

Articles

Total Synthesis of Fosfazinomycin A

Ik Joong Kang*, Suk In Hong†, and Yong Joon Kim†

Department of Chemical Engineering, Kyungwon University, Kyonggi-Do 461-701

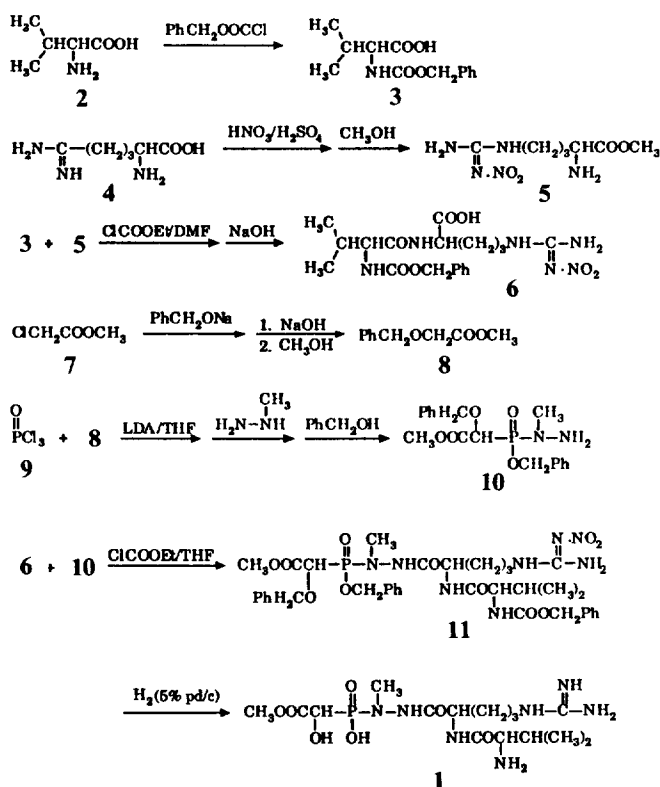
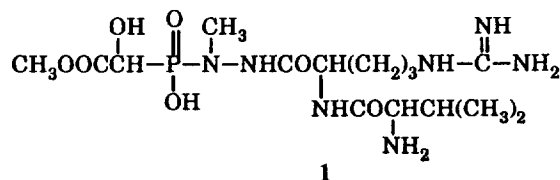
†Department of Chemical Engineering, Korea University, Seoul 136-701. Received February 1, 1990

Fosfazinomycin A(1), methyl valylarginylmethylhydrazinohydroxyphosphonohydroxyacetate, has been synthesized. N-Carbobenzyloxyvalylnitroarginine(6) was reacted with methyl methylhydrazinobenzyloxyphosphonobenzyloxyacetate (10) which has carbon-phosphorus bond, to give a coupled product of methyl N-Carbobenzyloxyvalylnitroarginylmethylhydrazinobenzyloxyphosphonobenzyloxyacetate(11). The deprotection of (11) by hydrogenation yielded Fosfazinomycin A(1).

Introduction

Most of the organic compounds in nature are composed of carbon-carbon bond. But it has been proved that the compounds having carbon-phosphorus bond are also stable. Recently aminophosphonic acids and their derivatives have attracted attention because of their antibiotic, herbicidal, pesticidal, anticancer and enzyme inhibitory activities, and particularly their structural similarity to the biologically important amino acid. Since 2-aminophosphonic acid (2-AEPn) was isolated from sheep rumen in 1959 by Horiguchi and his coworkers,¹ twenty six aminophosphonic acids and their derivatives have been discovered from living organism. Aminophosphonic acids are also discovered in mammalian tissues like human muscles, sheep liver, and ox brain.²⁻⁸ Its concentration in human tissues was higher in heart and skeletal muscles than in liver and brain.

Fosfazinomycin A(1), formerly called AM 630, is a new antifungal substance isolated from the fermentation broth of *Streptomyces lavendofoliae*.⁹⁻¹¹



Scheme 1.

