VI are the first two examples of main-group metal containing dithiaborane clusters. The isolation of **V** and **VI** illustrates that *hypho*-$S_2B_7H_{10}^-$ may be used in future to incorporate even larger numbers and types of main-group metal atoms into dithiaborane cage systems resulting in the production of new classes of hybrid clusters.

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Synthesis and Properties of Novel Pt(II)-containing Polyphosphazenes

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Poly(dichlorophosphazene) having low molecular weight ($\bar{M}w \sim 10^4$) was synthesized by the thermal reaction of hexachlorocyclotriphosphazene in the presence of excess $AlCl_3$ (>2%) as catalyst. Using the poly(dichlorophosphazene), poly[bis(ethylglycino)phosphazene], poly[bis(glycinemethylamido)phosphazene], and poly[(glycinemethylamido)(methylamino)phosphazene] were prepared. Diammineplatinum(II) complex cation was introduced into these derivatized phosphazene polymers, and the resultant polymers containing the platinum(II) moiety were charaterized by means of elemental analysis, IR and NMR spectroscopies, and then subjected to *in vitro* and *in vivo* assays of antitumor activity.

Introduction

Hydrolytically sensitive polyphosphazenes[1~3] are recently attracting a remarkable attention because of their potential applicability to biomedical materials[4~15] such as substrates for drug delivery systems and absorbable suturing materials.

Polyphosphazenes are polymers with an inorganic backbone consisting of alternating nitrogen and phosphorous atoms linked by alternating single and double bonds. Starting from the poly(dichlorophosphazene) a variety of polymers with variable properties can be prepared by nucleophilic substitution with various organic groups. Allcock and co-workers[1,2,16] who extensively explored the field of polyphosphazenes reported that polyphosphazenes substituted with amino

acid esters are susceptible towards hydrolytic degradation and hold promising properties as biodegradable materials. However, poly(dichlorophosphazene) has been synthesized in most cases by melt polymerization[17~19] to high-molecular weight polymers ($\bar{M}w \sim 10^6$) in relatively low yield (<50%), which may be not appropriate for application to drug delivery system. Recently a new method was developed by the authors[20] for preparation of poly(dichlorophosphazene) having low molecular weight ($\bar{M}w \sim 10^4$) in nearly quantitative yield.

In this paper we describe the preparation and characterization of such low molecular weight polyphosphazene substituted with amino acids and their novel platinum(II) derivatives. The antitumor activity of the polyphosphazene derivatives containing platinum complexes has been evaluated *in vitro* and *in vivo* systems.

Experimental

Materials. Hexachlorocyclotriphosphazene was purchased from Aldrich and purified by fractional vacuum sublimation at 55 ℃. Benzene, tetrahydrofuran and hexane were purchased from Baker and distilled over sodium/benzophenone and stored over molecular sieves. Methylamine was purchased from Matheson and dried over sodium before use. Triethylamine was purchased from Aldrich and dried by boiling over barium oxide and was distilled just before use. Acetone (Baker), glycine (Aldrich) and potassium tetrachloroplatinate (Kojima) was used as received.

Measurements. ^{1}H NMR spectra were recorded on a Varian Gemini-300 spectrometer operating at 300 MHz in the Fourier transform mode. Proton-decoupled ^{31}P NMR spectra were measured with the same spectrometer operated at 121.4 MHz and their chemical shifts are relative to external triphenyl phosphate. All the NMR data were obtained in D_2O or acetone-d_6 solution. Infrared spectra of polymer samples were measured with a Midac FT-IR 101025 spectrometer as film cast on potassium bromide or sodium chloride plates. Gel permeation chromatograms were obtained with the use of a Waters Associates HPLC/GPC 150C instrument fitted with a refractive index detector. In the water-insoluble polymer, tetrahydrofuran containing 0.25 g/L tetrabutylammonium bromide was used as solvent. Sample concentrations were 0.16-0.25%. Molecular weight calibration was carried out using m-styragel columns with narrow molecular weight polystyrene standards. In the water soluble polymers, sample concentrations were *ca.* 0.15% (w/v) in deionized/distilled water. Poly(ethlyene oxide) standards of known molecular weight were used to calibrate the columns. Elemental analyses were performed at the Chemical Analysis Center at KIST. The glass transition temperature (Tg) was measured with the use of a Perkin-Elmer DSC-2 programmed to operate from −100 to 40 ℃ with a scane rate of 10 ℃ min^{-1} under helium flow. The thermogravimetric analysis of the polymers was performed using Perkin-Elmer TGA-2 with a heating rate of 20 ℃ min^{-1}. The samples were maintained in a dry nitrogen atmosphere during measurement.

