Journal of the Korean Chemical Society
1997, *Vol. 41, No. 3*
Printed in the Republic of Korea

단 신

1-Oxa-4,7,10,13-Tetraazacyclopentadecane 및 그 유도체의 합성

金昌錫 · 金東洹† · 鄭龍淳† · 崔琪泳†† · 李鎔一††† · 洪春杓††††
충북대학교 사범대학 과학교육과
†충북대학교 자연과학대학 화학과
††목원대학교 화학과
†††건양대학교 화학과
††††공주대학교 사범대학 화학교육과
(1996. 10. 14 접수)

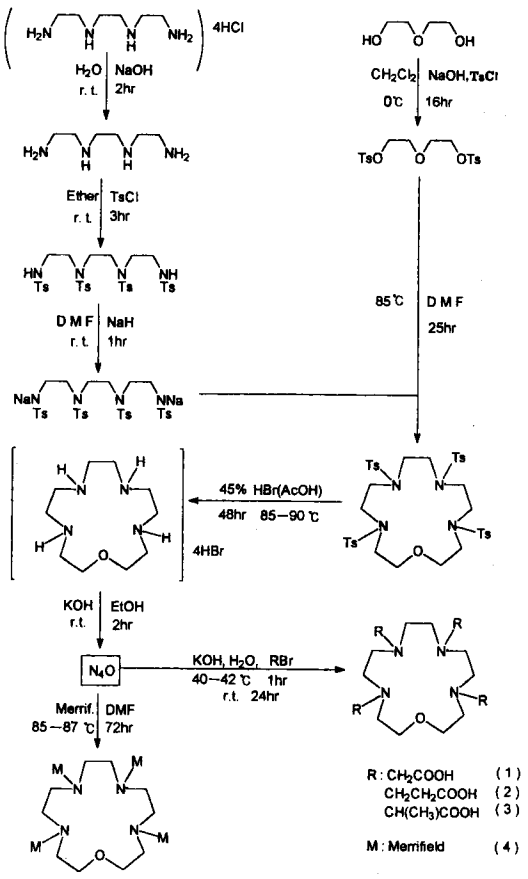
Synthesis of 1-Oxa-4,7,10,13-Tetraazacyclopentadecane and Its Derivatives

Chang Suk Kim, Dong Won Kim†, Yong Soon Chung†, Ki Young Choi††, Yong Ill Lee†††, and Choon Pyo Hong††††
Department of Chemistry Education, Chungbuk National University, Cheongju 361-763, Korea
†Department of Chemistry, Chungbuk National University, Cheongju 361-763, Korea
††Department of Chemistry, Mokwon University, Daejeon 301-729, Korea
†††Department of Chemistry, Gonyang University, Nonsan 320-800, Korea
††††Department of Chemical Education, Kongju National University, Kongju 314-701, Korea
(Received October 14, 1996)

Cyclic polyoxa and polyaza ligands which form stable complexes with a variety of metal ions are of current interest either because of their usefulness in new processes of organic synthesis or as models for the study of certain biological reactions or systems.[1] Especially, polyaza macrocyclic ligands with ionizable functional side groups are primarily of interest because they possess additional characteristics which affect their complex formation, including cavity size, steric factors, conformation, ligand basicity, and rigidity.[2] The effects of cavity size and of conformation on the spectroscopic and magnetic properties of the metal complexes on the kinetics of complex formation and on the thermodynamic stability of the species formed have also been studied by many inorganic chemists.[3~5] Further developments have been devoted to macrocyclic receptors containing both oxygen and nitrogen donor atoms in their frameworks, which can bind more than one transition metal ion.[6~8] Kim *et al.* synthesized the new azacrown containing pyridines as subcycle unit[9] and reported that selectivity tendency of azacrown for metal ions.[10~13] Choi14 reported the macrocyclic azacrown ligand like dioxatriazacyclopentadecane was effective for the separation of lanthanide ions. In the process of our studies on kinetics of transition and lanthanide metal complexes of macrocyclic ligands, we needed to prepare new azacrown ligands. New macrocyclic ligands from 1-oxa-4,7,10,13-tetraazacyclopentadecane were prepared. The synthetic procedures were outlined in *Scheme* 1.