It has the structure of tetrapeptides which contain carbon-phosphorus-amine bond. In this paper, the authors wish to report the first total synthesis of Fosfazinomycin A(1), as shown in Scheme 1.

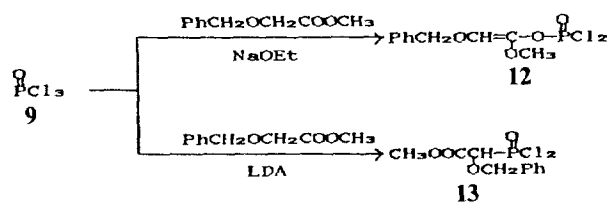
Results and Discussion

A synthesis of Fosfazinomycin A(1) was carried out using inexpensive chemicals. N-Carbobenzyloxyvaline(3) was prepared in 85% yield by protecting amino group of DL-valine with carbobenzyloxychloride. L-Arginine was nitrated and then methylated to give methyl nitroarginate(5) in 72% yield. The peptide(6) was prepared by coupling of N-Carbobenzyloxyvaline(3) with methyl nitroarginate(5) in the pres-

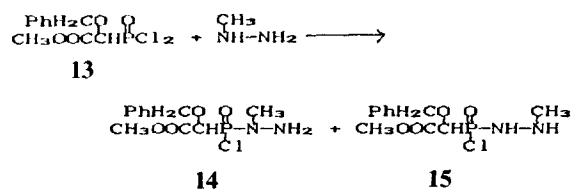
ence of ethyl chloroformate in 62% yield.

The reaction from trichlorophosphinoyl(9) to methyl methylhydrazinobenzyloxyphosphonobenzyloxyacetate(10) was carried out by one-pot reaction under nitrogen atmosphere in 12% yield since the reaction mixture was moisture sensitive. The carbon-phosphorus-amine bonded compound was produced by the reaction of trichlorophosphinoyl(9) with methyl benzyloxyacetate(8), followed by replacement of chloride with methylhydrazine, and benzyl alcohol successively. In reaction of methyl benzyloxyacetate with trichlorophosphinoyl(9), it has been known that O-phosphonylated compound(12) which is an unwanted product, was obtained with the aid of weak base, but the desired C-phosphonylated com-

pound(13) was obtained employing a strong base such as LDA.¹²



There are two possible products in the reaction of methyl hydrazine with methyl dichlorophosphonobenzoyloxyacetate (13) because methylhydrazine has two amine groups. One is primary amine substituted compound(14) and the other is secondary amine substituted compound(15). It was suspected that the secondary amine of methylhydrazine would be substituted easily because it is slightly stronger nucleophile.¹³



The reaction of benzyl alcohol with methyl methylhydrazino-chlorophosphonobenzoyloxyacetate(14) produced methyl methylhydrazinobenzoyloxyphosphonobenzoyloxyacetate(10) which has carbon-phosphorus-amine bond.

The coupling of protected dipeptide(6) with phosphonoacetate(10) produced tetrapeptide(11) in 71% yield. Fosfazinomycin A(1) was obtained by hydrogenation in the presence of palladium on charcoal in 65% yield. In conclusion, Fosfazinomycin A(1), a new kind of phosphorus compound, was synthesized efficiently in 12 steps in 0.7% overall yield.

Experimental part

All reactions were carried out with the unusual precaution for rigorous exclusion of air and moisture. The solvents, ether and tetrahydrofuran, were purified by refluxing for several hours in the presence of sodium metal and benzophenone followed by distillation under nitrogen prior to use. Melting points were measured by Mettler F61 mp. apparatus. IR spectra were recorded with Beckmann acculab T.M.I spectrometer, and proton NMR spectra were taken on Varian EM-360 (80 MHz) spectrometer with TMS as an internal standard. Low pressure hydrogenation was carried out with PARR Instrument hydrogenation apparatus.

