Synthesis of Cephalosporins Having a Heterocyclic Group at the C-3 Position

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3-(3-Bromotetrahydrofuran-2-yl)-3-cephem **7** was obtained from 3-(2-hydroxyethyl)vinyl-3-cephem **6** by the cyclization reaction using N-bromosuccinimide. Compound **5** was prepared by Wittig reaction, namely a coupling of cephem-derived triphenylphosphonium salt **3** with aldehyde component **4** in the presence of base.

Introduction

As shown in Figure 1, cephalexin possesses a methyl group at C-3 position and exhibits better oral absorption than cephaloglycin which contains acetoxymethylene group at the same position[1]. Also cefaclor, in which chlorine atom is attached to C-3 position, turned out to have improved biological activity in comparison with cephalexin[2]. Cephalosporins like SPD-391[3], containing 3-[(S)-2-methylisoxazolidin-5-yl] group not only show improved activity against Gram-negatives including *Pseudomonas aeruginosa* but also have broad spectrum of antibacterial activity. The isoxazole moiety of SPD 391 was previously prepared by 1,3-dipolar addition of nitrone to the corresponing olefin diastereoselectively in a ratio of 2.7 : 1 (Scheme 1). Herein we would like to describe synthetic efforts directed toward new cephalosporin antibiotics by introduction of heterocycles to the cefixime system through endo selective brominative cyclization using N-bromosuccinimide.

Results and Discussion

In order to synthesize 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-bromotetrahydrofuran-2-yl)-3-cephem-4-carboxylic acid **11**, the requisite intermediate 3-(2-tetrahydropyranyl-oxyethyl)vinyl-3-cephem derivative **5** was prepared in 37% yield from cephem-1-oxide-derived triphenylphosphonium salt **3** and 3-(tetrahydropyranyloxy)propanal **4**[4,5] in the presence of Na_2CO_3 in CH_2Cl_2 as shown in Scheme 2[6,7]. The coupling constant (11 Hz) between two vicinal vinyl protons in **5** indicates the stereochemistry[8]. The two vinylic proton signals appeared as a doublet at δ 6.20 (H_a) and as

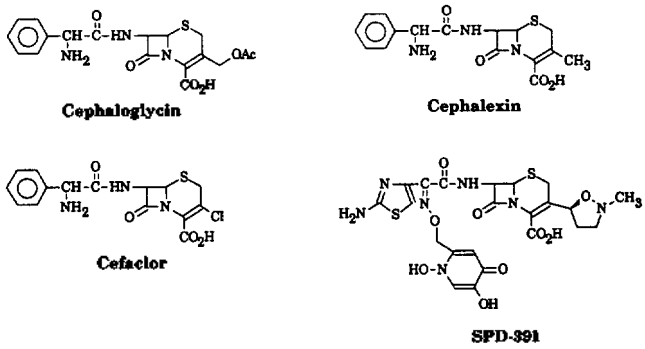
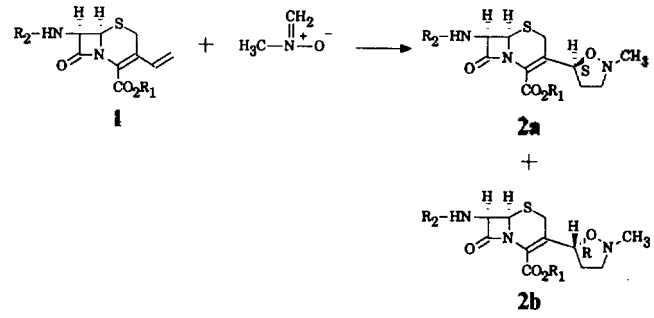
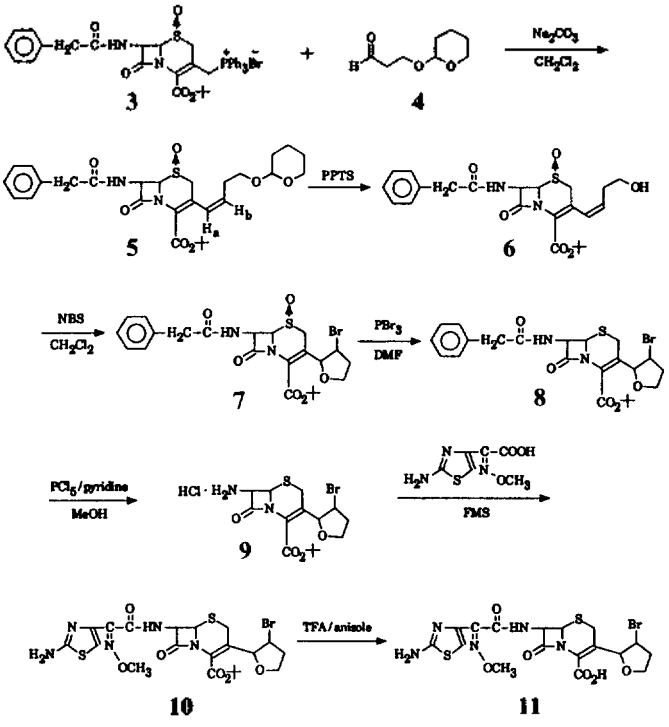


Figure 1.



