K_I due to an insufficiently large chemical shift.

The good comparability between different NMR titration experiments was proven by the coincidence of the K_{Na} values obtained by ^{1}H NMR (K_{Na} = 394 ± 14 M^{-1}) and ^{13}C NMR (K_{Na} = 406 ± 60 M^{-1}) of **7** with NaI. The larger error in the case of the latter is attributed to the fewer data points that were accessible for the fitting process.[23]

Regarding the cooperativity of the ion-pair recognition, the cation-binding affinity calculated by the titration of **7** with $NaBPh_4$ (K_{Na} = 434 ± 6 M^{-1}) revealed nearly the same result as the titration of **7** with NaI (K_{Na} = 394 ± 14 M^{-1}) indicating that the cation binding is clearly dominated by the multidentate coordination within the macrocycle. Potentially, the cation binding of **7** could be enhanced in the presence of iodide due to the additional Coulomb attraction and a cooperative polarization of the 1,2,3-triazole ring; however, as NaI is not expected to be fully solvent-separated in $CD_2Cl_2:CD_3CN$ (3 : 1), the enhanced ion-pair separation in **7** with NaI deteriorates the cooperative effects. In contrast, the presence of the coordinated cation significantly enhanced the anion-binding affinity of **7**. Noteworthy, as the anion recognition only relies on a monodentate XB interaction with the iodo-triazole, cooperativity is still observed in this case. This cooperative effect is ascribed to an additional electrostatic contribution[29] and, in particular, an enhancement of the C–I bond polarization (Fig. S51, ESI†). While the ability to partially separate two ions underlined the strength of the XB interaction, the relatively large ion-pair distance expected for **7** with NaI (Fig. S52, ESI†) also caused a reduction of the electrostatic contribution and, consequently, cooperative effects in the ion-pair recognition are not fully exploited for the presented receptor type.

The expected decrease of the binding affinity by changing from the XB- to the analogous HB-based interaction[13] led to an insufficient chemical-shift migration during the NMR titration and, thus, precluded a reliable quantification of the anion-binding affinity of **6**. Moreover, comparing the cation-binding

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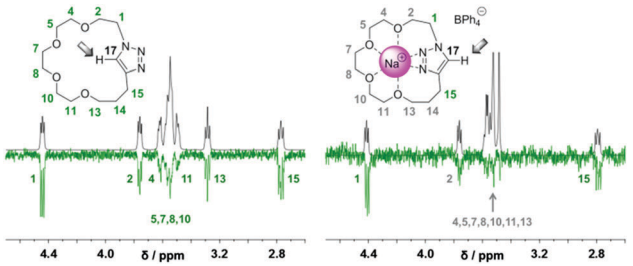


Fig. 3 Schematic representation of the ROE contacts; the selectively excited proton (H_{17}) is marked with a shaded arrow and strong as well as weak contacts are indicated with green and grey numbers, respectively. ^{1}H NMR (black) and selective ROESY spectra (green) for **6** [20 mM] in the absence (left) as well as in the presence of 8 equiv. of $NaBPh_4$ (right) in a CD_2Cl_2 : CD_3CN (3 : 1) solvent mixture.

affinities of the XB- and the HB-based receptor ($K_{Na} = 434 \pm 6\ M^{-1}$ for **7** and $K_{Na} = 126 \pm 6\ M^{-1}$ for **6**, respectively), also a significantly decreased K_{Na} was observed for the latter. This lowered cation-binding affinity was attributed to a possible intramolecular HB formation, which was also observed for the solid-state structures (Fig. 1) and would cause an interference with the cation complexation of the crown ether. To prove this assumption, selective ROESY experiments of **6** in a CD_2Cl_2 : CD_3CN (3 : 1) solvent mixture were performed (Fig. 3).[23] After selective excitation of the triazole proton (H_{17}) in the free macrocycle **6**, strong ROE signals of all protons indicated a freely rotatable triazole moiety and, thus, also a possible formation of an intramolecular HB between H_{17} and oxygen atoms of the crown ether. In contrast, upon addition of $NaBPh_4$ (Fig. 3 and Fig. S46, ESI†), the ROE signals of all protons located at the cation-binding site decreased (Table S2, ESI†).[23] Consequently, the possibility of an intramolecular HB formation is lowered as the triazole moiety is involved in the complexation of the cation within the macrocycle. Conversely, the intramolecular HB lowers the cation affinity of **6**. While this behavior cannot be studied for **7**, the size of the macrocycle's binding pocket is simply too small to establish an analogous intramolecular XB, which is in line with the intermolecular XB observed in the solid state (Fig. 1).

