*Journal of the Korean Magnetic Resonance Society* **2022**, *26*, 40-45
DOI 10.6564/JKMRS.2022.26.4.040

# Synthesis of a small molecular cage consisting of three aminomethyl pyrroles and its selective fluoride recognition

**Nam Jung Heo, Hye Jin Han, Jaewon Choi,* and Sung Kuk Kim***

Department of Chemistry and Research Institute of Natural Science, Gyeongsang National University, Jinju 52828, Republic of Korea

*Received Oct 24, 2022; Accepted Nov 8, 2022*

**Abstract** A small cage-like molecule (**2**) composed of three aminomethyl pyrroles and two hexa-substituted benzenes has been prepared by reduction of its iminopyrrole analogue (**1**) using $NaBH_4$. It was revealed by $^1H$ NMR spectroscopic analyses that cage molecule **2** strongly binds the fluoride anion in polar DMSO-$d_6$ relative to $CDCl_3$. Compared to that of compound **1**, the lowered affinity of **2** for the fluoride anion is attributable to its increased electron density resulting from the production of thesecondary amine groups.

**Keywords** molecular cage, anion recognition, fluoride, affinity, selectivity

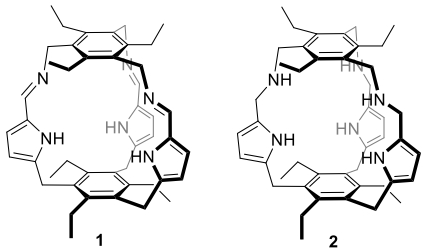
## Introduction

Cage-like molecules have recently attracted increasing attention because of their distinct applications in fields as diverse as gas adsorption and separation, recognition of ions and neutral molecules, and catalysis for organic reactions.[1-4] The inside of a cage molecule provides a microenvironment different from its exterior protecting encapsulated guest species from solvents or other reactive reagents including oxygen ($O_2$) and carbon dioxide ($CO_2$) molecules.[2] Therefore, a cage molecule can act as an effective receptor for unstable chemical species keeping them intact under ambient conditions.[2] The reactions most commonly employed for the construction of a cage molecule include an amide coupling reaction of an amine-functionalized reactant with a carboxylic acid or acid chloride derivative and an imine-forming condensation reaction between an amine and an aldehyde or ketone analogue.[1-4] A cage molecule has a highly-preorganized three-dimensional cavity suitable for hosting various guest chemical species and its cavity size can be readily tuned by syntheses using various available subcomponents with reactive sites as starting materials.[1-4] Moreover, the cage molecule has been utilized as a host for various anions with different geometry.[5-8] For instance, compared with cage **1**, the molecular cage having additional amide likers between the pyrrole subunits and the benzene capping unit was reported to bind relatively large oxoanions such as dihydrogen phosphate, hydrogen pyrophosphate, sulfate, and hydrogen sulfate with high affinity.[9] By contrast, cage **1** with a relatively small cavity was found to complex the fluoride anion with exclusive selectivity and high affinity.[10]

The fluoride anion is a special but challenging target for selective recognition because it not only plays critical roles in a range of environmental, biological, and chemical processes but is also associated with public health and medicine.[11-16] In spite of numerous efforts devoted to the development of anion receptors selective for the fluoride anion,[17-21] few anion

* Address correspondence to: **Sung Kuk Kim & Jaewon Choi**, Department of Chemistry and Research Institute of Natural Science, Gyeongsang National University, Jinju 52828, Republic of Korea, Tel: 82-55-772-1494; E-mail: sungkukkim@gnu.ac.kr (S. Kim), Tel: 82-55-772-1481; E-mail: cjw0910@gnu.ac.kr (J. Choi)

receptors have been reported to have exclusive selectivity for this anion.[20] This is attributable to the small size and high charge density, and relatively large hydrophilicity of the fluoride anion as well as its large Lewis basicity. To attain high selectivity for the fluoride anion, the size matching of the receptor cavity with the fluoride anion and preorganization of anion binding motifs are of critical importance.[17-21] Also, the structural rigidity and geometry of the receptor should be considered for achieving better fluoride selectivity.[22,23] In this vein, a small cage molecule could be efficiently used for selective recognition of the fluoride anion.[10] Here, we report the synthesis and unique fluoride binding property of a small cage molecule (**2**) with three aminomethyl pyrroles.