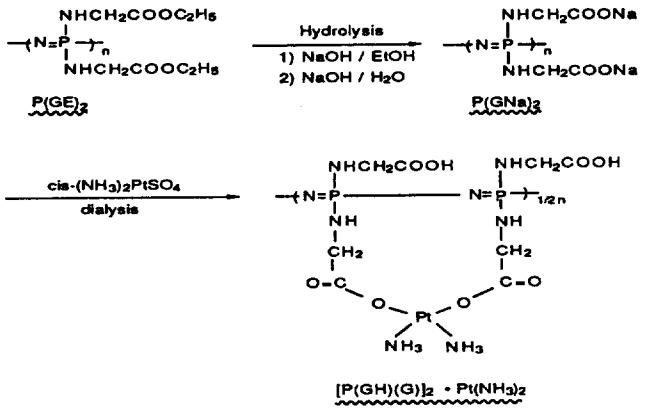
Synthesis of Poly(dichlorophosphazene). Purified hexachlorocyclotriphosphazene (4.0 g) and $AlCl_3$ (0.25 g) as catalyst were placed in a 22 cm×2.3 cm Pyrex ampule in an argon-filled dry box. The ampule was then evacuated for 30 min. at a pressure of 0.1 mmHg and then isolated from the vacuum line. The ampule was sealed and then heated in a thermoregulated convection at 250 ℃ for 4 h. When the ampule was cooled to room temperature, the resultant product was a transparent viscous liquid without any solidified material. The ampule was cut into small pieces in argon filled glove box, and dry THF or benzene (100 mL) was added. The product became a slightly viscous, pale yellow solution by continuous agitation for 1 h. Poly(dichloro-phosphazene) thus prepared exhibited a sharp singlet at −0.2 ppm (benzene-d_6) in the ^{31}P NMR spectrum indicating that the trimer was nearly quantitatively converted to the polymer, and therefore, the chloropolymer solution was directly used for the preparation of the following derivatives.

Synthesis of Poly[bis(ethylglycino)phosphazene] [P(GE)$_2$] and Poly[bis(glycinemethylamido)phosphazene] [P(GA)]$_2$. These polymers were prepared by the methods in literatures.[1,16]

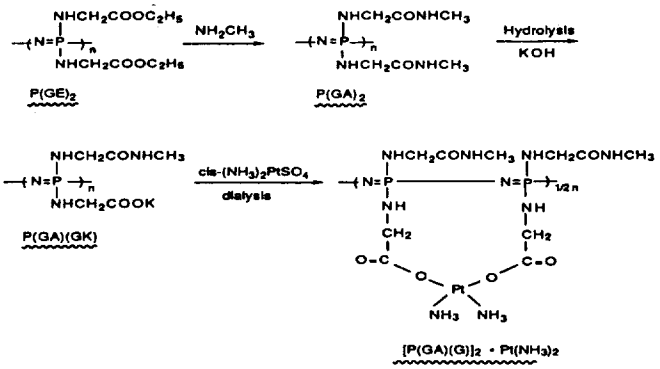
Synthesis of Poly[(glycinemethylamido)(methylamino)phosphazene] [P(GA)(MA)]. A suspension of 10.1 g of glycine ethylester hydrochloride (72.5 mmol) and 10.1 ml of triethylamine (72.5 mmol) was stirred in boiling benzene (400 mL) for 4 h. The mixture was cooled to 0 ℃ and filtered under dry nitrogen atmosphere to remove triethylamine hydrochloride. To the filtrate was added dropwise with stirring a solution of poly(dichlorophosphazene) (4.0 g) in THF (100 mL) under dry nitrogen atmosphere. The mixture was stirred at 0 ℃ for 4 h and then allowed to warm slowly to 25 ℃ as stirring continued for an additional 6 h. The mixture was cooled again to 0 ℃ and treated rapidly with a large excess of methylamine (100 mL) by means of a dry ice condenser. The suspension was stirred at 0 ℃ for 4 h and then at 25 ℃ for 16 h. The solvent was removed with the use of a rotary evaporator. Purification was effected by dissolution of the product in methanol and dialysis against water through Spectrapor-132725 dialysis tube for 72 h. The solution was concentrated to 50 mL in a rotary evaporator and then poured into a large excess amount of THF or benzene for reprecipitation of the polymer.

