LETTER

Improved complexation between dibenzo-24-crown-8 derivatives and dibenzylammonium salts by ion-pair recognition†

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The introduction of a urea-based anion binding site onto dibenzo-24-crown-8 can enhance the complexation between dibenzo-24-crown-8 derivatives and dibenzylammonium cation by ion-pair recognition.

Threaded structures, based on host–guest chemistry, have been attractive to scientists not only because of their topological importance, but also due to their many potential applications.[1] The preparation efficiency of these threaded structures is strongly dependent on the complexation strength, reflected by the association constant (K_a), between the host and guest. Scientists have devoted much effort into raising the K_a values by both developing new recognition systems and derivating the known ones.[2] For the latter, a classic example is the ion-pair recognition using heteroditopic receptors.[3] It is well known that the binding of inorganic salts by synthetic receptors in organic solvents, especially in low-dielectric-constant solvents, is weak because the target salts exist as associated ion-pairs which can hinder the single-ion recognition process.[4] However, the binding can be improved by using heteroditopic receptors that can simultaneously bind both cations and anions. Since Reetz et al. reported one of the first successful examples of heteroditopic receptors for associated ion pairs in 1991,[5] much work has been done in this area for its many applications, such as solubilization, extraction, and membrane transport.[3,6]

Crown ethers, including dibenzo-24-crown-8 (DB24C8) **1**, and their derivatives have been widely used in the preparation of threaded structures as hosts for organic salts, such as dialkylammonium salts and paraquat derivatives.[1] The threading of secondary dibenzylammonium salts through the cavity of crown ethers was the genesis of a diverse range of mechanically interlocked threaded structures including molecular machines.[7] Most of the dibenzylammonium cation binding studies have been conducted in organic solvents and have used non-competing counterions. Dibenzylammonium hexafluorophosphate derivatives have been used in many cases for their good solubility and relatively weak ion-pairing in organic solvents. However, the luxury of the non-competing counterions is not always available and organic salts usually exist as

their Cl^- or Br^- salts, known as tight ion-pairs, in many real-life situations.[8] Therefore, the study of the complexation of tight ion-paired salts is important for understanding the operation mechanisms of some natural supramolecular systems. However, up to now only little has been done to investigate this field.[9] It is well known that urea derivatives can be used as anion receptors. In order to improve the preparation efficiencies of threaded structures based on the well-known DB24C8/dibenzylammonium salt recognition motif,[1] we are interested in improving complexation between the DB24C8 derivatives and dibenzylammonium salts. Herein, we report the synthesis of some DB24C8 derivative heteroditopic hosts **2** (Scheme 1) containing urea-based anion binding sites and their ion-pair recognition for dibenzylammonium salts **3** with different anions (Scheme 2). We will demonstrate not only that the complexation between DB24C8 derivatives and dibenzylammonium salts can be improved but also that the improvement can be tuned by controlling the binding strength of anions through the introduction of electron-withdrawing substituents onto the urea-based anion binding site.

The key starting material, **4**, was prepared in excellent yield according to the literature.[10a] The intermediates **5** and **6** were synthesized according to a similar method reported by Gibson et al.[10b] The reaction of **4** with 1.2 equiv. of potassium phthalimidate afforded **5** (Scheme 1). The amine **6** was obtained by hydrazinolysis of **5** (Scheme 1). The heteroditopic hosts **2** were obtained in good yield by the reaction of **6** with corresponding phenyl isocyanates in $CHCl_3$ (Scheme 1). Dibenzylammonium salts **3** were prepared as described in the literature.[9]

The ^1H NMR spectrum (Fig. 1b) of an equimolar solution of **2a** and **3b** in $CDCl_3$–CD_3CN (3 : 2, v : v) shows a slow-exchange complexation on the ^1H NMR time scale which is similar to the complexation between **1** and **3a**.[1b] The new peak at 4.61 ppm is attributed to the complexed benzylic methylene protons H_{11c}. The multiplet at 3.41–3.47 ppm corresponds to the complexed γ-OCH_2 protons of **2a**. The complexation between **2a** and **3b** has 1 : 1 stoichiometry as determined by integration of these peaks. After complexation, the peak at 5.40 ppm corresponding to protons H_9 of **2a** was split into two different signals at 5.56 ppm and 6.44 ppm, respectively (Fig. 1b and c). The same phenomenon was observed for protons H_{10} of **2a** (Fig. 1b and c). This should result from the coexistence of a fast-exchange complexation between the urea moiety and the trifluoroacetate anion and a slow-exchange complexation between the dibenzo-24-crown-8 cavity and the dibenzylammonium cation.