**1** **2**

## Experimental Methods

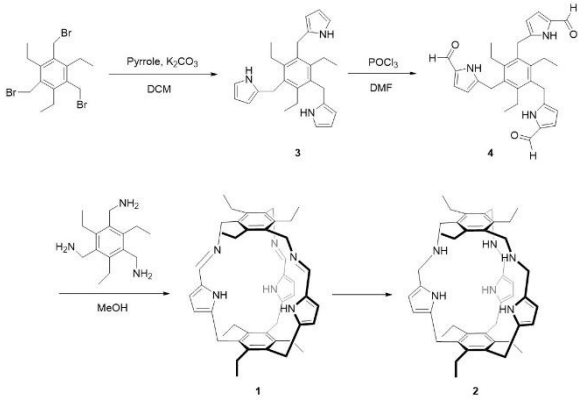
Solvents and reagents used for syntheses were purchased from Aldrich, TCI, or Alfa Aesar and used without further purification. Compounds **1**, **3**, and **4** were prepared following a literature procedure.[10] $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker Advance-300 MHz instrument. TMS (tetramethylsilane) was used as an internal reference for NMR spectroscopy and the NMR solvents were purchased from either Cambridge Isotope Laboratories or Aldrich. Fast atom bombardment mass spectra (FABMS) were recorded on a JMS-700 (JEOL) spectrometer. TLC analyses were performed using Sorbent Technologies silica gel (200 mm) sheets. Column chromatography was carried out on Sorbent silica gel 60 (40–63 mm).

**Synthesis of cage 1.** To a solution of methanol/chloroform (3/1) containing compound **1** (400 mg, 0.59 mmol) was slowly added $NaBH_4$ (156 mg, 4.12 mmol) in an ice bath. The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. To the resulting solid, $CH_2Cl_2$ (75mL) was added and the organic layer was separated off and washed three times with 100 mL of water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed by evaporation in vacuo to afford the desired compound (**2**) as an off-white solid (371 mg, 0.54 mmol, 92%). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 3H), 6.01 (t, J = 2.9 Hz, 3H), 5.91 (t, J = 2.9 Hz, 3H), 3.99 (s, 6H), 3.87 (s, 6H), 3.58 (s, 6H), 2.78 (q, J = 7.5 Hz, 6H), 2.53 (q, J = 7.4 Hz, 6H), 1.09 (q, J = 7.6 Hz, 18H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 142.0, 141.8, 133.8, 132.6, 130.5, 128.0, 107.3, 104.9, 77.3, 46.1, 45.5, 27.8, 23.3, 22.8, 17.0, 14.7. HRMS (FAB) m/z 685.4952 $[M + H]^+$ calc. for $C_{45}H_{61}N_6$, found 685.4986.

## Results and Discussion

The synthetic scheme for cage **2** is depicted in Scheme 1. Compounds **1**, **3**, and **4** were prepared by following a literature procedure.[10] The desired cage molecule (**2**) was synthesized by reducing the imine groups of cage **1** using $NaBH_4$ in methanol/chloroform (3/1). Cage **2** with three secondary amines and pyrroles was completely characterized by means of standard spectroscopic techniques including $^{1}$H and $^{13}$C NMR spectroscopy and high-resolution mass spectrometry (HRMS).