Hydrolysis of P(GE)$_2$, P(GA)$_2$ and P(GA)(MA). 3.0 g of P(GE)$_2$ (12.1 mmol) dissolved in 30 mL of ethanol was added to a solution of 0.97 g of sodium hydroxide (24.2 mmol) in 30 mL of ethanol. The mixture was stirred at 25 ℃ for 30 min. and the precipitated polymer was filtered out. In order to complete hydrolysis reaction, this solid polymer was dissolved in 50 mL of 2 N NaOH aqueous solution and the mixture was stirred at 25 ℃ for 2 h. The solvent was removed using a rotary evaporator and the solid product P(GNa)$_2$ was dried under vacuum after washing with a large excess of ethanol. The hydrolysis of P(GA)$_2$ and P(GA)(MA) was performed by the same procedure using KOH instead of NaOH.

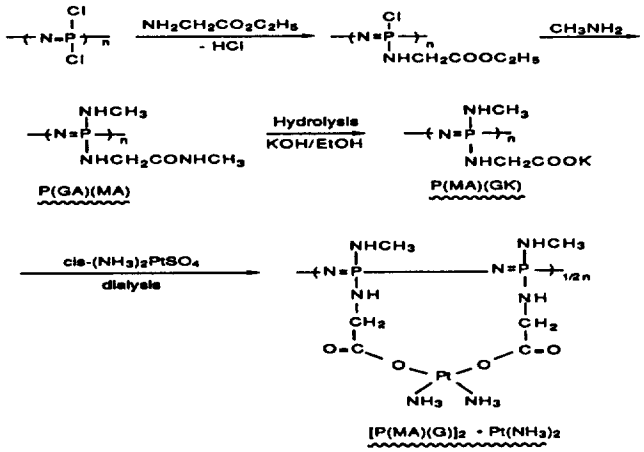
Platination of P(GE)$_2$, P(GA)$_2$ and P(GA)(MA). 5.0 g of K_2PtCl_4 (12.1 mmol) and 8.03 g of KI (48.4 mmol) were dissolved with stirring in 100 mL of water in a light-protected flask at room temperature. After stirring for 4 h, ammonia solution (25.4 mmol) was added dropwise. The resultant yellow precipitate, cis-$(NH_3)_2PtI_2$, was filtered, washed with water, cold ethanol and ethylether successively, and then vacuum-dried. The yield was over 90%.



Scheme 1.



Scheme 2.



Scheme 3.

1.17 g of cis-$(NH_3)_2PtI_2$ (2.42 mmol) thus obtained was suspended in 80 mL of water to which 0.75 g of silver sulfate (2.42 mmol) was added with stirring. The reaction mixture was further stirred for 4 h and the yellow precipitate (AgI) was filtered off. To the filtrate was added dropwise 80 mL of an aqueous solution of 1.30 g of $P(GNa)_2$ (4.84 mmol) and the reation mixture was stirred for 4 h. The mixture was concentrated at 40 ℃ to approximately 30 mL on a rotary evaporator and was subjected to dialysis through a cellulose tube (m.w. cutoff: approx 1000) against deionized water. After dialysis for 72 h, the polymer was isolated by precipitation into acetone. The polymer was filtered, washed with acetone and ethylether, and then vacuum dried. The same procedure was applied for P(GA)(GK) and P(GA)(GK)P(MA)(GK).