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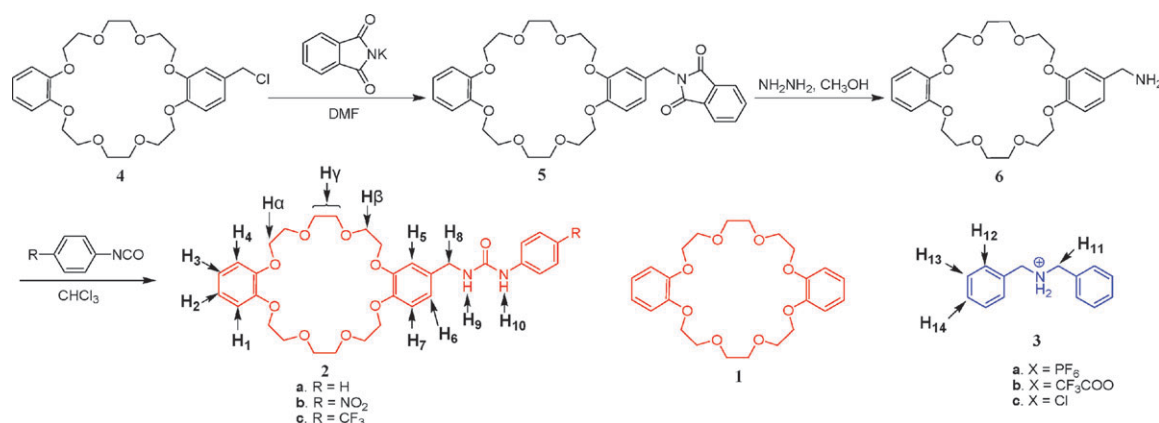
Scheme 1 Synthesis of dibenzo-24-crown-8 derivatives **2** and structures of chemicals used in this study.
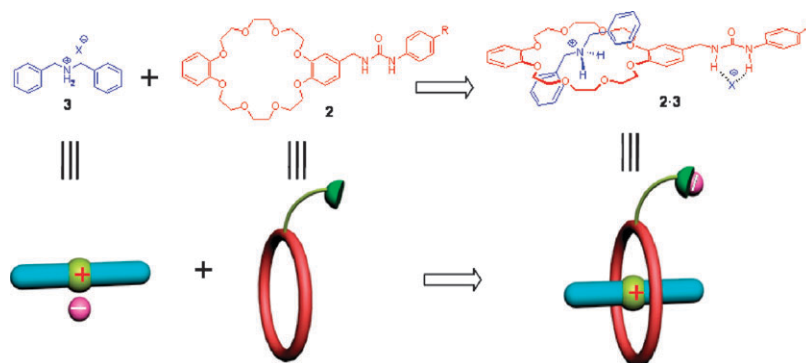
Scheme 2 Cartoon representation of the ion-pair recognition between host **2** and guest **3**.
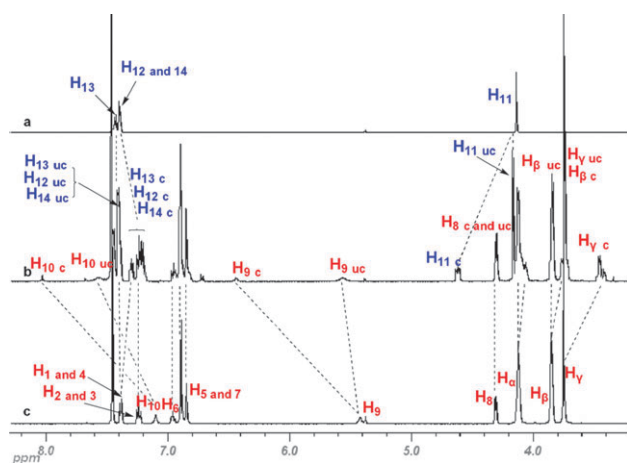

Fig. 1 Partial ^{1}H NMR spectra (500 MHz, 3 : 2 CDCl$_3$–CD$_3$CN, 22 °C) of 2.00 mM **3b** (a), 2.00 mM **2a** and **3b** (b), and 2.00 mM **2a** (c). Complexed and uncomplexed species are denoted by "c" and "uc", respectively.

