Received: 20 April 2021 | Revised: 3 June 2021 | Accepted: 7 June 2021

DOI: 10.1002/jhet.4329

ARTICLE

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Construction of unsymmetrical bis-urea macrocyclic host for neutral molecule and chloride-ion binding

Biprajit Paul | **Ayan Mukherjee** | **Deepak Bhuyan** | **Samit Guha**

Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata, India

Correspondence
Samit Guha, Department of Chemistry, Organic Chemistry Section, Jadavpur University, Kolkata 700032, India.
Email: samitfsu@gmail.com; samit.guha@jadavpuruniversity.in

Funding information
Science and Engineering Research Board, Grant/Award Number: ECR/2017/001405

Abstract

Construction of synthetic macrocyclic host that can bind with neutral molecules and anions has potential applications in supramolecular chemistry. Herein, we have designed and synthesized blue light emitting an unsymmetrical neutral bis-urea macrocyclic host. This macrocycle can bind with neutral DMF molecule (1:1) as well as Cl^- ion (1:1) through noncovalent interactions. X-Ray crystal structure, ^1H NMR titrations with Job's Plot, HRMS with isotropic distribution pattern, FT-IR, and density functional theory analysis revealed the binding of bis-urea macrocyclic host with the guest molecule.

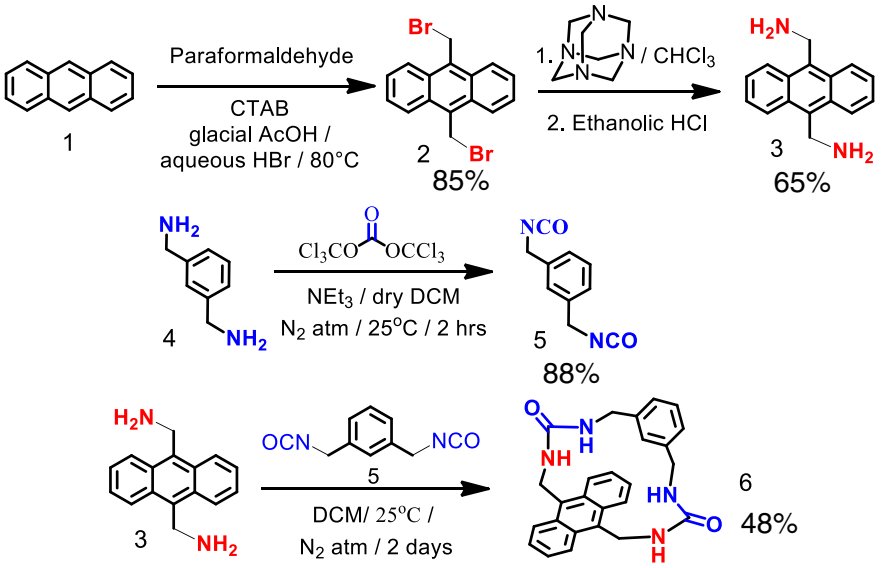
1 | INTRODUCTION

Neutral molecules and ions are indispensible for life and have a wide range of chemical, biological, environmental, and industrial applications [1]. Design and construction of synthetic receptors for neutral molecules and anions have attracted great attention in supramolecular chemistry [2]. Misregulation of Cl^- transport is associated with nephrolithiasis (kidney stones), myotonia, Bartter's syndrome, and cystic fibrosis [3]. Synthetic Cl^- receptors and transporters could be an encouraging strategy in 'channel replacement therapy' for the treatment of cystic fibrosis [4]. The majority of the receptors depend on noncovalent interactions such as hydrogen bonding, hydrophobic effect, π–π interactions, anion–π interactions, van der Waals forces, and electrostatic interactions for binding of ions or neutral molecules. The preorganized macrocyclic receptors such as crown ethers [5], calix[n]arenes [6], calix[n]pyrroles [7], cucurbit[n]urils [8], and cyclodextrins [9] are well known in the literature. Cyclic peptide-based receptors are also used for ion recognition and transportation [10]. Incorporation of appropriate hydrogen bond donors, such as amide or specifically urea groups, helps to form a stringently defined supramolecular architecture [11]. The urea NH groups are respectable hydrogen bond donors, and the urea O is an excellent hydrogen bond acceptor. The directionality of the hydrogen bonds to construct host–guest compound also depends on the geometry of the receptor. Shimizu's group has seminal contributions for the development of symmetrical bis-urea macrocycles that self-assemble to form columnar structures [12]. Jiang and co-workers have also reported the synthesis and host–guest chemistry of urea macrocycles [13]. Herein, we have designed and constructed blue light emitting unsymmetrical neutral macrocyclic receptor with urea functionality. The unsymmetrical bis-urea macrocyclic receptor is capable of binding with neutral dimethylformamide (DMF) molecule and Cl^- ion.