Assay of antitumor activity. Evaluation for the anticancer activity of the polyphosphazenes containing platinum (II) moiety was performed by the routine method.[21]

Results and Discussion

Synthetic Aspects. In order to introduce diammineplatinum(II) moiety into our low molecular weight polyphosphazenes, glycine ethylester or glycine methylamide groups were substituted into the polymer as spacer group according to the method by Allcock, *et al.*[1~3] In addition to these known substituted polymers, we have also prepared a new phosphazene copolymer containing equimolar glycine methylamide and methylamine to improve solubility of the final polymer product involving platinum moiety. Polyphosphazenes fully substituted with glycine ethylester or with glycine methylamide were subjected to hydrolysis in the presence of alkali to convert to water soluble alkali metal salts, and then reacted with diammineplatinum(II) sulfate in aqueous solution. Our attempted synthetic routes for introduction of platinum moiety into polyphosphazene fully substituted with glycine ethylester and glycine methylamide may be respresented in Scheme 1 and 2, respectively.

Hydrolysis reactions of both $P(GE)_2$ and $P(GA)_2$ in the alcoholic NaOH or KOH solution take place only partially, and in order to complete hydrolysis of $P(GE)_2$, aqueous alkaline solution was also used to obtain water soluble platinated product. The synthetic route for copolymerization and platination is also displayed in Scheme 3.

The synthesis of [P(GA)(MA)] was accomplished by introduction of the amino acid ester residue first, followed by treatment with methylamine to obtain equimolar substituted copolymer. The reverse order of substitution of the substitutents did not give rise to a clean copolymer because of the high reactivity of methylamine.

The substituted polyphosphazenes appearing in the above reaction schemes were characterized by means of ^1H- and ^{31}P NMR spectroscopy. In particular, from the ^1H NMR spectra of the polymers the composition of the substituents could be estimated as shown in Table 1. It is seen from the table that hydrolysis reactions of $P(GE)_2$, $P(GA)_2$ and P(GA)(MA) are not completed as already above-mentioned, and furthermore, a considerable amounts of organic substituents are replaced by hydroxy group. Therefore, the reaction intermediates and products illustrated in the synthetic schemes are only ideal forms, and their molecular formula should be modified as shown in the table in abbreviated forms reflecting the real molecules.

Table 2 lists the analytical data of the hydrolysis and platination products of the substituted polymers compared with the calculated based on the compositions of the substituents given in Table 1 . Considering the complexity of the polymer molecules, the results of analysis are roughly in accord with the calculated values. Other important ^1H- and ^{31}P NMR data of the polymers are given along with their IR data in Table 3. The ^{31}P NMR spectra of homopolymers $P(GE)_2$ and $P(GA)_2$ shown in Figure 1 exhibit each a singlet at 19.8 and 23.1 ppm, respectively, as expected. However, the copolymer

Table 1. The Composition of Polyphosphazene Derivatives from Integration of ^{1}H NMR

Polyphosphazenes	-P=N-	-$NHCH_2CO_2C_2H_5$	-$NHCH_2CONHCH_3$	-$NHCH_2CO_2Na$(K, H)	-$NHCH_2CO_2$-	-$NHCH_3$	$Pt(NH_3)_2$	-OH
$[P(GE)_2]$	1	2						
$[P(GNa)_2]\cdot 2H_2O$	1	0.1		1.9				
[P(GH)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 2H_2O$	1			0.52	0.88		0.44	0.6
$[P(GA)_2]$	1		2					
$[P(GA)(GK)]\cdot 2H_2O$	1		0.4	1.6				
[P(GA)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 3H_2O$	1		0.4		1.0		0.5	0.6
[P(GA)(MA)]	1		0.96			1.04		
[P(GA)(GK)P(MA)(GK)] $\cdot 3/2H_2O$	1		0.2	0.8		1.0		
[P(GA)(G)P(MA)(OH)] $\cdot Pt(NH_3)_2\cdot 2H_2O$	1		0.2	0.35	0.28	0.9	0.14	0.27