Scheme 1



Scheme 2

a doublet of triplet at δ 5.65 (H_b). Subsequently, deprotection of the tetrahydropyranyl group under acidic conditions employing pyridinium *p*-toluenesulfonate afforded the (Z)-3-(2-

hydroxyethyl)vinyl-3-cephem **6** in 70% yield[9]. In the next step, the expected product was obtained by means of brominative cyclization of compound **6** with N-bromosuccinimide. Bromonium ion formation followed by the capture of the more stable carbocation by the alcohol resulted in the formation of the tetrahydrofuran ring[10]. The proton signals of the ring appeared at 5.12 ppm for H_2 and at 3.98 ppm for H_3 as typical triple-doublet pattern with the coupling constants of $^3J_{trans}=8$ Hz and $^3J_{cis}=18$ Hz[11]. 3-(3-Bromotetrahydrofuran-2-yl)-3-cephem-1-oxide **7** was reduced to sulfide **8** using phosphorus tribromide (DMF, 0℃, 1 h, 75% yield). Deprotection of the phenylacetyl group in **8** was carried out in one-pot process with PCl_5 and pyridine-methanol to give the 7-amino-3-(3-bromotetrahydrofuran-2-yl)-3-cephem derivative **9**. The coupling reaction of **9** with (Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetic acid using 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole[12] afforded the cephem derivative **10** in 90% yield. In the final stage, hydrolysis of the ester **10** with trifluoroacetic acid in anisole afforded the final product **11** in 10% yield after column chromatography. We are presently studyings possile derivatizations of **11** in an attempt to prepare cephalosporin antibiotics.

Experimental

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and uncorrected. ^{1}H-NMR spectra were recorded on a 200 MHz Varian Gemini 200 NMR spectrometer or 300 MHz Brucker AM-300 NMR spectrometer using TMS as an internal standard. IR spectra were taken on a Shimadzu IR-435 spectrometer.

3-(2-Tetrahydropyranyl)oxypropanal (4). To a mixture of 1,3-propanediol (7.60 g, 0.1 mol) and *p*-toluenesulfonic acid monohydrate (0.20 g, 1.1 mmol) in CH_2Cl_2 (80 m*l*) was added dropwise 3,4-dihydro-2*H*-pyran (8.41 g, 0.1 mol). The reaction mixture was stirred at room temperature for an additional 30 minutes. Water was added, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the residue was purified by column chromatography on silica gel using EtOAc as an eluent to give 3-(2-tetrahydropyranyl)oxypropanol (11.50 g, yield: 72%). To a suspension of pyridinium chlorochromate (10.50 g, 0.049 mol) on Celite (10.50 g) in CH_2Cl_2 (50 m*l*) was added dropwise 3-(2-tetrahydropyranyl)oxypropanol (11.50 g, 0.072 mol) in CH_2Cl_2 (20 m*l*) at room temperature over a 3 hr period. To the reaction mixture after addition of diethyl ether (70 m*l*) was filtered. The organic layer was evaporated *in vacuo*. The residue was chromatographed on silica gel to afford 10.22 g (90%) of **4**: IR(NaCl) cm^{-1} 1720 (aldehyde C=O); ^{1}H-NMR ($CDCl_3$) δ 1.40-2.00 (8H, m, 3-H, 4-H, 5-H tetrahydropyran ring and 2-H), 2.58 (2H, m, 6-H tetrahydropyran ring), 3.30-4.20 (4H, m, 2-H, 3-H), 4.58 (1H, m, 2-H tetrahydropyran ring), 9.70 (1H, bs, CHO).

***t*-Butyl 7-phenylacetamido-3-(Z)-(2-tetrahydropyranyloxyethyl)vinyl-3-cephem-4-carboxylate-1-oxide (5).** To a solution of **3** (22.37 g, 0.03 mol) in CH_2Cl_2 (200 m*l*) was added Na_2CO_3 (4.40 g, 0.04 mol) in H_2O (10 m*l*). The mixture was stirred at room temperature for 30 minutes. Then, to the mixture was added **4** (4.00 g, 0.03 mol) at the same temperature. After 20 hrs, the reaction mixture adjusted to pH 6 with 10% HCl, and the separated organic layer was washed with brine, and evaporated *in vacuo*. The residue was purified on silica gel using toluene-EtOAc, 3 : 1, as eluent to give 5.00 g (37%) of **5**: mp. 154-155℃; IR(KBr) cm^{-1} 1778 (β-lactam C=O); ^{1}H-NMR ($CDCl_3$) δ 1.49, 1.70, 2.30 (8H, m, 3-H, 4-H, 5-H tetrahydropyran ring), 3.10-3.85 (m, 6H, ethyl, 2-H), 3.60 (2H, bs, CH_2CO), 4.45 (1H, d, 6-H, $J=5$ Hz), 4.52 (1H, m, 2-H tetrahydropyran ring), 5.65 (1H, dt, H_b vinyl, $J=7$ Hz, 11 Hz), 6.00 (1H, dd, 7-H, $J=5$ Hz, 9 Hz), 6.20 (1H, d, H_a vinyl, $J=11$ Hz), 6.82 (1H, d, NH, $J=9$ Hz), 7.25 (5H, m, Ph).