2 | RESULTS AND DISCUSSION

2.1 | Synthesis

The bis-urea macrocycle (**6**) is synthesized by multistep reactions using commercially available low-cost starting materials, for example, anthracene (**1**) and *m*-xylylenediamine (**4**) outlined in Scheme 1 with reasonable yield (48%). At first, 9,10-bis(aminomethyl)anthracene (**3**, yield 65%) is synthesized by an efficient way from anthracene via 9,10-bis(bromomethyl)anthracene (**2**, yield 85%). The *m*-xylylene diisocyanate (**5**, yield 88%) is prepared from easily available *m*-xylylenediamine (**4**) and solid triphosgene (safer equivalent of phosgene gas). The macrocycle **6** is constructed by



SCHEME 1 Synthesis of unsymmetrical bis-urea macrocycle

simple drop wise mixing of the two compounds **3** (diamine) and **5** (diisocyanate) in ice cold condition over a period of 6 h using high-dilution technique in DCM followed by the continuation of the reaction (monitored by TLC) for two days at room temperature to favor macrocyclization over polymerization (see Data S1). The macrocycle **6** is purified and characterized by ^{1}H NMR, ^{13}C NMR, high resolution mass spectrometry (HRMS), FT-IR, X-ray powder diffraction, and X-Ray crystallography (Figures S5–S11).

2.2 | Photophysical characterization

The photophysical property of the bis-urea macrocycle is examined in DMSO (Figure S8). The absorption spectra of the macrocycle displayed characteristic peaks at 343 nm, 360 nm, 380 nm, and 401 nm in DMSO and it is due to anthracene chromophore (Figure S8a). The macrocycle exhibited large molar extinction coefficient of $1.5 \times 10^4\ M^{-1}\ cm^{-1}$. The bis-urea macrocycle contains a blue light emitting anthracene chromophore (Figure S8b). The fluorescence emission of the bis-urea macrocycle is observed at 408 nm, 430 nm, 454 nm, and 486 nm in DMSO ($\lambda_{ex} = 365$ nm) (Figure S8b).

2.3 | Single-crystal X-Ray diffraction study

Light yellow monoclinic crystals with space group $P\ 2_1/c$ of the bis-urea macrocycle suitable for X-ray diffraction studies are obtained from DMF solvent by slow vapor diffusion of hexane (Table S1). Tables of hydrogen bonds, data collection, and refinement details can be found in the Data S1. The bis-urea macrocycle crystallizes with one DMF molecule in the asymmetric unit. The cocrystallized guest–solvent DMF in the solid state is associated with the macrocycle (1:1) through strong hydrogen bonding between the NH group of the urea macrocycle and >C═O group of the DMF with the H-bond length 2.07 Å and N—H—C bond angle 160° along with two weak hydrogen bonding in between CH of the macrocycle and >C═O group of the DMF and CH of the DMF and urea >C═O group of the macrocycle (Figure 1(A), Figure S10 and Table S2). Although *trans-trans* urea bond is more favorable, however, in our case, urea groups adopt *trans–cis* conformations that are thought to be less favorable energetically. In compound **6**, the urea groups are oriented approximately perpendicular to the plane of the macrocycle and the urea carbonyl groups pointing in opposite directions to each other presumably to minimize dipole interactions. Bis-urea macrocycles are further self-assembled through intermolecular hydrogen bonding and offset π–π stacking of anthracene residues (Figure 1(B) and Figure S10). The crystals of the macrocycle **6** are grounded to a powder and studied by X-ray powder diffraction (XRPD). XRPD of the microcrystalline powders indicate that they are single phase and retain structural similarity to the single crystals (Figure S11).