RESULTS AND DISCUSSION

Many of the previous syntheses of the azacrowns have used the reaction of a tosylated amine and diol for ring closure of the tosylated azacrowns, forming the azacrowns by detosylation



Scheme 1.

of the resulting tosylated azacrowns. However, the yield of the detosylation of $N_4O \cdot 4Ts$ was very low under the HBr, 30 wt% solution in acetic acid and the duration of 20 h. While our reaction conditions were used for the preparation of $N_4O \cdot 4HBr$, a large amount of desirable product was formed, and the yield was high. Although there are many procedures published for the syntheses of substituted-azacrowns, we found that it is simpler to prepare these ligand 1, 2 and 3(*Scheme* 1). Aliphatic acid-substituted azacrowns showed the interesting IR and NMR spectral behavior. The N-C stretching absorptions for ligands 1~3 were not distinct in their IR spectra. The carboxyl stretching absorptions for all three compounds appeared at 1710 and 1720 cm^{-1}, respectively. The NMR spectra of methylene protons of azacrown ring appeared downfield splitting into a triplet with the increasing the number of methylene unit of α-position to carboxylic acid for ligand 1 and 2(peaks at 3.66 and 3.73), while for ligand 3 appeared upfield at 3.54. For the aliphatic acid-substituted azacrowns, the methylene protons of aliphatic acid absorptions were at the same 2.9 as ligand 1 and 2. In the TGA thermogram, the degradation of the merrifield peptide resin began at 290 ℃ and ended up at 405 ℃, and T_{max} was 360 ℃. However, the degradation of the ligand 4 began at 303 ℃ and ended up at 469 ℃, and T_{max} was 408 ℃. Ligand 4 was degraded in the higher temperature than merrifield peptide resin.

EXPERIMENTAL

Materials and methods. The compounds obtained from commercial sources were as follows: triethylenetetramine, *p*-toluenesulfonyl chloride, sodium hydride, diethylene glycol, HBr 45 wt% solution in acetic acid, phenol, Dowex 1X8-50 ion exchange resin, from Aldrich Chem. Co. All these materials were used as supplied without further purification. 1-Oxa-4,7,10,13-tetratosyl-4,7,10,13-tetraazacyclopentadecane[$N_4O \cdot 4Ts$] was prepared by previously reported procedure.[1,5,15] 1-Oxa-4,7,10,13-tetraazacyclopentadecane tetrahydrobromide obtained by detosylation of [$N_4O \cdot 4Ts$].[16] The ^1H NMR spectra of products were obtained by using a DPX-300 FT-NMR Spectrometer. Infrared spectra were obtained by a Hitachi 10 Spectrometer. Elemental Analysis was carried out with a FISONS EA-1108 Elemental Analyzer. Thermogravimetric analysis was performed with SDT 2960 Thermal Analyzer.

Synthesis of 1-oxa-4,7,10,13-tetraazacyclopentadecane tetrahydrobromide[$N_4O \cdot 4HBr$]. To 0.913 g(1 mmol) of the $N_4O \cdot 4Ts$, 0.94 g(10 mmol) phenol and 150 mL of hydrogen bromide, 45 wt% solution in acetic acid were added and this mixture was heated at 85-90 ℃ for 48 h. A white precipitate was separated. After cooling at room temperature the white precipitate was collected by fitration, washed with ether and absolute ethyl al-

cohol; yield 68%. ^{1}H NMR(D_2O, δ) 3.68(t, 2H, O-CH_2CH$_2$-N), 3.41(t, 2H, O-CH$_2$CH_2-N), 3.48(s, 2H, N-CH$_2$CH_2-N). IR(KBr pellet, cm^{-1}): 3400 (amine), 1000~1090(C-O-C), 800(CH_2). Anal. Calcd. for $C_{10}H_{28}N_4Br_4O$: C, 22.24; H, 5.23; N. 10.38. Found: C, 22.37; H, 5.12; N, 10.54.