In conclusion, well-defined macrocycles capable of HB (**6**) and XB (**7**) interactions were synthesised using highly efficient CuAAC-type reactions under pseudo-high-dilution-conditions. Subsequently, the capability of a crown-ether-embedded 5-iodo-1,2,3-triazole to coordinate simultaneously cation and anion guests was proven by solid-state analysis and supported by quantum chemical calculations. Subsequently, detailed ^{1}H and ^{13}C NMR titration experiments in solution were performed with sodium iodide as representative ion pair to quantify the cooperative effect of the cation complexation on the anion-binding affinity. For this purpose, several challenges had to be overcome first, namely (1) the low organosolubility of sodium iodide and, thus, the very low concentrations of the host solutions; (2) low anion-binding affinities; (3) comparatively weak cation-binding affinity of the macrocycle due to the non-ideal fit of the sodium with the cation cavity; (4) interference of an intramolecular HB with the cation-binding site in case of **6**. Nonetheless, a consistent and reliable analysis of the binding affinities as well as the determination of the cooperative effect was successfully demonstrated for the presented 5-iodo-1,2,3-triazole-derived model system. Considering both, the already observed promising cooperative effect of the simultaneous metal coordination on the XB-based anion recognition by the iodo-triazole and the potential to further improve the cation-binding cavity using highly efficient CuAAC-type reactions, more powerful ion-pair receptors can be designed building on this fundamental study.

Notes and references

1 S. K. Kim and J. L. Sessler, *Chem. Soc. Rev.*, 2010, **39**, 3784.
2 P. D. Beer and M. J. Langton, *Macrocyclic and Supramolecular Chemistry*, 2016, , DOI: 10.1002/9781119053859.ch3.
3 A. J. McConnell and P. D. Beer, *Angew. Chem., Int. Ed.*, 2012, **51**, 5052.
4 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.
5 S. C. Picot, B. R. Mullaney and P. D. Beer, *Chem. – Eur. J.*, 2012, **18**, 6230.
6 B. Schulze and U. S. Schubert, *Chem. Soc. Rev.*, 2014, **43**, 2522.
7 Y. Hua and A. H. Flood, *Chem. Soc. Rev.*, 2010, **39**, 1262.
8 H. Tomiyasu, N. Shigyo, X.-L. Ni, X. Zeng, C. Redshaw and T. Yamato, *Tetrahedron*, 2014, **70**, 7893.
9 M. A. D. C. González, F. Otón, R. A. Orenes, A. Espinosa, A. Tárraga and P. Molina, *Organometallics*, 2014, **33**, 2837.
10 G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimägi, G. Resnati and G. Terraneo, *Chem. Rev.*, 2016, **116**, 2478.
11 L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney and P. D. Beer, *Chem. Rev.*, 2015, **115**, 7118.
12 M. H. Kolář and P. Hobza, *Chem. Rev.*, 2016, **116**, 5155.
13 R. Tepper, B. Schulze, M. Jäger, C. Friebe, D. H. Scharf, H. Görls and U. S. Schubert, *J. Org. Chem.*, 2015, **80**, 3139.
14 T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667.
15 M. Erdelyi, *Chem. Soc. Rev.*, 2012, **41**, 3547.
16 R. Tepper, B. Schulze, H. Görls, P. Bellstedt, M. Jäger and U. S. Schubert, *Org. Lett.*, 2015, **17**, 5740.
17 D. Bulfield and S. M. Huber, *Chem. – Eur. J.*, 2016, **22**, 14434.
18 Y. Zhao, Y. Cotelle, N. Sakai and S. Matile, *J. Am. Chem. Soc.*, 2016, **138**, 4270.
19 A. Brown and P. D. Beer, *Chem. Commun.*, 2016, **52**, 8645.
20 A. Mele, P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *J. Am. Chem. Soc.*, 2005, **127**, 14972.
21 A. Vargas Jentzsch, D. Emery, J. Mareda, P. Metrangolo, G. Resnati and S. Matile, *Angew. Chem., Int. Ed.*, 2011, **50**, 11675.
22 S. Binauld, C. J. Hawker, E. Fleury and E. Drockenmuller, *Angew. Chem., Int. Ed.*, 2009, **48**, 6654.
23 See ESI† for more detailed explanations.
24 A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
25 P. Thordarson, *Chem. Soc. Rev.*, 2011, **40**, 1305.
26 Although a possible formation of a 1 : 2 complex was also indicated by the solid state structures, the 1 : 1 binding model was chosen since it should describe the complexation in solution most properly (see Fig. S27 and S28 (ESI†) for detailed explanations).
27 Z. Wang, S. H. Chang and T. J. Kang, *Spectrochim. Acta, Part A*, 2008, **70**, 313.
28 L. Maugeri, J. Asencio-Hernandez, T. Lebl, D. B. Cordes, A. Slawin, M.-A. Delsuc and D. Philp, *Chem. Sci.*, 2016, **7**, 6422.
29 Calculated $Na^+ \cdots I^-$ distance of 5.6 Å (Fig. S52, ESI†) is below the expectable Bjerrum-length (see for example R. Moritz, G. Zardalidis, H.-J. Butt, M. Wagner, K. Müllen and G. Floudas, *Macromolecules*, 2014, **47**, 191) of ions in an unpolar solvent mixture.