N-Carbobenzoyloxyvaline(3). In a 1000 ml three neck round bottomed flask, 25 g (0.21 mol) of DL-valine, 69.465 g (0.5 mol) of potassium carbonate and 350 ml of distilled water were added. While stirring at 0°C, 31.95 ml (0.22 mol) of carbobenzyloxy chloride was added carefully through a dropping funnel over 30 minutes. After being stirred 4 hours, this solution was washed with chloroform and ether successively. 8 N aqueous HCl solution was added to the residual aqueous layer until it was acidified. White oily organic layer was extracted with ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. After the solvent was removed by evaporation *in vacuo*, the crude product was

chromatographed on a silica gel column using ethyl acetate and *n*-hexane (1:1, v/v). Recrystallization with ethyl acetate and *n*-hexane gave a white crystal in 85% yield.

mp. 65°C; ¹H-NMR(CDCl₃): 0.9(m, 6H, -CH(CH₃)₂), 2.0(m, 1H, -CH(CH₃)₂), 3.0(d, 1H, J = 5 Hz, -CHCO-), 5.1(s, 2H, -OCH₂C₆H₅); 7.35(s, 5H, -OCH₂C₆H₅), IR(KBr): 3350(NH), 1710 cm⁻¹ (C=O).

Methyl Nitroarginate(5). In a 250 ml three neck round bottomed flask fitted with a mechanical stirrer and dropping funnel, was placed 21.3 ml (0.71 mol) of fuming sulfuric acid. To this flask 33 ml (0.6 mol) of fuming nitric acid was added dropwise and 25 g (0.142 mol) of arginine was added with stirring carefully at -5°C. This dropping funnel was washed with 10 ml of concentrated sulfuric acid. After being stirred for 1 hour, this solution was basified with ammonium hydroxide and neutralized with glacial acetic acid. White oily organic layer has been extracted with ethyl acetate, and dried over anhydrous magnesium sulfate, and the solvent was removed by evaporation *in vacuo*. After the white product which has been obtained by recrystallizing with water was dissolved in 190 ml of methanol, a solution 12.7 ml (0.18 mol) of thionyl chloride and 10 ml of anhydrous methanol was added carefully through the dropping funnel over 20 minutes and the resultant mixture was stirred for 1 day at room temperature. After the solvent was removed by evaporation *in vacuo*, the crude product was recrystallized with methanol and ether several times. A white crystal was obtained in 72% yield.

mp. 157°C; ¹H-NMR(D₂O): 1.7(m, 4H, -NHCH₂CH₂CH₂CH-), 3.3(m, 3H, -NHCH₂CH₂CH₂CH-), 3.8(s, 3H, -OCH₃), IR(KBr): 3500(guano group), 1760 cm⁻¹ (C=O).

N-Carbobenzoyloxyvalylnitroarginine(6). In a 250 ml three neck round bottomed flask fitted with a dropping funnel, 11.59 g (0.046 mol) of N-Carbobenzoyloxyvaline in 46.5 ml of dry tetrahydrofuran was added. While stirring under nitrogen at 0°C, 6.35 ml of triethylamine and 4.425 ml (0.046 mol) of ethyl chloroformate were added carefully through the dropping funnel over 20 minutes. After stirring for 30 minutes, a solution of 15 g (0.046 mol) of methyl nitroarginate in 50 ml of N,N-dimethylformamide and 23 ml of tetrahydrofuran was added carefully through the dropping funnel during 40 minutes and the resultant mixture was stirred for 24 hours at 0°C. After the solvent was removed by evaporation *in vacuo*, 50 ml of ethyl acetate was added. This mixture was washed with 1 N HCl, distilled water, and saturated aqueous solution of sodium bicarbonate successively, then the organic layer was dried over anhydrous sodium sulfate. After the solvent was removed by evaporation *in vacuo*, the crude product was recrystallized with methanol and *n*-hexane. A white crystal of methyl N-Carbobenzoyloxyvalylnitroarginate was obtained in 67% yield (17.4 g). In a 50 ml three neck round bottomed flask fitted with dropping funnel, a solution of 0.47 g of this white crystal in 3 ml of acetone and 3 ml of distilled water was added. While stirring at room temperature, 1.1 ml of 1 N sodium hydroxide was added carefully through the dropping funnel over 10 minutes and stirred for 1.5 hours at room temperature. After the solvent was removed by evaporation *in vacuo*, the crude product was washed with ether and chloroform successively and acidified with concentrated HCl. The oily product was extracted with ethyl acetate. The solvent was evaporated *in vacuo* to

give a white crystal in 62% yield.