2.4 | Anion-binding experiments

We have focused on the anion-binding capability of the neutral bis-urea macrocyclic receptor. We have established the anion-binding capability of the host by HRMS, FT-IR, NMR titration, and theoretical calculation. From anion-binding assay, it is clear that the neutral macrocycle can bind selectively with the spherical Cl^- among the other halide anions Br^- and I^-.

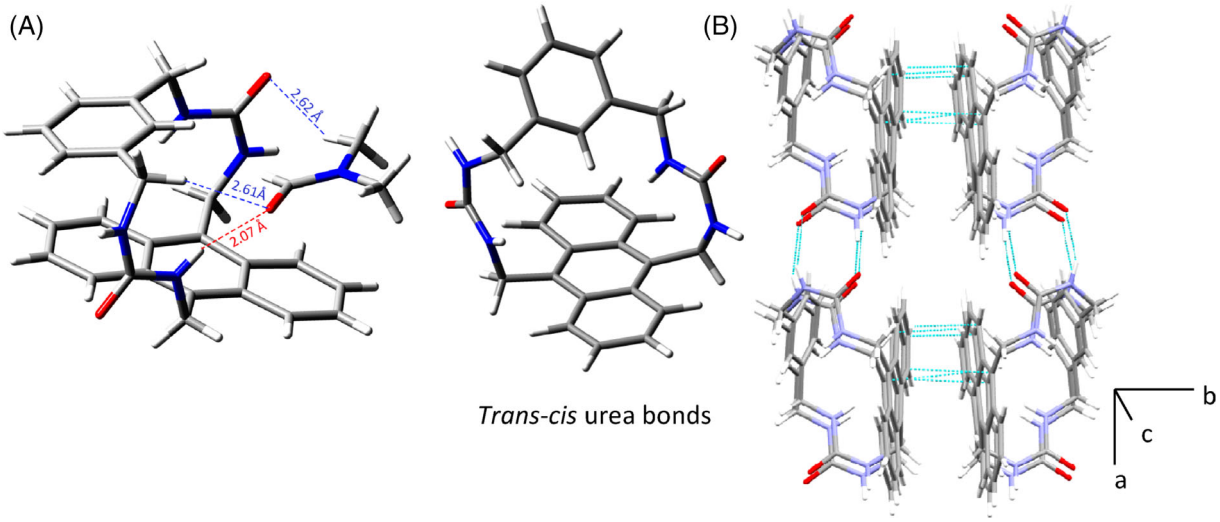
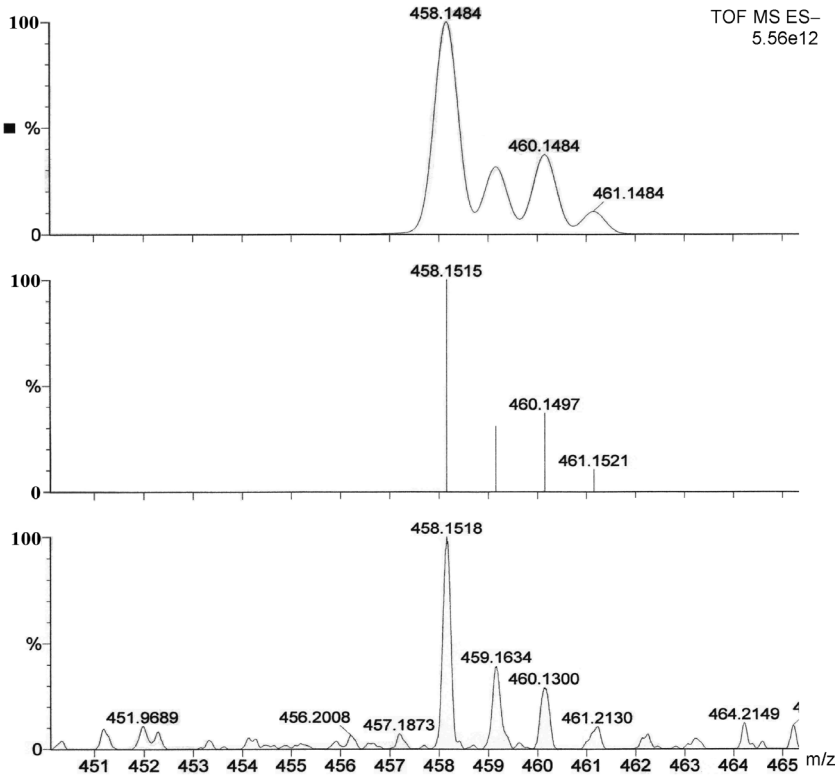