The ESI$^+$-MS mass spectrum of an equimolar acetonitrile solution of **2a** and **3b** confirmed the 1 : 1 stoichiometry of the complexation between the dibenzo-24-crown-8 cavity and dibenzylammonium cation by a mass fragment at m/z 794.3 (57%) for [**2a·3b** − CF$_3$COO]$^+$. The ESI$^-$-MS mass spectrum of the same solution gave a single mass fragment at 709.1 (100%) corresponding to the complex [**2a** + CF$_3$COO]$^-$,

confirming the 1 : 1 stoichiometry of the complexation between **2a** and the trifluoroacetate anion.

As shown in Fig. 1b, c, 2b and c, chemical shift changes after the complexation between **2a** and **3c** in CDCl$_3$–CD$_3$CN (3 : 2, v : v) are similar to those seen after the complexation between **2a** and **3b**. The benzylic methylene protons H$_{11}$ of **3c** moved downfield to 4.62 ppm (Fig. 2a and b), almost at the same place as in the case for **2a** and **3b** (Fig. 1a and b). The γ-OCH$_2$ ethyleneoxy protons of **2a** also have the same chemical shift at 3.41–3.47 ppm (Fig. 2b), the same as in the case for **2a** and **3b** (Fig. 1b) upon complexation. The peak corresponding to protons H$_9$ of **2a** in the equimolar solution were also split into two different signals at 5.58 ppm and 6.37 ppm, respectively (Fig. 2b and c). The same phenomenon was observed for the protons H$_{10}$ of **2a** in the same equimolar solution. This difference should also result from the coexistence of a fast-exchange complexation between the urea moiety and the chloride anion and a slow-exchange complexation between the dibenzo-24-crown-8 cavity and the dibenzylammonium cation. The ESI$^+$-MS mass spectrum of an equimolar acetonitrile solution of **2a** and **3c** confirmed the 1 : 1 stoichiometry of the complexation between the dibenzo-24-crown-8 cavity and dibenzylammonium cation by a mass fragment at m/z 794.4 (100%) for [**2a·3c** − Cl]$^+$. The ESI$^-$-MS mass spectrum of the same solution gave mass fragments at 631.3 (100%) corresponding to [**2a** + Cl]$^-$ and at 1227.5 (10%) for [**2a** + **2a** + Cl]$^-$. Therefore, the complexation between **2a** and the chloride anion
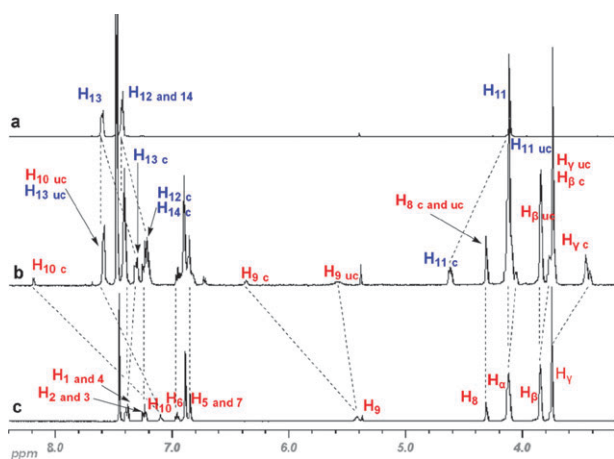
Fig. 2 Partial ^{1}H NMR spectra (500 MHz, 3 : 2 CDCl$_3$–CD$_3$CN, 22 °C) of 2.00 mM **3c** (a), 2.00 mM **2a** and **3c** (b), and 2.00 mM **2a** (c). Complexed and uncomplexed species are denoted by "c" and "uc", respectively.

has the 1 : 1 and 2 : 1 stoichiometries simultaneously in the gaseous state. This is because the binding of the spherical chloride anion by the urea moiety can adopt both two-coordinate complex (Fig. 3a) and four-coordinate tetrahedral geometry (Fig. 3b),[11] while the binding of the trifluoroacetate anion takes only the Y-shaped geometry (Fig. 3c).[11,12]