**Scheme 1**. Synthesis of receptor **2**.



In the $^1$H NMR spectrum of cage **2** recorded in $CDCl_3$, a distinct singlet proton signal for the pyrrole NHs appeared at δ = 8.31 ppm while the β-pyrrole proton signals emerged at high field region relative to those of cage **1** (Fig. 1). By contrast, after reduction of cage **1**, its imine CH proton signal ($H_b$) displayed at δ = 7.70 ppm completely disappeared and a new single signal corresponding to the methylene CHs ($H_b$) was exhibited at δ = 3.87 ppm in $^1$H NMR spectrum of cage **2** (Fig. 1(b)). These findings verify that the imine groups of cage **1** was successfully converted to aminomethyl groups giving rise to cage **2**. This interpretation was further confirmed by high-resolution mass spectrum showing a peak at m/z = 685.4986 corresponding to [**2** + $H^+$]. In contrast to what was seen in the $^1$H NMR spectrum of cage **2** recorded in $CDCl_3$, complicated and uninterpretable proton signals were shown in DMSO-$d_6$ (Fig. 1(c)). This finding can be rationalized by the presumption that polar DMSO solvent molecules interact with cage **2** via hydrogen bonds slowing conformational motion of the cage on the NMR time scale. Accordingly, seemingly equivalent protons are placed in different magnetic environments in DMSO producing different chemical shifts of the proton signals.

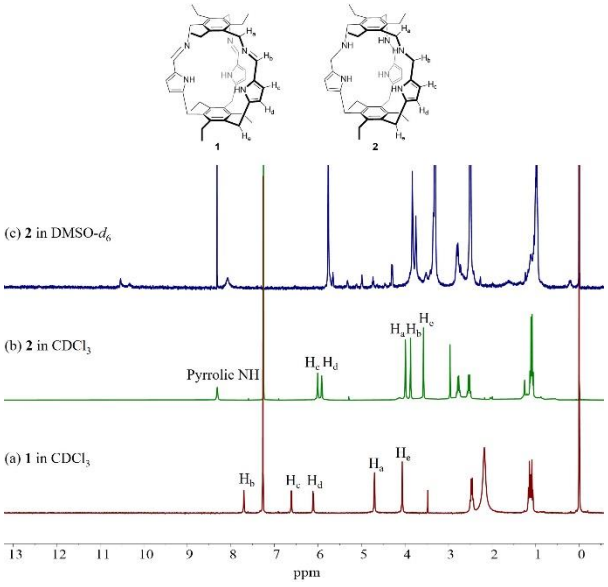



**Figure 1.** Partial $^1$H NMR spectra of (a) **1** (3 mM) in $CDCl_3$, (b) **2** (3 mM) in $CDCl_3$, and (c) **2** (3 mM) in DMSO-$d_6$.

The ability of cage **2** to bind certain anions was evaluated via $^1$H NMR spectroscopy using $CDCl_3$ as the solvent. The pyrrole NH proton resonance appearing in lower field region relative to pyrrole-containing macrocycles such as calix[4]pyrroles suggests that the pyrrole NHs form intramolecular or intermolecular hydrogen bonds with the amine N atoms (Fig. 2(a)). This presumption is further supported by the absence of the amine NH proton signal in $^1$H NMR spectrum. Upon exposure of cage **2** to various anions in excess such as $F^-$, $Cl^-$, $Br^-$, $I^-$, $SO_4^{2-}$, $H_2PO_4^-$ and $HP_2O_7^{3-}$ (as their respective tetrabutylammonium ($TBA^+$) salts), only the fluoride anion produced a change in $^1$H NMR spectrum ascribable to anion binding (Fig. 2). Specifically, in the presence of an excess quantity of the fluoride anion, the pyrrolic NH proton signal disappeared while the β-pyrrolic CH proton signal ($H_d$) was appreciably upfield-shifted with the methylene CH proton resonances ($H_a$ and $H_b$) undergoing slight chemical shift changes (Fig. 2(a)). This observance suggests that cage **2** binds fluoride with high selectivity over other test anions.

To quantify the affinity of cage **2** for the fluoride anion, a $^1$H NMR spectroscopic titration experiment was carried out in $CDCl_3$. When cage **2** was treated with incremental amounts of the fluoride anion, the pyrrole NH proton resonance continued to be slightly downfield shifted with gradually reduced intensity in $^1$H NMR spectra while other proton signals remained unchanged (Fig. 3). These spectral changes proposed that cage **2** weakly binds the fluoride anion with low affinity ($K_a$ < 10 $M^{-1}$), which stands in sharp contrast to what was seen with the iminopyrrole cage (**1**) having an association constant ($K_a$) of > $10^4$ $M^{-1}$.[10] The significantly small association constant of cage **2** relative to that of cage **1** is presumably ascribed to the enhanced electron density of **2** having three electron-rich secondary amine groups as well as presumed intermolecular or intermolecular hydrogen bonds between the pyrrole NHs and the amine groups.