FIGURE 1 (A) X-ray crystal structure of bis-urea macrocycle cocrystallized with DMF solvent. *Trans-cis* urea bonds are oriented almost perpendicular to the plane of the macrocycle and the urea carbonyl functionalities pointing in opposite directions to each other. (B) Packing diagram of bis-urea macrocycle. It is self-assembled through intermolecular H-bonding and offset π–π stacking of anthracene residues

FIGURE 2 HRMS (ESI, −ve mode) of bis-urea macrocycle:Cl^- (1:1) with isotropic distribution pattern



2.5 | High-resolution ESI-MS (−ve mode)

The direct experimental evidence for Cl^- binding of the macrocycle in the gas phase is obtained from the HRMS (ESI-MS, −ve mode) study. HRMS study with isotropic distribution pattern confirms the 1:1 binding of the macrocyclic host with Cl^- in negative (−ve) mode (Figure 2). The neutral bis-urea macrocyclic host captures the Cl^- ion selectively, and the overall negatively charged 1:1 host–guest complex gives a peak at $m/z = 458.1484$ (Figure 2).

2.6 | FT-IR study

The characteristic stretching frequency of the N—H bond of the bis-urea macrocycle 6 is observed at

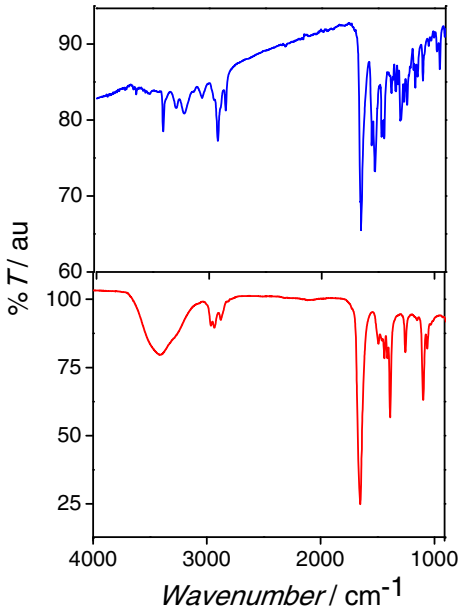


FIGURE 3 FT-IR spectra of the host bis-urea macrocycle (blue) and bis-urea macrocycle·Cl^- (red) host–guest complex

3408 cm^{-1}. This macrocycle shows a broad IR absorption for N—H stretching in the presence of Cl^- (Figure 3). This indicates host–guest complexation through hydrogen bonding interaction between the urea NH and Cl^-.