Synthesis of 1-oxa-4,7,10,13-tetraazacyclopentadecane-4,7,10,13-tetraacetic acid 1. 0.25 g(85%, 4 mmol) of ground KOH pellets were added to a suspension of 0.54 g(0.001 mol) of 1-oxa-4,7,10,13-tetraazacyclopentadecane tetrahydrobromide(N_4O·4HBr) and 10 mL of absolute ethanol. This mixture was stirred at room temperature for 2 h. Precipitate KBr was removed by filtration, and the solvents were removed *in vacuo*. The oily residue obtained was dissolved in 5 mL of water. 0.695 g(5 mmol) of bromoacetic acid was dissolved in 10 mL of ice cold water. A solution of 0.66 g(12 mmol) of KOH(85%) in 10 mL of water was added dropwise to form potassium bromoacetate at 2~5 ℃ until the pH of the solution became 12. The [N_4O] and $BrCH_2COOK$ solutions were mixed and heated to 40~42 ℃. The pH of reaction mixture was maintained to 11.5~12.0. The mixture was stirred at 40~42 ℃ for 1 hr and then at room temperature for 24 h. It was neutralized to pH 9.0 with 6 M HCl, and then concentrated to 5 mL. The resulting solution was loaded on a Dowex 1X 8-50 ion exchange resin in the OH form in a 2× 20 cm (*dXh*) column. The column was eluted successively with 100 mL of water, 100 mL of 0.01 M HCl, and 150 mL of 0.1 M HCl. The eluent with pH=3 contained 0.26 g of the pure oily ligand **1**; yield 56%. ^{1}H NMR(D_2O, δ): 3.66(t, 2H, O-CH$_2$CH_2-N), 3.25(t, 2H, O-CH$_2$CH_2-N), 3.46(s, 2H, N-CH$_2$CH_2-N). 2.87(t, 2H, N-CH_2COOH). IR (NaCl, cm^{-1}): 3200~3400(amine), 1720(C=O), 1000~1100(C-O-C), 790(CH_2). Anal. Calcd for $C_{18}H_{32}O_9N_4$: C, 48.21; H, 7.19; N, 12.49. Found: C, 48.57; H, 6.92; N, 12.21.

Synthesis of 1-oxa-4,7,10,13-tetraazacyclopentadecane-4,7,10,13-tetrapropionic acid 2. The compound 2 was prepared by the same method of a synthesis of ligand **1**. It obtained 0.242 g of product from 0.54 g(1 mmol) of N_4O·4HBr and 0.765 g(5 mmol) of 3-bromopropionic acid as a colorless oil; yield 48%. ^{1}H NMR(D_2O, δ): 3.73(t, 2H, O-CH$_2$CH_2-N), 3.25(t, 2H, O-CH$_2$CH_2-N), 3.55(s, 2H, N-CH$_2$CH_2-N), 2.9(t, 2H, N-CH_2CH$_2$COOH), 2.51(t, 2H, N-CH$_2$CH_2COOH). 1.08(t, 2H, N-CH$_2$C-H_2COOH). IR(NaCl, cm^{-1}): 3200~3400(amine), 1720(C=O), 980~1060(C-O-C), 760(CH_2). Anal. Calcd for $C_{22}H_{40}O_9N_4$: C, 52.37; H, 7.99; N, 11.10. Found: C, 52.54; H, 7.55; N, 10.88.

Synthesis of 1-oxa-4,7,10,13-tetraazacyclopentadecane-4,7,10,13-tetraisopropionic acid 3. The compound 3 was prepared by the same method of a synthesis of ligand **1**. It obtained 0.393 g of product from 0.54 g(1 mmol) of N_4O·4HBr and 0.765 g(5 mmol) of 2-bromopropionic acid as a colorless oil; yield 75%. ^{1}H NMR(D_2O, δ): 3.98(q, 1H, N-CH(CH$_3$)COOH), 3.54(t, 2H, O-CH_2CH$_2$-N), 1.22 (d, 3H, N-CH(CH_3)COOH). IR(NaCl, cm^{-1}): 3200~3420(amine), 1710(C=O), 1390(CH_3), 960~990(C-O-C). Anal. Calcd for $C_{22}H_{40}O_9N_4$: C, 52.37; H 7.99; N, 11.10. Found: C, 52.12; H, 7.14; N, 10.97.