***t*-Butyl 7-phenylacetamido-3-(Z)-(2-hydroxyethyl)vinyl-3-cephem-4-carboxylate-1-oxide (6).** A solution of **5** (10.89 g, 0.02 mol) in EtOH (100 m*l*) was treated with pyridinium *p*-toluenesulfonate (0.50 g, 0.002 mol) at 55℃ for 4 hours. After removal of the EtOH under reduced pressure, the residue was treated with EtOAc (200 m*l*) and aq. $NaHCO_3$. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel [toluene-EtOAc (1 : 1)] to give 6.50 g (71%) of **6** as a solid: mp. 147-149℃; IR(KBr) cm^{-1} 1775 (β-lactam C=O); ^{1}H-NMR ($CDCl_3$) δ 1.50 (9H, bs, *t*-butyl), 1.80, 2.25 (4H, m, ethyl), 3.20, 3.80 (2H, ABq, 2-H, $J=18$ Hz), 3.62 (2H, s, CH_2CO), 4.49 (1H, d, 6-H, $J=5$ Hz), 5.65 (1H, dt, H_b vinyl, $J=6$ Hz, 12 Hz), 6.02 (1H, dd, 7-H, $J=5$ Hz, 9 Hz), 6.24 (1H, d, H_a vinyl, $J=12$ Hz), 6.95 (1H, d, NH, $J=9$ Hz), 7.30 (5H, m, Ph).

***t*-Butyl 7-phenylacetamido-3-(3-bromotetrahydrofuran-2-yl)-3-cephem-4-carboxylate-1-oxide (7).** To a solution of **6** (6.00 g, 0.013 mol) in CH_2Cl_2 (60 m*l*) at 0℃ was added N-bromosuccinimide (2.34 g, 0.013 mol). After stirring at room temperature for 4 hours, the reaction mixture was poured into a mixture of CH_2Cl_2 (100 m*l*) and H_2O (100 m*l*). The separated CH_2Cl_2 layer was washed with brine, dried, and evaporated *in vacuo*. The residue was purified on silica gel [toluene-EtOAc (1 : 2)] to give 4.30 g (61%) of **7** as a solid: IR(KBr) cm^{-1} 1769 (β-lactam C=O); ^{1}H-NMR ($CDCl_3$) δ 1.50 (9H, bs, *t*-butyl), 2.45, 2.70 (2H, m, 4-H tetrahydrofuran ring), 3.12, 4.05 (2H, ABq, 2-H), 3.58 (2H, s, CH_2 CO), 3.95 (1H, td, 3-H tetrahydrofuran ring $J=8$ Hz, 18 Hz), 4.25, 4.40 (2H, m, 5-H tetrahydrofuran ring), 4.62 (1H, d, 6-H), 5.10 (1H, m, 2-H tetrahydrofuran ring), 6.05 (1H, dd, 7-H), 6.88 (1H, d, NH), 7.30 (5H, m, Ph).

***t*-Butyl 7-phenylacetamido-3-(3-bromotetrahydrofuran-2-yl)-3-cephem-4-carboxylate (8).** To a solution of **7** (2.00 g, 3.7 mmol) in DMF (20 m*l*) at 0℃ was dropwise added PBr_3 (0.7 m*l*). After stirring at room temperature for 2 hours, the reaction mixture was poured into a mixture of EtOAc (100 m*l*) and aq. $NaHCO_3$. The separated organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was triturated with *n*-hexane to afford 1.47 g (76%) of **8**: IR(KBr) cm^{-1} 1772 (β-lactam C=O); ^{1}H-NMR ($CDCl_3$) δ 1.50 (9H, bs, *t*-butyl), 2.40, 2.65 (2H, m, 4-H tetrahydrofuran ring), 3.48, 3.80 (2H, ABq, 2-H, $J=18$ Hz), 3.63 (2H, s, CH_2CO), 4.05, 4.25 (2H, m, 3-H, 5-H tetrahydrofuran ring), 4.94 (1H, d, 6-H, $J=5$ Hz), 4.99, 5.08 (2H, m, 2-H, 5-H tetrahydrofuran ring), 5.83 (1H, dd, 7-H, $J=5$ Hz, 9 Hz), 6.23 (1H, d, NH, $J=9$ Hz), 7.30 (5H, m, Ph).