2.7 | NMR titration

^1H NMR titration is performed to find the interaction between the bis-urea macrocyclic host and the anionic guest Cl^-. Commercially available solid tetrabutyl ammonium chloride (TBACl) is used as the source of Cl^-. For the experiment, initially a stock solution of the macrocycle and a stock solution of the guest (TBACl) are prepared in polar aprotic DMSO-d_6 solvent. Then ten NMR samples are prepared separately by varying the amount of TBACl from very lower to extremely higher; however, the concentration of the macrocycle and total solvent volume remains constant. The experiment was performed at room temperature. In case of bis-urea macrocycle, the chemical shift values of urea NH appeared at δ 5.99 ppm signifying the absence of intramolecular NH···O═C hydrogen bonding. The —NH protons shifted gradually toward downfield region with the increasing concentration of the guest (Figure 4(A), Figures S12 and S13). This downfield shift indicates the hydrogen bonding interaction between the —NH groups of host and Cl^- guest. Initially, the two types of —NH protons, which are merged together and appeared as a broad coagulated signal at 5.99 ppm in the NMR spectrum of the macrocyclic host, got separated on addition of TBACl. The two NH group has shifted to downfield from 5.99 ppm to almost 6.20 ppm in the presence of Cl^-. DMSO-d_6 does not solvate Cl^- well, however, strongly interacts with the macrocyclic urea N—Hs through hydrogen bond. Cl^- binding to these urea N—Hs, therefore, requires displacement (at least partial) of DMSO-d_6 molecules. The Job's Plot indicates 1:1 binding stoichiometry between the macrocycle and Cl^- (Figure 4(B), Table S3, Figure S14) which is also in good agreement with the HRMS data. Moreover, no significant ^1H NMR chemical shift changes of bis-urea macrocycle are perceived in presence of excess of Br^- and I^- ions which indicates selectivity of Cl^- among the other halide anions. It could be attributed that the hydrogen-bonding interactions of neutral macrocycle to Cl^- is stronger than those to Br^- and I^-. Moreover, size of spherical Cl^- is smaller than those to Br^- and I^-.

2.8 | Theoretical calculation

Theoretical calculation is used to determine the binding energy. Gaussian-09 program is applied to optimize the structure of the macrocycle using B3LYP functional and 6-31+G** basis set. The density functional theory (DFT) optimized structure of the macrocyclic host (Figure S15) adopted C_1 symmetry with the energy value $E_1 = -1374.4206$ a.u. Electrostatic potential (ESP) map of this optimized structure indicates the electron-deficient regions of the macrocycle where the anion can be bound (Figure S15). We have also optimized the structure of the host–guest complex using the same program and same basis set. B3LYP/6-31+G** energy minimization shows that all the urea N-Hs of the macrocycle point toward the Cl^- and serve as an extremely preorganized receptor able to bind Cl^- through four N—H···Cl^- hydrogen bonds with N—H···Cl^- distances of 2.40 Å and 2.54 Å (Table 1, Figure 5). In the macrocycle·Cl^- (1:1) host–guest complex, urea groups adopt *trans–trans* conformations as expected thermodynamically unlike the macrocycle. Moreover, in macrocycle·Cl^- (1:1) complex the urea groups are oriented almost perpendicular to the plane of the macrocycle and urea carbonyl groups pointing in the same directions to each other. The energy value $E_2 = -1835.1522$ a.u is obtained from the DFT energy optimized structure of the host–guest complex. The ESP map of the host–guest complex is depicted in Figure S16. From this theoretical calculation, the binding energy is calculated to $\Delta E = -460.7316$ a.u. ($\Delta E = E_2 - E_1$). Here the highly negative value of ΔE confirms the association of the Cl^- with the macrocycle.