mp. 176°C; $^1\text{H-NMR}(\text{CDCl}_3)$: 0.9(m, 6H, $-\text{CH}(\text{CH}(\text{CH}_3)_2)_2$), 1.7(m, 4H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.0(m, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.2(m, 3H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 5.1(s, 2H, $-\text{OCH}_2\text{C}_6\text{H}_5$), 7.35(s, 5H, $-\text{OCH}_2\text{C}_6\text{H}_5$), IR(KBr): 3500(guano group), 1760(C=O), 1660 cm^{-1} (amide).

Methyl Benzyloxyacetate(8). In a 500 ml three neck round bottomed flask fitted with a dropping funnel, 23 g (1 mol) of sodium metal was added under nitrogen. With stirring the metal, 240 ml (2.2 mol) of benzyl alcohol was added carefully through the dropping funnel at 0°C. While stirring at 0°C, a solution of 88.24 ml (1 mol) of methyl chloroacetate in 50 ml of benzyl alcohol was slowly added to the flask at 0°C, stirred for 2 hours, and refluxed for 4 hours. After cooling, 50 ml of water and 250 ml of ethyl acetate were added. The residual aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous magnesium sulfate. After the solvents were removed by evaporation *in vacuo*, the crude product of benzyl benzyloxyacetate was chromatographed on a silica gel column using ethyl acetate and *n*-hexane (1:1, v/v). To the purified product of benzyl benzyloxyacetate in 170 ml of acetone, a solution of 42 ml of distilled water and 840 ml of 1 N NaOH was added carefully through a dropping funnel at room temperature and stirred for 2 hours. After the solvent was removed by evaporation *in vacuo*, the aqueous layer was washed with ether and chloroform successively. The aqueous mixture was acidified to pH 3 with 6 N HCl, cooled for 24 hours at 0°C, and then extracted with ethyl acetate. After the organic layer was evaporated *in vacuo*, the crude product was dissolved in 270 ml of methyl alcohol, and dry HCl gas was added to the solution for 3 hours. After the solvent was removed by evaporation *in vacuo*, the organic residue was distilled under reduced pressure to give an oil which was purified by silica gel column using ethyl acetate and *n*-hexane (1:1, v/v), to give methyl benzyloxyacetate in 32% yield.

bp. 120-142°C (0.1 mmHg); $^1\text{H-NMR}(\text{CDCl}_3)$: 3.8(s, 3H, $-\text{OCH}_3$), 4.1(s, 2H, $-\text{OCH}_2\text{CO}-$), 4.6(s, 2H, $-\text{OCH}_2\text{C}_6\text{H}_5$), 7.35(s, 5H, $-\text{OCH}_2\text{C}_6\text{H}_5$), IR(neat): 1700 cm^{-1} (C=O).

Methyl Methylhydrazinobenzyloxyphosphonobenzyloxyacetate(10). In a 100 ml three neck round bottomed flask fitted with a dropping funnel, 2.93 ml (0.032 mol) of trichlorophosphine oxide in 20 ml anhydrous tetrahydrofuran was added slowly under nitrogen at -78°C . While stirring, a solution of 21 ml (0.05 mol) of *n*-butyllithium, 5.95 ml (0.04 mol) of diisopropylamine, and 5.76 g (0.032 mol) of methyl benzyloxyacetate in 20 ml of tetrahydrofuran was added to the flask slowly. After stirring the solution for 4 hours, a solution of 1.68 ml (0.032 mol) of methylhydrazine and 2.6 ml of pyridine was added carefully under nitrogen. After stirring the mixture for 6 hours, a solution of 3.34 ml (0.03 mol) of benzyl alcohol and 2.6 ml of pyridine was added carefully under nitrogen, and the mixture was stirred for 4 hours at -78°C and 8 hours at room temperature. A few ml of H_2O added to the solution, and the resulted mixture was extracted with ether and ethyl acetate successively. The combined organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed by evaporation *in vacuo*. The crude product was chromatographed on a silica gel column using ethyl acetate and *n*-hexane (1:1, v/v) to give an oily product in 12% yield.