Table 2. Elemental Analysis of Polyphosphazene Derivatives

Polyphosphazenes	C, %		H, %		N, %		P, %		Pt, %	
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$[P(GNa)_2]\cdot 2H_2O$	18.4	18.9	3.44	3.22	15.4	13.9	11.3	11.9		
[P(GH)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 2H_2O$	11.4	12.3	4.08	3.39	15.6	13.9	10.5	10.1	29.1	30.8
$[P(GA)(GK)]\cdot 2H_2O$	17.8	16.7	3.26	3.33	16.1	15.8	10.5	12.0		
[P(GA)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 3H_2O$	11.6	11.8	4.65	3.46	16.1	15.0	9.35	9.17	29.5	31.2
[P(GA)(GK)P(MA)(GK)] $\cdot 3/2H_2O$	18.4	18.7	4.24	4.39	21.4	20.1	14.8	15.1		
[P(GA)(G)P(MA)(OH)] $\cdot Pt(NH_3)_2)\cdot 2H_2O$	16.3	15.7	5.28	3.67	18.6	19.1	15.2	13.8	13.4	13.1

Table 3. Data of Polyphosphazene Derivatives

Polyphosphazenes	IR, cm^{-1}	^{1}H NMR, ppm	^{31}P NMR, ppm	Mw($\times 10^4$)
$[P(GE)_2]$	1743 (COOEt) 1205, 1136 (PN)	1.3 ($CO_2CH_2\underline{CH_3}$, 3H) 3.7 ($NH\underline{CH_2}CO_2$, 2H) 4.2 ($CO_2\underline{CH_2}CH_3$, 2H)	19.8	1.2
$[P(GNa)_2]\cdot 2H_2O$	1593 (COONa) 1230, 1118 (PN)	3.4 ($NH\underline{CH_2}CO_2$, 2H)	24.3 (br.)	0.9
[P(GH)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 2H_2O$	1649 (COOPt) 1593(COONa), 1133 (PN)	3.4-3.7 ($NH\underline{CH_2}CO_2$, 2H)	22.9-28.4 (br.)	0.3
$[P(GA)_2]$	1652, 1561 (CONH, I, II) 1257, 1192 (PN)	3.5 ($NH\underline{CH_2}CO$, 2H) 2.7 ($NH\underline{CH_3}$, 3H)	23.1	2
$[P(GA)(GK)]\cdot 2H_2O$	1646 (CONH) 1587 (COOK) 1229, 1122 (PN)	3.4-3.7 ($NH\underline{CH_2}$ CONH, $NH\underline{CH_2}$COOK) 2.7 ($CONH\underline{CH_3}$)	23.1(br)	1
[P(GA)(G)P(OH)(G)] $\cdot Pt(NH_3)_2\cdot 3H_2O$	1645 (CONH) 1595 (COOPt)	3.4-3.5 ($NH\underline{CH_2}CONH$, $NH\underline{CH_2}COOPt$)	23.2-28.8	0.5
[P(GA)(MA)]	3386(NH) 1660, 1556 (CONH, I, II) 1250, 1109 (PN)	3.6 ($NH\underline{CH_2}CO$, 2H) 2.7 ($CONH\underline{CH_3}$, 3H) 2.5 ($NH\underline{CH_3}$, 3H)	23.2, 25.7 28.4	2
[P(GA)(GK)P(MA)(GK)] $\cdot 3/2H_2O$	1651 (CONH) 1589 (COOK)	3.4-3.7 ($NH\underline{CH_2}CONH\underline{CH_3}$, $NH\underline{CH_2}COOK$) 2.7 ($CONH\underline{CH_3}$), 2.5 ($NH\underline{CH_3}$)	22.8, 25.5 28.9	1.5
[P(GA)(G)P(MA)(G)] $\cdot Pt(NH_3)_2\cdot 2H_2O$	1655 (CONH) 1600 (COOPt) 1245, 1126 (PN)	3.4-3.9 ($NH\underline{CH_2}COOPt$, $NH\underline{CH_2}CONH$) 2.8 ($CONH\underline{CH_3}$), 2.5 ($NH\underline{CH_3}$)	22.9-28.9(br)	0.8