***t*-Butyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimi-**

noacetamido]-3-(3-bromotetrahydrofuran-2-yl)-3-cephem-4-carboxylate (10). To a suspension of PCl_5 (0.64 g, 3.0 mmol) in CH_2Cl_2 at the ice-bath temperature was added pyridine (0.24 g, 3.0 mmol). The mixture was stirred at the same temperature for 10 minutes before addition of **8** (1.47 g, 2.8 mmol). After treated with 2 hours at −10℃ the reaction mixture was carefully MeOH (30 m*l*) at −30℃. The resulting mixture was stirred at 0℃ and concentrated under reduced pressure. The residue was pulverized with diethyl ether to give 0.87 g (70%) of **9**. Compound **9** was used in the subsequent reaction without further purification. To a solution of 2-(2-aminothiazole-4-yl)-2-methoxyiminoacetic acid (0.50 g, 2.5 mmol) and 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS, 0.65 g, 2.3 mmol) in DMF (15 m*l*) at 0℃ was added triethylamine (0.25 g, 2.5 mmol) and **9** (0.87 g, 2 mmol). After stirring at room temperature for 2 hours, the reaction mixture was poured into a mixture of EtOAc (100 m*l*) and aq $NaHCO_3$. The separated EtOAc layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was triturated with *n*-hexane to give 0.78 g (67%) of **10** as a powder: IR(KBr) cm^{-1} 1782 (β-lactam C=O); ^{1}H-NMR ($CDCl_3$) δ 1.50 (9H, bs, *t*-butyl), 2.42, 2.65 (2H, m, 4-H tetrahydrofuran ring), 3.54, 3.88 (2H, ABq, 2-H, J=18 Hz), 4.06 (3H, s, $-OCH_3$), 4.04, 4.25 (2H, m, 3-H, 5-H tetrahydrofuran ring), 5.08 (1H, d, 6-H, J=5 Hz), 5.15, 5.25 (2H, m, 2-H, 5-H tetrahydrofuran ring), 6.00 (1H, dd, 7-H, J=5 Hz, 9 Hz), 6.95 (1H, s, aminothiazol-H), 7.05 (1H, d, NH, J=9 Hz).

7-[(Z)-2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-bromotetrahydrofuran-2-yl)-3-cephem-4-carboxylic acid (11). A mixture of **10** (0.59 g, 1 mmol), trifluoroacetic acid (5 m*l*) and anisole (5 m*l*) in CH_2Cl_2 (30 m*l*) was stirred at −10℃ for 30 minutes and at room temperature for 4 hours, and concentrated under reduced pressure. The residue was triturated with diethyl ether to give 0.30 g (56%) of **11** as a crude product, which was purified by column chromatography on silica gel using CH_3CN-MeOH, 4 : 1, as eluent. 52 mg (10%) of **11** as a solid: mp. 150-151 ℃ (dec.); IR(KBr) cm^{-1} 1778 (β-lactam C=O); ^{1}H-NMR (DMSO-d_6) δ 2.30, 2.70 (2H, m, 4-H tetrahydrofuran ring), 3.80 (3H, s, OCH_3), 3.62, 3.80, 3.95, 4.15 (4H, m, 3-H, 5-H tetrahydrofuran ring and 2-H), 4.95 (1H, d, 6-H), 5.05, 5.18 (2H, m, 2-H, 5-H tetrahydrofuran ring), 5.78 (1H, dd, 7-H), 6.70 (1H, s, aminothiazol-H), 7.25 (2H, bs, NH_2), 9.70 (1H, d, NH).

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The Gelation Studies of N-Methylolated PAAms in Aqueous Media

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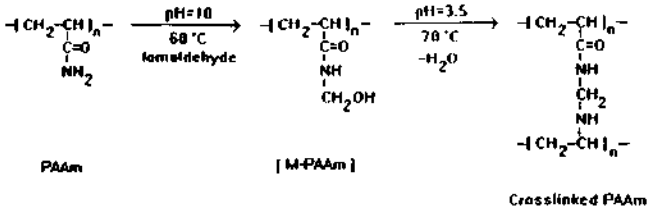
The gelation phenomena of N-methylolated PAAm (M-PAAm) in aqueous media was studied. The critical gelation concentration (CGC) was very close to the calculated C* of the scaling theory. But the CGC of lower MW M-PAAm deviated from C* due to contamination of small molecules. We propose that the CGC is the close packing configuration of polymer molecules in solution. The experimental results of the gelation of M-PAAm/PAAm mixture proved that the close packing configuration is essential to make a gel. We calculated the minimum quantity of M-PAAm to make M-PAAm/PAAm mixture a gel by using the close packing configuration. We used a lattice model.