It is well known that the introduction of electron-withdrawing groups to the urea group can enhance the acidity of the urea protons and promote its binding ability to anions.[13] In order to investigate how electron-withdrawing substituents on the phenyl ring of the host can influence the cation binding properties, nitro and trifluoromethyl groups were introduced onto the *para* site of the phenyl ring (Scheme 1). The K_a values were determined by a single-point method.[14] All of the hosts **1**, **2a**, **2b** and **2c** exhibited rather low K_a values (column 1 in Table 1) for guest **3b** in acetonitrile, which is probably because **3b** exists as a tight ion-pair and the complexation between the urea moiety and anions is weak in this polar organic solvent. However, due to the urea moiety providing a weak binding for anions in acetonitrile, the heteroditopic hosts **2** have a little higher K_a values for **3b** than the simple cation-binding crown ether host **1**. In order to increase the binding strength between the urea unit and anions, we changed to a less polar solvent system, a mixture of acetonitrile and chloroform (2 : 3, v : v). In this solvent system, **2a·3a** exhibits a lower K_a value than **1·3a** (column 2 in Table 1). This can be explained by the very weak binding of the urea group to the PF$_6^-$ anion and the
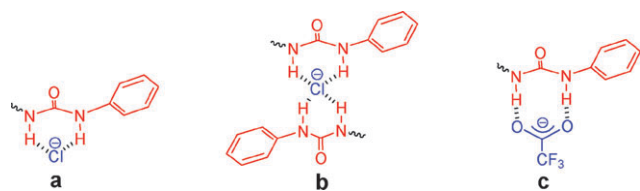

Fig. 3 Illustrations of the binding models of anion complexation by the urea portion: (a) two-coordinate complex for the chloride anion, (b) four-coordinate tetrahedral geometry for the chloride anion, and (c) Y-shaped geometry for the trifluoroacetate anion.

Table 1 Association constants (K_a/M^{-1}) for the 1 : 1 complexes between hosts (2.00 mM) **1** and **2** and guests (2.00 mM) **3** in different solvents at 22 °C

	3b[a]	**3a**[b]	**3b**[b]	**3c**[b]
1	59	1687	193	63
2a	78	1589	388	266
2b	102	1200	413	385
2c	176	1377	487	475

[a] Determined in CD$_3$CN. [b] Determined in CD$_3$CN–CDCl$_3$ (2 : 3).

electron-withdrawing nature of the urea group, which can reduce the electron density of the oxygen atoms of the crown ether cavity and the strength of hydrogen bonds between the ether oxygen atoms of the DB24C8 cavity and the acidic hydrogens of the dibenzylammonium cation.[15] Because of the introduction of electron-withdrawing nitro and trifluoromethyl groups, **2b·3a** and **2c·3a** have even lower K_a values than **2a·3a** (column 2 in Table 1).

In the contrast, the K_a value of **2a·3b** is higher, about one fold, than the K_a value of **1·3b** in the mixture of acetonitrile and chloroform (2 : 3, v : v) (column 3 in Table 1). This is different from the case of **3a**. It means that by the introduction of an anion binding site onto DB24C8, the complexation between the DB24C8 derivatives and dibenzylammonium salts can be improved by ion-pair recognition. Both **2b·3b** and **2c·3b** exhibited even higher K_a values than **2a·3b** (column 3 in Table 1). This can be attributed to the increase in the binding strength of the urea unit to the trifluoroacetate anion resulting from the introduction of the electron-withdrawing nitro or trifluoromethyl group onto the urea unit.

Since **3c** is a tighter ion-pair than **3b**,[9] **3c**-based complexes have lower K_a values than **3b**-based ones (columns 3 and 4 in Table 1). However, the improvement in the K_a value caused by ion-pair recognition is more obvious when **3c** instead of **3b** is used as the guest. An increase, up to more than 6-fold, in the K_a value was observed for **2c·3c** compared with **1·3c**.

In conclusion, we have demonstrated that the complexation between DB24C8 derivatives and dibenzylammonium salts could be improved by ion-pair recognition after a urea unit was introduced. The improvement can be tuned by controlling the binding strength of anions through the introduction of electron-withdrawing substituents onto the anion binding site. Currently, we are using these heteroditopic hosts in the efficient preparation of mechanically interlocked threaded structures and exploring how to improve complexation of other organic guests by ion-pair recognition.

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