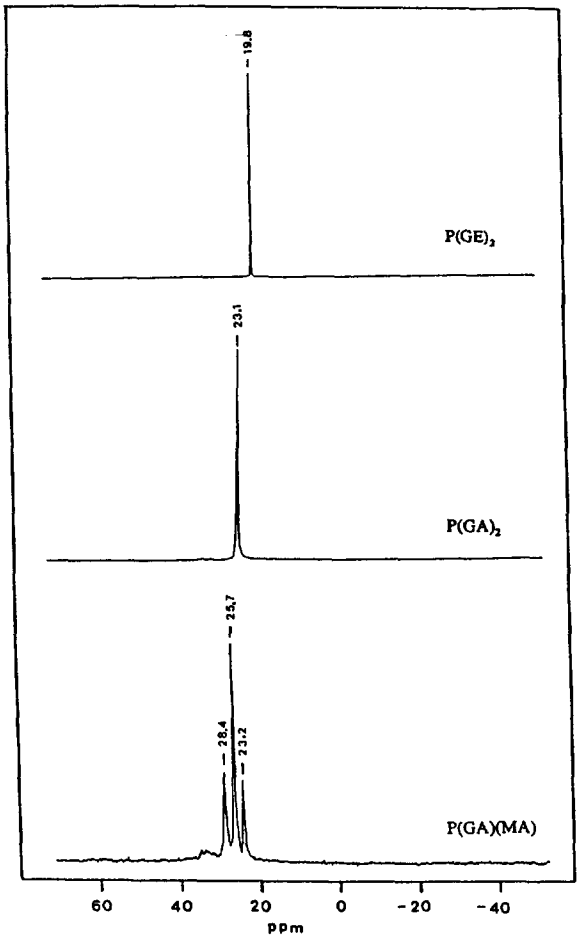


Figure 1. ^{31}P NMR spectra of polyphosphazene derivatives.

Table 4. Thermal Properties of Polyphosphazene Derivatives

Polyphosphazenes	$T_{ini.}$ (℃)	Tg (℃)	$T_{max.}$ (℃)	Residual wt. (%)
$[P(GE)_2]$	153	−21	197	49
$[P(GNa)_2]\cdot 2H_2O$	209	−23	264	72
$[P(GA)_2]$	154	−22	205	63
$[P(GA)(GK)]\cdot 2H_2O$	177	−29	232	72
[P(GA)(MA)]	163	−22	191	62
[P(GA)(GK)P(MA)(GK)] $\cdot 3/2H_2O$	178	−23	238	73

P(GA)(MA) shows three resonances at 23.2, 25.7 and 28.4 ppm, indicating that there are three different microenvironments probably comprising of RHN-P-NHR, RHN-P-NHR' and R'HN-P-NHR'. The ^{31}P NMR chemical shifts of all the final platinated polymer products appear as a broad peaks at around 23-29 ppm.

Properties and Antitumor Activity. The homopolymer $P(GA)_2$ is an opaque elastomer, which is soluble in alcohols, acetone, THF and benzene, but insoluble in water and *n*-hexane. $P(GA)_2$ and P(GA)(MA) are light yellow powder which are soluble both in alcohol and water, but insoluble in acetone and most other organic solvents. All the hydrolysis products of $P(GE)_2$, $P(GA)_2$ and P(GA)(MA) are very soluble in water, but their platinated products are only moderately soluble. The molecular weights of substituted polymers, hydrolized and its platinated products measured by GPC (Table 3) exhibit that the phosphazene polymers were degraded to a certain degree during the hydrolysis and platination processes. The glass transition temperature (Tg) and thermal properties of the phosphazene polymers are listed in Table 4.