Introduction

Gelation is needed to make crosslinked polymers, which have many important uses in polymer and other fields of science. The method of gelation is divided into two. One is the most popular one step copolymerization of monomer



Scheme 1.

and crosslinking agent (in situ polymerization). The other one is two step gelation which is to make linear polymer first and crosslink it afterwards. We studied the gelation of N-methylolated polyacrylamide (M-PAAm) in aqueous media. This belongs to the two step gelation. Curing of rubber is the typical case of this. The theory of curing[1] is applicable only to melt system, and can not be applicable to our solution system. To explain the gelation of PAAm solution, we adopted the scaling theory.[2]

To obtain PAAm gel, we used formaldehyde. Two stages are needed to complete gelation.[3] At the first stage, formaldehyde react with the amide group in PAAm at the condition of pH=10. Then partly N-methylolated PAAm (M-PAAm) is produced. When pH is high, M-PAAm does not go gelation by itself.[4] Gelation completes by lowering pH to 3.5. The nitrogen atom in amide group attacks the carbon in N-methylol group, and a crosslinkage is formed by eliminating a water molecule. This is depicted in Scheme 1. One fact that must be emphasized is that formaldehyde is not a crosslinking agent. It is a methylolating agent. We always get rid of residual formaldehyde after methylolation. Crosslinking is proceeded by the reaction of N-methylol group and amide group at low pH condition.

Experimental

Polymerization

50 g of acrylamide (Katayama Chemical) was dissolved in 1000 m*l* of deionized water. Then a redox initiator of 1 : 1 sodium thiosulphate ($Na_2S_2O_3$) and ammonium persulphate ($(NH_4)_2S_2O_8$) were added to the monomer solution. The mixture was purged in N_2 atmosphere and polymerized by heating to 60℃ for 5 hrs. After the reaction, the prepared PAAm solution was dialyzed to remove small molecules and freeze dried. Five samples of different molecular weights were prepared by the same procedure differing only in the amount of initiator.

Molecular weights of the samples were measured by intrinsic viscosity experiments. The equation for MW calculation is[5] $[\eta]=6.31\times10^{-3}\ M_w^{0.8}$.

Polydispersity

Polydispersities of sample PAAms were measured by a GPC. A column used was Tosoh TSKgel G5000 PWXL. Standard polymers for calibration of the column were Sigma MW-GF-1000 molecular weight markers. Polydispersities of sample polymers are not greater than 1.2.

Methylation of PAAm

Each of 5 g of dry PAAm sample was dissolved in 100 m*l* of distilled water. Then, 2.1 m*l* of formaldehyde (1 : 3 in monomer mol ratio) was added, and a dropwise of conc NaOH solution was added to adjust the mixture to pH=10. Finally the mixture was sealed and left at 60℃ for 2 hrs. The prepared M-PAAm were dialyzed for 8 hrs to get rid of unreacted formaldehyde and freeze dried. This carefully treated M-PAAm did not crosslink with each other and dry M-PAAms dissolved in water readily.

Table 1. Characteristics of Synthesized PAAms and Degress of Methyloation for M-PAAms

# of Sample	MW of PAAm[a]	Polydispersity[b]	Degree of methylolation (%)[c]
1	562,000	1.14	10.5
2	389,000	1.08	11.2
3	170,000	1.13	11.9
4	85,000	1.12	12.6
5	51,000	1.19	13.1

[a]Measured by viscometric method. [b]Measured by a GPC. [c]Measured by the conductometric titration for M-PAAm samples.

Conductometric Titration

To know the extent of methylolation, we conducted a conductometric titration experiment.[6] We first made acetylating agent which is a mixture of 12 m*l* acetic anhydride and 88 m*l* anhydrous pyridine. 20 m*l* of this blank acetylating agent is diluted in 100 m*l* of distilled water and standardized by titrating with 1 N NaOH solution. A conductivity meter was used for this titration.

Each of 1 g of dry M-PAAm was dissolved in 20 m*l* of freshly prepared blank acetylating agent. The mixture was then refluxed for 1 hr at 80℃, and titrated with 1 N NaOH solution.

Gelation

Gelation of M-PAAm. To point out the critical gelation concentration of each M-PAAm, we prepared five M-PAAm solution of different concentration for each sample. In 1.5 cm diameter test tubes, calculated amounts of dry M-PAAm were dissolved in 20 m*l* of distilled water and pH was adjusted to 3.5 by dropwisely adding 0.1 N HCl solution. Then mixtures were sealed and left at 70℃ for 3 hrs. Tubes that did not flow when tilted are crosslinked. We define here the gel as the material which i) does not flow and ii) maintains its shape and iii) has no gel fraction in it. Tubes that flow when tilted are crosslinked partly but not crosslinked totally. Intrinsic viscosities were measured for these partly crosslinked tubes.

Gelation of Mixtures of PAAm and M-PAAm at the critical gelation concentration. In test tubes PAAm and M-PAAm solutions of critical gelation concentration were preapred for each sample. Then, two solutions were mixed at various ratios in other tubes. The total polymer concentration of the mixed solution was the same as the critical gelation concentration. The gelation procedures were the same as the previous M-PAAm case.