$^1\text{H-NMR}(\text{CDCl}_3)$: 2.87(d, 3H, $J_{\text{H-P}}=6$ Hz, $-\text{NCH}_3$), 3.8(s, 3H, $-\text{OCH}_3$), 4.6(s, 2H, $-\text{CHOCH}_2\text{C}_6\text{H}_5$), 5.0(d, 2H, $J=8$ Hz, $-\text{P}(\text{O})\text{OCH}_2\text{C}_6\text{H}_5$), 5.5(s, 1H, $-\text{CHCOOCH}_3$), 7.35(s, 10H, $-\text{OCH}_2\text{C}_6\text{H}_5$), IR(neat): 3370(NH), 1700(C=O), 1200(P=O), 980 cm^{-1} (P-O-C).

Methyl N-Carbobenzyloxyvalylnitroarginylmethylhydrazinobenzyloxyphosphonobenzyloxyacetate(11).

In a 50 ml three neck round bottomed flask fitted with a dropping funnel under nitrogen, 0.845 g (1.87 mmol) of N-Carbobenzyloxyvalylnitroarginine(6) in 3 ml of tetrahydrofuran and 0.26 ml of triethylamine were added. While stirring at 0°C, 0.37 ml of ethyl chloroformate was added carefully through the dropping funnel. After stirring for 30 minutes, a solution of 0.71 g (1.87 mmol) of methyl methylhydrazinobenzyloxyphosphonobenzyloxyacetate(10) in 2.4 ml of tetrahydrofuran and 0.26 ml of triethylamine was added slowly at 0°C. After stirring for 12 hours at 5°C, the resulted mixture was extracted with ethyl acetate and water successively. After the solvent was removed by evaporation *in vacuo*, the residue was purified by silica gel column eluting with ethyl acetate and *n*-hexane (1:1, v/v) to give an oily product in 71% yield.

$^1\text{H-NMR}(\text{CDCl}_3)$: 1.7(m, 4H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.0(m, 1H, $-\text{CH}(\text{CH}_3)_2$), 2.87(d, 3H, $J_{\text{H-P}}=6$ Hz, $-\text{NCH}_3$), 3.0(d, 1H, $J=5$ Hz, $-\text{CHCH}(\text{CH}_3)_2$), 3.2(m, 3H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 3.8(s, 3H, $-\text{OCH}_3$), 4.6(s, 2H, $-\text{CHOCH}_2\text{C}_6\text{H}_5$), 5.0(d, 2H, $J=8$ Hz, $-\text{P}(\text{O})\text{OCH}_2\text{C}_6\text{H}_5$), 5.1(s, 2H, $-\text{COOCH}_2\text{C}_6\text{H}_5$), 5.5(s, 1H, $-\text{CHCOOCH}_3$), 7.35(s, 15H, $-\text{OCH}_2\text{C}_6\text{H}_5$), IR(neat): 3400(NH), 1700(C=O), 1200(P=O), 1000 cm^{-1} (P-O-C).