Totally different changes in $^1$H NMR spectra took place when the solvent of $CDCl_3$ was replaced with DMSO-$d_6$ for a fluoride titration experiment. For instance, when cage **2** was subjected to titration with the fluoride anion in DMSO-$d_6$, new proton signals

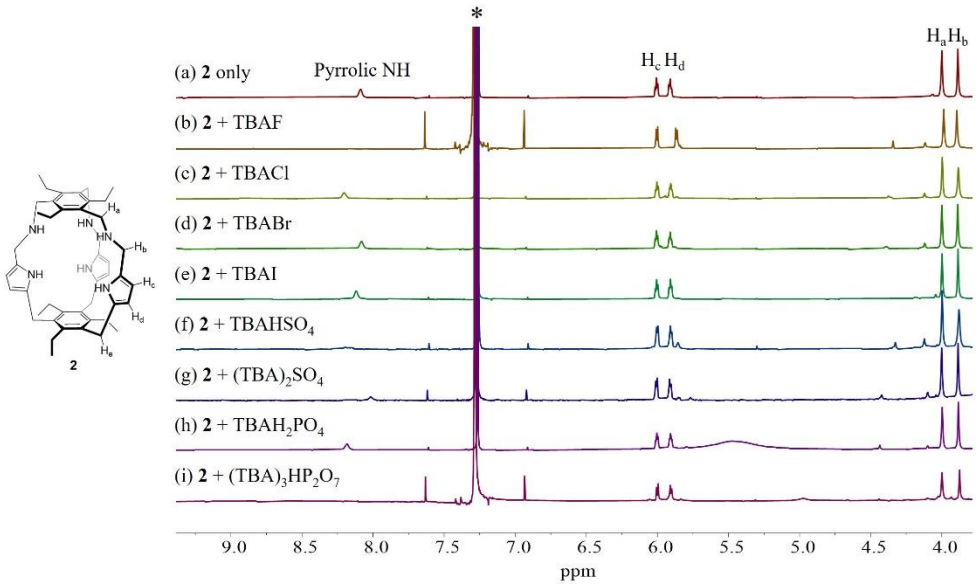



**Figure 2.** Partial $^1$H NMR spectra of (a) **2** (3 mM) only, (b) **2** + excess TBAF (tetrabutylammonium fluoride), (c) **2** + excess TBACl (tetrabutylammonium chloride), (d) **2** + excess TBABr (tetrabutylammonium bromide), (e) **2** + excess TBAI (tetrabutylammonium iodide), (f) **2** + excess $TBAHSO_4$ (tetrabutylammonium hydrogen sulfate), (g) **2** + excess $(TBA)_2SO_4$ (bis(tetrabutylammonium) sulfate), (h) **2** + excess $TBAH_2PO_4$ (tetrabutylammonium dihydrogen phosphate), and (i) **2** + excess $(TBA)_3HP_2O_7$ (tris-tetrabutylammonium hydrogenpyrophosphate) in $CDCl_3$.