Results and Discussion

Five PAAm sample polymers of molecular weights from 51,000 to 562,000 are prepared. Their molecular weight distributions after thorough dialysis are not greater than 1.2 as shown in Table 1. Methylolation was conducted by using

Table 2. The Comparison of the Experimental CGCs of M-PAAms with the Calculated Values of C*

# of sample	MW	CGC[a]	CGC[b]	C*[c]
1	562,000	2.27	2.25	2.45
2	389,000	3.13	3.09	3.38
3	170,000	6.00	5.56	6.42
4	85,000	12.5	8.00	12.04
5	51,000	19.0	14.00	16.72

[a]The CGCs of M-PAAms which were obtained after dialysis for 74 hrs. [b]The CGCs of M-PAAms which were obtained after dialysis for 26 hrs. [c]Calculated from the equation[2] $C^* = a^{-3}N^{-4/5}$. [a,b,c]The unit is g/dl.

these five sample PAAms. The extent of methylolation for the methylolated polymer has the value between 10% and 13% which is observed by conductometric titration.

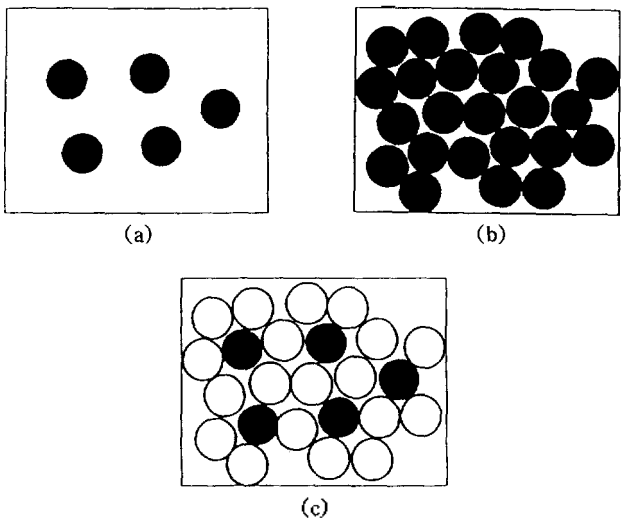
Gelation reaction was conducted with varying polymer concentration. Solutions became totally a gel phase when concentration reached a certain critical point. We call the lowest polymer concentration the critical gelation concentration (CGC) where gelation occurs for the first time.

The CGC depends on the molecular weight of M-PAAm. Table 2 shows that high molecular weight M-PAAm has lower CGC. We expect the CGC as a concentration of close contact between neighboring molecules. According to the scaling theory by de Gennes, the concentration of close contact is the overlap threshold concentration C*. Below this concentration, molecules maintain their own spherical shape (dilute regime). Above this concentration, interpenetration occurs between neighboring polymer molecules (semi dilute regime).[2] We compared the CGC with the calculated value of C* in Table 2. In the calculation we gave the C-C bond length as 1.54 A, and degree of polymerization N as MW/71.08. The formula weight of PAAm repeating unit is 71.08. We note here that the C* is the scaling value. It gives the tendency of MW dependence of the threshold concentration but not the absolute value.

We see a very good agreement between these two concentration when MW is 389,000 and 562,000. The fact that the CGC is very close to C* tells us that gelation at the CGC is due to the intermolecular close packing of neighboring molecules. The dependence of CGC on the molecular weight is as follows. A large molecule occupies large space in solution. When volume of solution is the same and the CGC is the close contact concentration, fewer numbers of large molecule are sufficient to pack the volume comparing with small sized molecule.

The CGC is somewhat smaller than C* when MW of M-PAAm is lower. We consider that this discrepancy is due to the molecular weight distribution which is unavoidable in synthetic polymers. Lower part MW components, especially oligomeric molecules seem to serve as arms between spheres. The CGC values obtained becomes much lower when gelation is conducted without thorough dialysis. We showed the experimental CGC data for poorly dialyzed samples in Table 2.

To prove the close contact picture at CGC, we conducted another experiment. We chose #2 sample of MW 389,000.

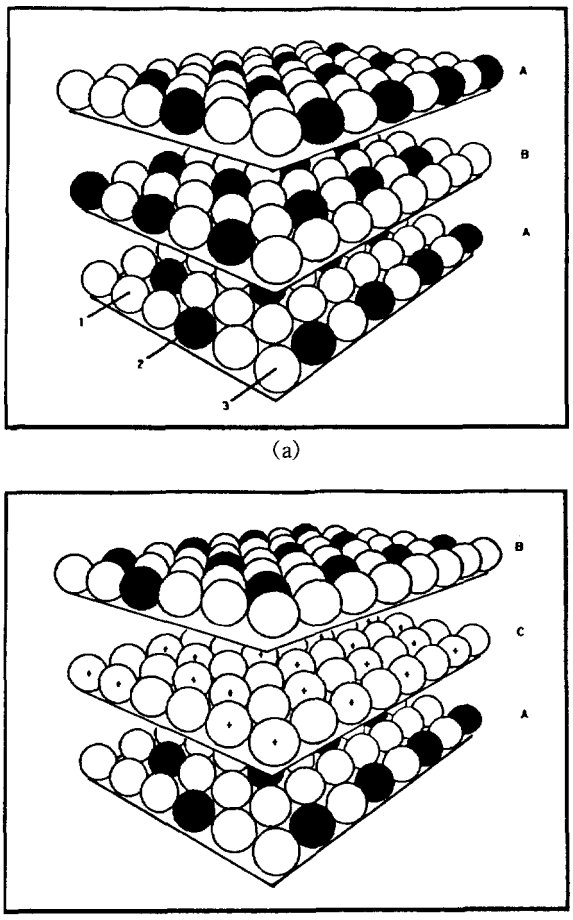


Scheme 2. Schematic representation of polymer solution in various concentration and composition. (a) C<C*: no gelation. (b) C=C*: critical concentration. (c) C*=C: mixture of PAAm (○) and M-PAAm (●).