Fosfazinomycin A(1). In a 250 ml parr low pressure hydrogenation apparatus, 0.65 g (0.8 mmol) of methyl N-carbobenzyloxyvalylnitroarginylmethylhydrazinobenzyloxyphosphonobenzyloxyacetate(11) in 20 ml of methanol and 0.4 g of 5% palladium on charcoal were added. Hydrogenation was accomplished under 15 psig of hydrogen pressure. After shaking for 4 hours at room temperature, 2.8 psi. of hydrogen pressure was consumed. After the mixture was filtered through Celite, the solvent was removed by evaporation *in vacuo*. The resulted yellow-green oil was chromatographed on silica gel column using ethyl acetate and *n*-hexane (2:1, v/v) as an eluent, to give a white crystal in 65% yield.

mp. 158°C 11 ; $^1\text{H-NMR}(\text{D}_2\text{O})$: 0.9(m, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.7(m, 4H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.0(m, 1H, $-\text{CH}(\text{CH}_3)_2$), 2.87(d, 3H, $J_{\text{H-P}}=6$ Hz, $-\text{NCH}_3$), 3.0(d, 1H, $J=5$ Hz, $-\text{CHCH}(\text{CH}_3)_2$), 3.2(m, 3H, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), 3.8(s, 3H, $-\text{OCH}_3$), 5.35(s, 1H, $-\text{CHCOOCH}_3$), IR(neat): 3600(OH), 1760(C=O), 1200(P=O), 980 cm^{-1} (P-O-C).

Acknowledgement. This work was supported by Post-Graduate Research Aid Program of the Daewoo Foundation, Republic of Korea.

References

1. M. Horiguchi and M. Kandatsu, *Nature*, **184**, 901 (1959).
2. M. Kandatsu and M. Horiguchi, *Agr. Bio. Chem.*, **29**, 781 (1965).
3. H. Shimizu, Y. Kakimoto, T. Nakajima, A. Danaza and I. Sano, *Nature*, **207**, 1197 (1965).
4. J. A. Alhadelff and G. D. Davis, *J. Biochem.*, **9**, 4866 (1970).
5. J. A. Alhadelff and G. D. Davis, *J. Biochem. Biophys. Acta*,

- 244, 221 (1971).
6. J. S. Kittridge and R. R. Hughes, *Biochemistry*, **3**, 991 (1964).
 7. J. S. Kittridge, A. F. Isbell, and R. R. Hughes, *Biochemistry*, **6**, 289 (1967).
 8. E. D. Korn, D. G. Dearborn, H. M. Fales, and E. A. Sokoloski, *J. Biol. Chem.*, **248**, 2257 (1973).
 9. H. Gunji and T. Beppu, *Annual Meeting of Agric. Chem. Soc. Jpn.*, Tokyo, Apr. 2-4, Abstr. 130 (1979).
 10. K. Ogita, Y. Fukazawa, A. Terahara, T. Kinoshita, H. Nagai, and T. Beppu, *Annual Meeting of Agric. Chem. Soc. Jpn.*, Sendai, Mar. 29-Apr. 1, Abstr. 130 (1983).
 11. T. Ogita, S. Gungi, Y. Fugazawa, A. Terahara, T. Kinoshita and, H. Nagai, *Tetrahedron Lett.*, **24**, 2283 (1983).
 12. E. Y. Spencer, A. R. Todd, and R. F. Webb, *J. Org. Chem.*, **32**, 1273 (1967).
 13. J. P. Majoral, *Tetrahedron*, **32**, 2633 (1976).
 14. I. R. Vaughan, JR, and J. A. Eiechler, *J. Am. Chem. Soc.*, **75**, 5556 (1953).
 15. K. Hofmann, W. D. Peckhan, and A. R. Hiener, *J. Am. Chem. Soc.*, **78**, 238 (1953).
 16. R. L. Elliot, N. Marks, M. J. Berg, and P. S. Portoghess, *J. Med. Chem.*, **28**, 1208 (1985).