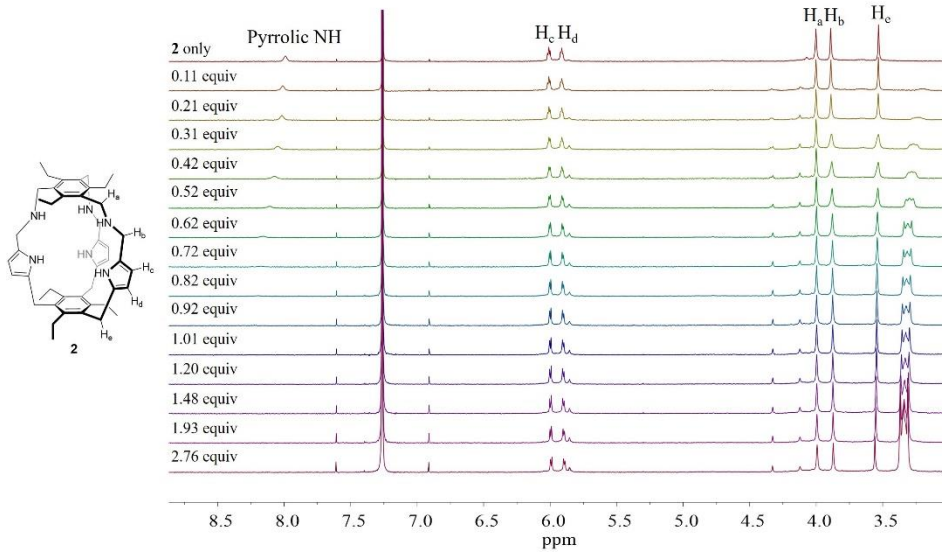



**Figure 3.** $^1$H NMR spectra recorded during the titration of **2** (3 mM) with tetrabutylammonium fluoride (TBAF) in $CDCl_3$.

corresponding to the pyrrole NHs and amine NHs appeared noticeably downfield-shifted displaying peaks at δ = 12.80 ppm and δ = 10.87 ppm, respectively, while the original proton signals of cage **2** in its anion-free form gradually disappeared before saturation was attained upon addition of 1.75 fluoride

equiv (Fig. 4). These spectral changes were taken as evidence for cage **2** forming a strong complex with the fluoride anion in this solvent system. This suggestion was further supported by the observance that the singlet pyrrole NH proton signals is split into a doublet (J = 54.0 Hz) by $^{1}$H-$^{19}$F spin coupling between the pyrrole NH protons and the bound fluoride anion (Fig. 4).[10] Well-defined $^{1}$H NMR spectra were observed in the presence of > 1.75 equiv of the fluoride anion, which led us to conclude that cage **2** adopts a symmetrical conformation after encapsulating the fluoride anion (Fig. 4). From this $^{1}$H NMR spectral titration, the association constant of cage **2** for the fluoride anion was approximated to be ≈ 1,000 $M^{-1}$ in DMSO-$d_6$.[24] The observed high affinity of cage **2** for the fluoride anion in DMSO-$d_6$ relative to in $CDCl_3$ is presumably due to weakened intermolecular or intramolecular hydrogen bonds of cage **2** in the more polar solvent.

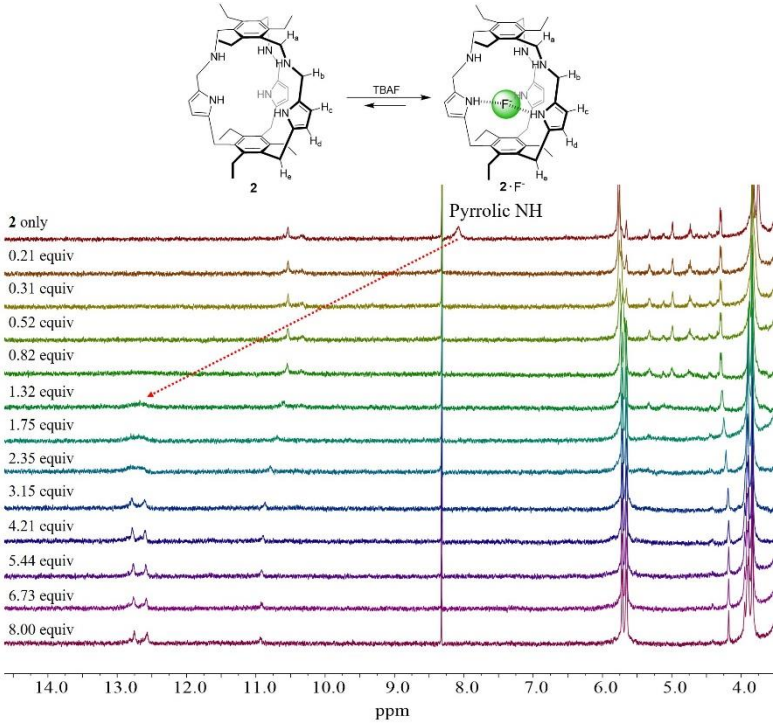



**Figure 4.** $^{1}$H NMR spectra recorded during the titration of **2** (3 mM) with tetrabutylammonium fluoride (TBAF) in DMSO-$d_6$.