Its CGC was 3.13 g/dl. We prepared mixed polymer solutions of #2 PAAm and #2 M-PAAm with various ratios, but total concentration is adjusted equally to 3.13 g/dl. Then gelation is conducted by lowering pH to 3.5 A total gel phase occurs when M-PAAm is more than 1/6 of the total weight of the mixture. This is shown at Scheme 2 in detail. One polymer molecule is expressed as a sphere. Black one is an M-PAAm and white one is a PAAm molecule respectively. The situation cited above is depicted in (c). To make the point more clear, we showed M-PAAm solution in (a) and (b). Below the CGC, polymers do not contact with each other as shown in (a), and no gelation occurs. (b) is M-PAAm solution at CGC, and it forms a total gel phase. Mixed polymer solution is shown in (c) and the total concentration of the solution is the same as (b), 3.13 g/dl. (c) makes a total gel phase also. PAAm does not make a gel by itself; M-PAAms in it does a role of crosslinkage. Suppose that we erase the white spheres in (c), it becomes (a). PAAm molecules contribute the close packing structure, which is the essential condition to give a total gel.

Samples other than #2 showed the similar behavior. When the M-PAAm porotion is lower than 1/6, crosslinkage point is not sufficient and do not make a gel effectively. We obtained the value of 1/7 for the samples of lower MW #4 and #5 samlples. One major reason of this lower value for low MW samples seems to be the small molecule contamination as discussed previously.

We consider the minimum quantity of M-PAAm to make M-PAAm/PAAm mixture a gel by using the lattice model. We express a polymer molecule in solution as a sphere again. The concentration is CGC, the closely packed configuration. The coordination number is chosen as 6. Scheme 3 (a) is one of the possible three dimensional configurations of solutions. Layers denoted by A and B differ only in the order of rows. Each layer is wholly bounded by the action of M-PAAm which is expressed in a black sphere. Rows denoted by 1, 2, 3 are the rows of 1 : 1 population of PAAm and M-PAAm which comes in turn. Rows which place in between



Scheme 3. Three dimensional lattice model of the mixture of M-PAAm and PAAm. The ratio of the number of PAAm (○) to the number of M-PAAm (●) is 3:1 (a) and 7:1 (b), respectively.

these 1 : 1 rows are composed by PAAm only. When the lattice is composed of such configuration, a total gelation occurs. The portion of M-PAAm is 1/4. In this configuration, all the molecules are bound together in a huge gel and it is one molecule in itself. If the M-PAAm portion is greater than 1/4, a more stable gel will be prepared.

Another meaningful configuration is Scheme 3 (b). The lattice is composed by BCABCA··· order. The layer C is composed of PAAm only. To form a total network, there must be several numbers of M-PAAms on the C layer in place of PAAms to link the layers A and B. But we neglect them because they are small with regard to the total number of M-PAAms. Molecules marked by + are not bound by M-PAAm molecules directly but bounded by the lattice. Therefore, this configuration is not totally one molecule. But the marked molecules do not diffuse out because of large dimension of network. The portion of M-PAAm in this configuration is 1/8, which is the minimum amount of M-PAAm to form a total gel phase. Our experimental result of the minimum amount of M-PAAm is in between these two models. This is another support of our close pack picture, though not accurate in model.

When concentration was below the CGC, no gelation occurred and solution in test tube flowed when tilted. Although this does not make a total gel, the solution becomes more viscous than the original solution because the gelation goes partially. We measured intrinsic viscosities of these partly crosslinked solutions for the sample #3 M-PAAm. Table 3 shows the results of this experiment. Intrinsic viscosity of sample #3 M-PAAm is 0.096 *l*/g. Intrinsic viscosity of partly crosslinked #3 M-PAAm increases when the concentration of solution is higher. We estimated the size of the partly crosslinked clusters from molecular weight calculation. When gelation concentration is 4.76 g/d*l*, 6.2 polymer molecules are bound together. When concentration is 5.26 which is just below the gelation point, average 14.5 polymers are bounded. These results are not sufficient to explain the gelation mechanism quantitatively. The Mark-Houwink relationship which was used for MW calculation is not applicable to the partially crosslinked M-PAAm. Therfore we present them as a qualitative picture of concentration dependence of the gelation phenomena.