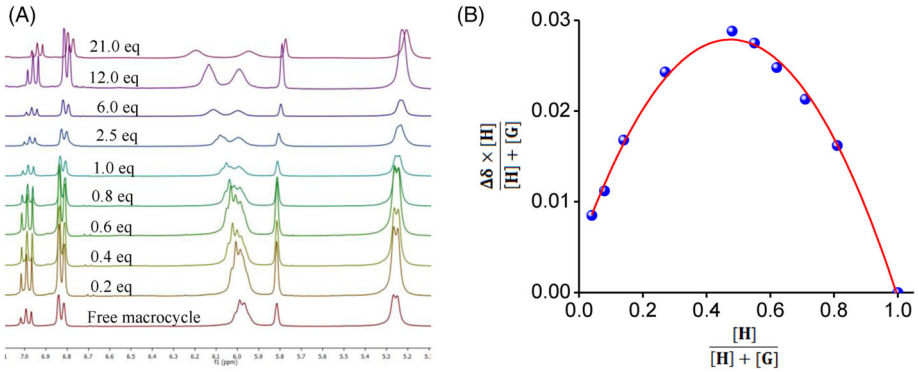


FIGURE 4 (A) Partial ^{1}H NMR stacking spectra (300 MHz, DMSO-d_6, 298 K) of macrocycle titrated with TBACl in DMSO-d_6 solution. (B) Job's plot supports the 1: 1 binding stoichiometry between the host bis-urea macrocycle and guest Cl^{-}

TABLE 1 Hydrogen bond parameters of bis-urea macrocycle·Cl^{-} (1:1) host–guest complex

D-H···A	H···A (Å)	D···A (Å)	D-H···A (deg)
N(4)-H (5)···Cl^{-}(56)	2.5	3.5	157
N(6)-H(57)···Cl^{-}(56)	2.4	3.4	157
N(3)-H(55)···Cl^{-}(56)	2.5	3.5	157
N(7)-H (8)···Cl^{-}(56)	2.4	3.4	157

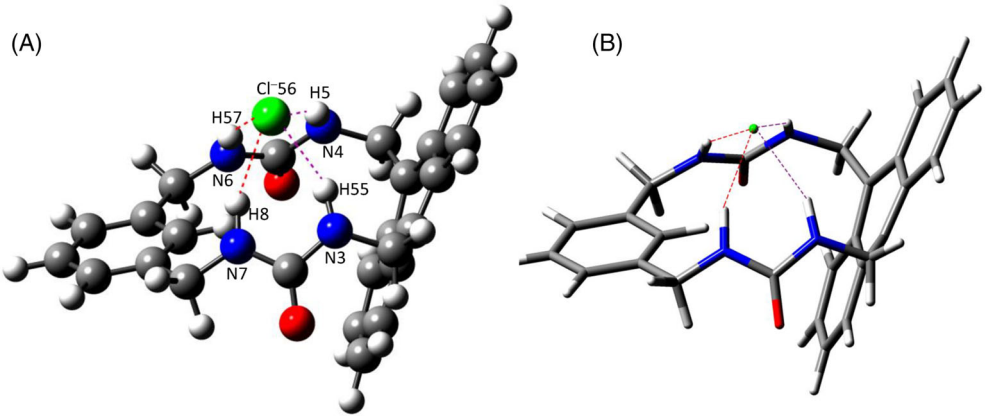


FIGURE 5 B3LYP/6-31 +G** energy minimized structure of the bis-urea macrocycle·Cl^{-} (1:1). (A) Ball and stick model. (B) Capped stick model

3 | CONCLUSIONS

In summary, we report the design, synthesis, and self-assembly of an unsymmetrical bis-urea macrocycle receptor and its structure is determined by single-crystal X-ray diffraction. This macrocycle can bind Cl^{-} anion and neutral DMF molecule through noncovalent interactions. Developments of synthetic neutral macrocyclic receptor that imitate the job of natural protein carriers have therapeutic potential. Chloride binding and transportation have potential future application in the treatment of both cystic fibrosis and cancer.

ACKNOWLEDGMENTS

This work is supported by grants from the DST-SERB, Govt. of India (file no. ECR/2017/001405).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Samit Guha https://orcid.org/0000-0001-6643-9882

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How to cite this article: B. Paul, A. Mukherjee, D. Bhuyan, S. Guha, *J Heterocyclic Chem* **2021**, 1. https://doi.org/10.1002/jhet.4329