In conclusion, a small molecular cage (**2**) with three aminomethyl pyrrole substituents was synthesized by subjecting its iminopyrrole analogue (**1**) to reduction using $NaBH_4$. Cage **2** was found to bind the fluoride anion more efficiently in DMSO-$d_6$ than in $CDCl_3$ because of its diminished intermolecular or intramolecular hydrogen bonds in relatively polar DMSO solvent. By contrast, the reduced affinity of cage **2** for the fluoride anion relative to cage **1** is attributable to the increased electron density in cage **2** by the conversion of the imine groups of **2** to the secondary amine groups.

**Acknowledgements**

This work was supported by the Gyeongsang National University Fund for Professors on Sabbatical Leave, 2022.

**References**

1. G. Montà-González, F. Sancenón, R. Martínez-Máñez, and V. Martí-Centelles, *Chem. Rev.* **122**, 13636 (2022)
2. N. Lopez, D. J. Graham, R. McGuire Jr., G. E. Alliger, Y. Shao-Horn, C. C. Cummins, and D. G. Nocera, *Science* **335**, 450 (2012)
3. S. O. Kang, D. VanderVelde, D. Powell, and K. Bowman-James, *J. Am. Chem. Soc.* **126**, 12272 (2004)
4. Y. Liu, W. Zhao, C.-H. Chen, and A. H. Flood, *Science* **365**, 159 (2019)
5. S. O. Kang, R. A. Begum, and K. Bowman-James, *Angew. Chem., Int. Ed.* **45**, 7882 (2006)
6. S. O. Kang, V. W. Day, and K. Bowman-James, *Inorg. Chem.* **49**, 8629 (2010)
7. S. O. Kang, D. VanderVelde, D. Powell, and K. Bowman-James, *J. Am. Chem. Soc.* **126**, 12272 (2004)
8. S. O. Kang, D. Powell, and K. Bowman-James, *J. Am. Chem. Soc.* **127**, 13478 (2005)
9. J. H. Oh, J. H. Kim, D. S. Kim, H. J. Han, V. M. Lynch, J. L. Sessler, and S. K. Kim, *Org. Lett.* **21**, 4336 (2019)
10. H. J. Han, J. H. Oh, J. L. Sessler, and S. K. Kim, *Chem. Commun.* **55**, 10876 (2019)
11. L. W. Ripa, *J. Publ. Health Dent.* **53**, 17, (1993)
12. M. S. McDonagh, P. F. Whiting, P. M. Wilson, A. J. Sutton, I. Chestnutt, J. Cooper, K. Misso, M. Bradley, E. Treasure, and J. Kleijnen, *Br. Med. J.* **321**, 855 (2000)
13. M. Kleerekoper, *Endocrinol. Metab. Clin. North Am.* **27**, 441 (1998)
14. D. Briancon, *Rev. Rhum.* **64**, 78 (1997)
15. Y. Michigami, Y. Kuroda, K. Ueda, and Y. Yamamoto, *Anal. Chim. Acta.* **274**, 299 (1993)
16. P. Grandjean and P. J. Landrigan, *Lancet.* **368**, 2167 (2006)
17. Y. Zhou, J. F. Zhang, and J. Yoon, *Chem. Rev.* **114**, 5511 (2014)
18. M. Cametti and K. Rissanen, *Chem. Soc. Rev.* **42**, 2016 (2013)
19. Brugnara, F. Topić, K. Rissanen, A. de la Lande, B. Colasson, and O. Reinaud, *Chem. Sci.* **5**, 3897 (2014)
20. S. K. Kim, V. M. Lynch, and J. L. Sessler, *Org. Lett.* **16**, 6128 (2014)
21. J. H. Oh, J. H. Lee, and S. K. Kim, *J. Kor. Magn. Reson. Soc.* **25**, 45 (2021)
22. P. D. Beer and P. A. Gale, *Angew. Chem., Int. Ed.* **40**, 486 (2001)
23. R. Martínez-Máñez and F. Sancenán, *Chem. Rev.* **103**, 4419, (2003)
24. Approximate binding constant from: Connors, K, A. Binding Constants: The Measurementof Molecular Complex Stability; Wiley-Interscience: New York, (1987)