The results of *in vitro* and *in vivo* assays against murine leukemia L1210 for the platinated polymers are given in Table 5. Among the three Pt(II)-containing polyphosphazenes only KBP 9263 is active comparably to carboplatin. The low antitumor activity of these polymers seems to be ascribed to low availability of the platinum(II) moiety *in vivo* which may be linked to intra- and/or intermolecular carboxylate groups. Further studies on molecular modifications of the polymer are underway to improve their anticancer activity and physicochemical properties.

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Table 5. Antitumor Activity of Polyphosphazene Derivatives Containing Platinum Complexes

Code. No.	Compound	*in vitro*	*in vivo*	
		ED_{50} (μg/mL)	Dose (mg/kg)	T/C (%)
KBP 9261	$[P(GH)(G)P(OH)(G)]\cdot Pt(NH_3)_2\cdot 2H_2O$	−	10	103
KBP 9263	$[P(GA)(G)P(OH)(G)]\cdot Pt(NH_3)_2\cdot 3H_2O$	13.4	10	110
			20	123
KBP 9264	$[P(GA)(G)P(MA)(OH)]\cdot Pt(NH_3)_2\cdot 2H_2O$	>40	10	97
			20	113
Carboplatin	$(NH_3)_2Pt(CBDCA)$	−10	20	128
Cisplatin	$(NH_3)_2PtCl_2$	0.3	4	174

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Syntheses and Characterizations of Lactam Cyclophanes. Attempted Synthesis of a Lactam Catenane Using Hydrogen Bonds

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New cyclophanes having multilactam linkages were synthesized and characterized. One-pot coupling reaction of 2,6-pyridinedicarbonyl dichloride and a diamine gave a tetralactam, a hexalactam, and a octalactam in good yields. The TLC behaviour, the molecular symmetry shown by ^{1}H NMR spectrum, and the fragmentation patterns shown by FAB mass spectrum of the octalactam support its monocyclic structure.

Introduction

Catenane[1] is a new topological isomer in which two or more cyclic compounds are interlocked each other to give a [2]catenane or a [n]catenane as shown in Figure 1. Rotaxane[1] is another topological isomer in which a chain component is threaded into a cyclic component but the chain component cannot escape due to the bulky groups at both ends. The first catenane was synthesized using statistical method in an extremely low yield.[2] But recently the high yields of new catenanes have been reported using metal templation,[3] charge-dipole interactions as well as π-π interaction.[4] Other weak molecular interactions such as dipole-dipole, hydrogen bonding, electrostatic, and hydrophobic interactions could be also applied in catenane synthesis, which implies that molecular recognition phenomena can be applied in articulate manner for designing and synthesizing new functional topological isomers in much improved yields.[5]

Cyclophanes, cyclic compounds in which aromatic units are incorporated, are good candidates for organizing those weak molecular interactions to give fruitful results in catenane chemistry.[6] Cyclophanes usually provide a hydrophobic cavity surrounded by aromatic rings facing each other. They were developed to charge transfer complexes, enzyme mimics, organic hosts, molecular sensors and etc. Enzyme mimics based on cyclophanes are attractive, because the designs and syntheses are easily accessible, the conformation is stable structurally, and various functional groups could be introduced to benzene rings.[7] Also, cyclophane hosts have the

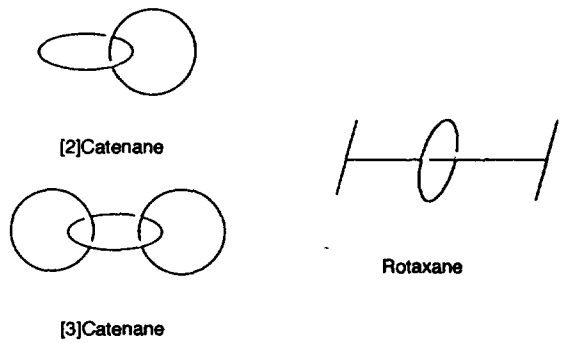

Figure 1. Illustration of Catenanes and Rotaxane.