Table 3. Intrinsic Viscosities of Partly Crosslinked #3 M-PAAms Depending on Gelation Concentration

	Conc. (g/d*l*)	$[\eta]^a$ (*l*/g)	M_w^b	Apparent number of molecules[c]
#3 M-PAAm		0.096	1.45×10^5	
Partly	4.76	0.32	9.01×10^5	6.2
Crosslinked	5.00	0.46	1.56×10^6	10.7
#3 M-PAAm	5.26	0.50	1.77×10^6	14.5
Gel	5.56	can not measure viscosity		

[a]Measured in water at 30℃. [b]$[\eta]=6.31\times10^{-3}M_w^{0.8}$. [c]Average number of molecules in a partly crosslinked cluster, calculated from the intrinsic viscosity data.

We expect from the result that clustering progresses when M-PAAm molecules contact with one another. In a very dilute concentration, sphere-like polymer molecules exist separately. Therefore, intermolecular contact is scarce. As concentration increases gradually, the opportunity to contact neighboring molecules also increases and average cluster size becomes larger. We notice here that this concentration region is below C*. Nevertheless, a contact would be sufficient to form a chemical bond between two spheres.

Above the CGC, gelation proceeded more readily; the density of gel was higher. We consider this as an interpenetration effect of neighboring polymers. Below the CGC only the N-methylol groups on the surface of the spherical shape play a role for crosslinking. As a result, N-methylol groups in the sphere contribute to crosslinking also as interpenetration proceeds and crosslink point increases.

Conclusion

We obtained the following results from our experiments:

1. Gelation of M-PAAm solution occurs at the CGC which is very close to C*.

2. The close packing configuration is essential to make a gel phase when concentration is C*.

3. The minimum portion of M-PAAm for gelation of PAAm/M-PAAm mixture is successfully explained by the close packing lattice model.
4. Interpenetration occurs above C* or the CGC, where gels are made more readily and density is higher.

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Studies on Thermal Decomposition of Barium Titanyl Oxalate by Factor Analysis of X-Ray Diffraction Patterns

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Factor analysis was applied to study the thermal decomposition of barium titanyl oxalate (BTO) which is used as the precursor of barium titanate. BTO was synthesized in H_2O solvent and calcined at various temperatures. The X-ray diffraction patterns were obtained to make the data matrix of peak intensity vs. 2θ. Abstract factor analysis and target transformation factor analysis were applied to this data matrix. It has been found that the synthesized BTO consists of the crystals of $BaC_2O_4 \cdot 0.5H_2O$ and $BaC_2O_4 \cdot 2H_2O$ as well as the amorphous solid of TiO-oxalate. The results also indicate that the BTO was transformed via $BaCO_3$ to $BaTiO_3$ and Ba_2TiO_4 during the thermal decomposition.

Introduction

Factor analysis has been used in the analysis of multivariate data where a number of independently contributing factors are required.[1] This method was applied to determine the contributing substances in IR spectra,[2,3] mass spectra,[4] UV spectra[5] and liquid chromatogram[6] for mixtures of substances.

A much veritable information is obtained with dozens of parameters that could possibly affect an analysis of data. A typical example of this is seen in a lot of lines which it is possible to obtain from a scanned X-ray diffraction pattern of even simple substance. For many years, the method used to obtain the useful information has been to focus on 1-3 lines and the diffraction pattern is compared with patterns of known substances until a match is obtained. This is a univariate approach to analysis and require skilled technique for the correct match of an X-ray pattern. For this reason, multivariate analysis such as factor analysis must be applied to all pattern data (d values and intensities).

In the present investigation, abstract factor analysis (AFA)[7] and target transformation factor analysis (TTFA)[7-9] have been used to determine the number of factors and to verify individually the presence of the suspected components contributing to the X-ray diffraction patterns, which were obtained during calcination of barium titanyl oxalate (BTO) synthesized in H_2O solvent system. Thus, the results of AFA and TTFA have been used to study the thermal decomposition process of the BTO.

BTO is a precursor of barium titanate ($BaTiO_3$), which is one of perovskite-type ceramics and is of interest for the effect of the positive temperature coefficients of resistivity (PTCR). Clabaugh *et al.*[10] reported that a high purity barium titanate of nearly perfect stoichiometry could be prepared by precipitating barium titanyl oxalate ($BaTiO(C_2O_4)_2 \cdot 4H_2O$ (BTO)) and subsequently converting this material to barium titanate by calcination. Kudaka *et al.*[11] also reported the optimum conditions for the formation of BTO in more detail. For the preparation of BTO, they added the mixed solution of barium chloride and titanium tetrachloride to the aqueous solution of oxalic acid.

Yamamura *et al.*[12] employed a revised Clabaugh method to prepare BTO in which the ethanol solution of the oxalic acid was added to the mixed starting solution of $Ba(NO_3)_2$ and $TiO(NO_3)_2$. Although Yamamura *et al.* speculated that the composition of the crystalline precipitate was $BaTiO(C_2O_4)_2 \cdot 3H_2O$ based on the thermogravimetric data, a recent study by Fang and Lin[13] showed that the precipitate produced by Yamamura method is composed of cyrstalline barium nitrate and amorphous titanium oxalate. They also performed