New Cryptand Complexes of Lanthanides(III) and Dioxouranium(VI) Nitrates

Oh-Jin Jung,* Chil-Nam Choi[†], and Hak-Jin Jung[‡]

Department of Environmental Chemistry, Chosun University, Kwangju 501-759

[†]*Department of Science Education (Chemistry Major), Chosun University, Kwangju 501-759*

[‡]*Department of Chemistry, Chosun University, Kwangju 501-759. Received July 4, 1990*

The following new cryptand 221 complexes of lanthanides(III) and dioxouranium(VI) nitrate have been synthesized: $(\text{Ln}(\text{C}_{16}\text{H}_{32}\text{N}_2\text{O}_5)(\text{H}_2\text{O})_2(\text{NO}_3)_3)$ and $((\text{UO}_2)_2(\text{C}_{16}\text{H}_{32}\text{N}_2\text{O}_5)(\text{H}_2\text{O})_4)(\text{NO}_3)_4$. These complexes have been identified by elemental analysis, moisture titration, conductivity measurements and various spectroscopic techniques. The proton and carbon-13 NMR as well as calorimetric measurements were used to study the interaction of cryptand 221 with La(III), Pr(III), Ho(III) and $\text{UO}_2(\text{II})$ ions in nonaqueous solvents. The bands of metal-oxygen atoms, metal-nitrogen atoms and O-U-O in the IR spectra shift upon complexation to lower frequencies, and the vibrational spectra (δNMN) of metal-amide complexes in the crystalline state exhibit lattice vibrations below 300 cm^{-1} . The NMR spectra of the lanthanides(III) and dioxouranium(VI) nitrate complexes in nonaqueous solvents are quite different, indicating that the ligand exists in different conformation, and also the ^1H and ^{13}C -NMR studies indicated that the nitrogen atom of the ring has greater affinity to metal ions than does the oxygen atom, and the planalities of the ring are lost by complexation with metal ions. Calorimetric measurements show that cryptand 221 forms more stable complexes with La^{3+} and Pr^{3+} ions than with UO_2^{2+} ion, and $\text{La}^{3+}/\text{Pr}^{3+}$ and $\text{UO}_2^{2+}/\text{Pr}^{3+}$ selectivity depends on the solvents. These changes on the stabilities are dependent on the basicity of the ligand and the size of the metal ions. The absorption band (230-260 nm) of the complex which arises from the direct interaction of macrocyclic donor atoms with the metal ion is due to $n\text{-}\delta^*$ transition and also that (640-675 nm) of UO_2^{2+} -cryptand 221 complex, which arises from interaction between two-dioxouranium(VI) ions in being out of cavity of the ligand ring is due to $d\text{-}d^*$ transition.

Introduction

Since the discovery of the metal-template synthesis by Curtis¹ and Buson² thirty years ago, the field of macrocyclic ligands has become a major area of research. The chemistry of first-row transition-metal ions complexed by macrocyclic ligands has been extensively developed and exhibits many unusual features compared to noncyclic analogues.

The macrocycles have been shown to stabilize high oxidation states of metal ions such as $\text{Ag}(\text{II})^3$ and $\text{Ni}(\text{III})^4$. They exhibit unusual ligand field strengths compared to noncyclic ligands with similar donor atoms⁵, and the formation constants of their metal complexes are often unusually high.

One of the fundamental properties of these ligands is the size of the macrocyclic ring. A change in ring size on high spin⁶ and on low spin⁷ complexes has been shown to affect

the electronic spectra, redox potentials and reactivity of complexes markedly. Many communications on the synthesis and structural characteristics of the dioxouranium(VI) and lanthanide(III) complexes with crown ether and crownand macrocyclic ligands have been published^{8, 23, 29}, as have communications on the synthesis and structural characteristics of some lanthanide complexes with cryptand 222 (Cryptand 222 = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-(8,8,8)hexacosane) using various spectroscopic and X-ray crystal studies¹¹. As an extension of our previous studies on the synthesis, structure and electronic properties of lanthanoid(III) and dioxouranium(VI) complexes⁹, we are now interested in a systematic investigation of coordination compounds of these metal ions with macrocyclic ligands of cryptand 221.

The cryptand 221(4,7,13,16,21-pentaoxa-1,10-diazabicyclo-(8,8,5)tricosan) ligand is fully saturated in donor electrons of