Synthesis of 1-oxa-4,7,10,13-tetraazacyclopentadecane-4,7,10,13-tetramerrifield peptide resin 4. The cyclic tetramerrifields were prepared by reaction of the corresponding cyclic amine[N_4O] with merrifield peptide resin in DMF. The synthetic procedure was described in the literatures.[16~21] In a 100 mL round bottom flask, 0.54 g(1 mmol) of N_4O·4HBr was suspended in 10 mL absolute ethanol. To this, 0.224 g(85%, 4 mmol) of KOH was added, and this mixture was stirred at room temperature for 2 h. The KBr was removed by filtration followed by removal of ethanol *in vacuo*. It gained an oily residue[N_4O]. Into a dry 500 mL three necked round bottom flask, equipped with a condenser, two additional funnels, and moisture protecter, were placed 100 mL of dry DMF and 1 mL of triethylamine. And then oily residue in 25 mL of dry DMF from one additional funnel and 2.94 g(4 mmol) of merrifield peptide resin in 25 mL of dry DMF from another additional funnel were added slowly. After the mixture was stirred for 72 h at 85~87 ℃, the residue was washed with water, and then was evaporated to dryness *in vacuo*. It gained a yellow powder. In IR(KBr) spec-

trum the -CH_2-Cl(690 cm^{-1}) peak gave lower intensity. IR(KBr, cm^{-1}): 2800~3400(N-H), 1580 (arom. C=C), 1100(C-O-C), 740(arom. C-H).

Acknowledgment. This work was supported by the Basic Science Research Institute Program, Ministry of Education, Korea, 1995, project NO. BSRI-95-3435.

REFERENCES

1. Delgado, D.; Frausto da Silva, J. J. R. *Talanta* **1982**, *29*, 815.
2. Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875.
3. Choi, K. Y.; Kang, S. H.; Kim, D. W.; Chung, Y. S.; Kim, C. S.; Oh, J. J.; Hong, C. P.; Lee, Y. I. *Supramolecular Chem.* **1996**, *7*, 27.
4. Choi, K. Y.; Lee, Y. I.; Kil, H. S.; Kim, D. W.; Chung, Y. S.; Kim, C. S.; Hong, C. P.; Sim, W. B. *Microchem. J.* **1996**, *53*, 180.
5. Amorim, M. T. S.; Delgado, R.; Frausto da Silva, J. J. R.; Candida, M.; Vaz, T. A.; Vilhena, M. F. *Talanta* **1988**, *35*, 741.
6. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.
7. Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475.
8. Andres, A.; Bazzicalupi, C.; Bencini, A.; Bianchi, A.; Fusi, V.; Garcia-Espana, E.; Paoletti, P.; Valtancoli, B. *Inorg. Chem.* **1994**, *33*, 617.
9. Kim, D. W.; Shin, Y. K.; Oh, J. J.; Kim, C. S.; Yang, J. H. *Bull. Kor. Chem. Soc.* **1991**, *12*, 591.
10. Kim, D. W.; Shin, Y. K.; Kim, C. S.; Oh, J. J.; Jeon, Y. S.; Kim, T. S. *J. Kor. Chem. Soc.* **1992**, *36*, 669.
11. Kim, D. W.; Kim, C. S.; Choi, K. Y.; Jeon, Y. S.; Yoon, Y. H. *ibid.* **1993**, *37*, 820.
12. Kim, D. W.; Kim, C. S.; Choi, K. Y.; Jeon, Y. S.; Hong, C. P. *J. Kor. Soc. Anal. Sci.* **1993**, *6*, 471.
13. Kim, D. W.; Kim, C. S.; Choi, K. Y.; Jeon, Y. S.; Park, S. U. *ibid.* **1994**, *7*, 201.
14. Choi, K. Y.; Kim, K. S.; Kim, J. C. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 267.
15. Rasshofer, W.; Wehner, W.; Vögtle, F. *Liebigs Ann. Chem.* **1976**, 916.
16. Delgado, R.; Sun, Y.; Motekaitis, R. J.; Martell, A. E. *Inorg. Chem.* **1993**, *32*, 3320.
17. Kusama, T.; Hayatsu, H. *Chem. Pharm. Bull.* **1970**, *18*, 319.
18. Tsukube, H.; Adachi, H.; Morosawa, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, *14*, 89.
19. Chen, D.; Squattrito, P. J.; Martell, A. E.; Clearfield, A. *Inorg. Chem.* **1990**, *29*, 4366.
20. Sun, Y.; Martell, A. E.; Welch, M. J. *Tetrahedron* **1991**, *47*, 8863.
21. Kim, D. W.; Kim, C. S.; Choi, K. Y.; Kim, T. S. *J. Kor. Chem. Soc.* **1992**, *36*, 955.