Kinetic Behavior and Interaction of Bacampicillin in Alginic Acid Solution at Neural pH Region[1)]

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Stabilization of bacampicillin (BAPC) in suspension was examined by the addition of alginic acid (Alg). BAPC formed a slightly water-soluble adduct (BAPC–Alg) with Alg, in which BAPC and Alg were presumed to be linked by ionic bonding. However, the suspension of this chemically stable adduct showed a similar lability to a suspension of BAPC alone; chemically very unstable particles of BAPC base were deposited in the suspension. In contrast, when BAPC–Alg adduct was suspended in 1.0% Alg solution at the same pH region, the precipitation of the particles of BAPC base were not observed. This stabilization is supposed to be due not only to the chemical stability of the adduct, but also to an inhibition of the deposition of an unstable BAPC base particles by Alg.

Keywords bacampicillin; suspension; alginic acid; bacampicillin–alginic acid adduct; precipitation; degradation; stabilization; solubility; partition coefficient; infrared spectrum

Bacampicillin (BAPC) was proved to degrade according to apparent first-order kinetics and an acid-base catalysis in a dilute solution.[2)] Bacampicillin in the gastrointestinal tract, however, is assumed to be a concentrated solution or a suspension from its usual clinical dose. Certain penicillins such as ampicillin (ABPC) are well known to show concentration dependence of degradation in solution.[3)] Therefore, the stability of BAPC in aqueous suspension was studied, and BAPC in suspension was found to be unstable compared to that in solution.[4)] This lability of BAPC was a consequence of the simultaneous degradation of the dissolved BAPC and the BAPC base precipitated from the solution.[4)]

Alginic acid (Alg) forms a viscous, colloidal solution and is used as a stabilizing colloid, insuring creamy texture and preventing the growth of ice crystals, and also as a emulsion stabilizer or suspending agent in pharmaceutic application.[5)] Ohbu and Toyoda[6)] reported complex formation between water-soluble polymer and surfactant, especially a cationic polymer and an anionic surfactant, and its usefulness in the pharmaceutical field. In the present work, interaction of BAPC with Alg was investigated with the aim of stabilizing BAPC in suspension, particularly at the neutral pH region, where BAPC suspension is very unstable in contrast to BAPC solution.

Experimental

Materials Bacampicillin hydrochloride (BAPC·HCl) was a gift from Yoshitomi Pharmaceutical Ind., Ltd., and its activity was 659 μg/mg as ABPC. Sodium ampicillin (Meiji Seika Kaisha Ltd.) was the normal commercial preparation for injection, and sodium alginate (AlgNa), Tween 80, hydroxypropyl cellulose (HPC) and methylcellulose (MC) were purchased from Wako Pure Chemical Ind., Ltd. Polyethylene glycol 4000 (PEG) was bought from Hoei Pharmaceutical Co., Ltd. All other chemicals were of the highest reagent grade and were used without further purification.

Analytical Methods I_2-colorimetry was used for BAPC or ABPC as reported in a previous paper.[2)] No effect of Alg on the I_2-colorimetry was observed. High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-5A apparatus equipped with a detector (Shimadzu, SPD-2A). The conditions for analysis were as follows: column, 15 cm × 4 mm i.d.; packing, TSK gel ODS 80-TM (TOSOH Manufacturing Co., Ltd.); mobile phase, 0.01 M phosphate buffer (pH 6.0)–MeOH (70 : 30) for ABPC; flow rate, 0.8 ml/min; wavelength, 225 nm; sensitivity, 0.02 a.u.f.s.

Preparation of BAPC–Alg Adduct A 2% aqueous solution of AlgNa (200 ml) was added dropwise to 300 ml of 0.04 M BAPC·HCl aqueous solution over a 30 min interval with stirring at 0 °C. After an additional stirring during 1 h at 0 °C, white precipitates were centrifuged down (2000 rpm, 20 min), followed by freeze-drying. The BAPC content in the precipitate (4.8 g) was 69.9 ± 1.1%.

Preparation of BAPC Base BAPC base was prepared by the method reported previously.[4)]

Determination of Alg in Aqueous Solution Alg in an aqueous buffered solution [AlgNa was dissolved into 0.05 M phosphate buffer (pH 6.00 and $\mu = 0.5$)] was determined by measuring viscosity. The flow times of the various concentrations of AlgNa solution were determined at 20 °C in Ubbelohde viscometer. Kinematic viscosity (v centistokes, cSt) was calculated by means of the following equation: $v = K_v t$ where K_v is a constant for the viscometer (cSt/s) and t is the flow time in seconds. The relation between the viscosity and the concentration of AlgNa is shown in Fig. 1, where the viscosity is linearly related to the concentration below 0.08%. No effect of BAPC addition on the viscosity was observed (Table I).

Determination of Solubility of BAPC The solubility of BAPC in various concentrations of Alg aqueous solution, which was prepared by dissolving AlgNa in 0.15 M phsophate buffer (pH 4.00—6.00), was determined at 0 °C. A suitable amount of BAPC·HCl was suspended in the

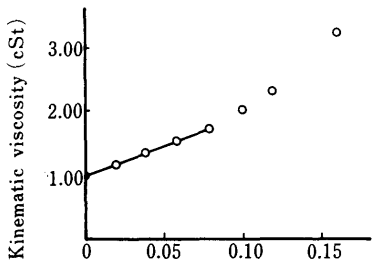

Fig. 1. Relation between Kinematic Viscosity and Concentration of Alg Solution at 20 °C

Alg solution was made by dissolving sodium alginate in 0.05 M phosphate buffer of pH 6.00 and $\mu = 0.5$.

TABLE I. Effect of BAPC Addition on the Kinematic Viscosity of Alg

Concentration of AlgNa (%)	Kinematic viscosity (cSt)	
	Without BAPC	With BAPC (1.8×10^{-2} M)
0	0.983	1.01
0.05	1.45	1.41
0.10	2.02	2.03

Each value represents the mean of two experiments.

Alg solution under stirring at 100 rpm with a magnetic stirrer. After equilibrium was reached, the suspension was filtered through an artificial membrane (Millipore filter, 0.45 μm), and the concentration of BAPC in the resultant filtrate was determined by I_2-colorimetry.

Kinetic Studies All kinetic experiments were undertaken in a constant temperature bath at 35 ± 0.1 °C and at pH 5.00—7.00. In the case of the time courses in solution, BAPC–HCl or BAPC–Alg adduct was dissolved in a reaction solution, which contained 0.1% Tween 80 and which was adjusted to an ionic strength of 0.5 by the addition of KCl and to the desired pH value by using a pH-stat (Toa pH-STAT, model HSM-10A and Toa pH-Meter, model HM-18ET). The initial concentration of BAPC was 1.0×10^{-3}—5.5×10^{-3} M according to the pH conditions. At suitable intervals, samples were taken out and assayed immediately for total penicillins (BAPC + ABPC) by I_2-colorimetry and for ABPC by the HPLC method. In the case of the time courses in suspension, BAPC–Alg adduct was suspended in the same reaction solution as that of the reaction in solution, and the pH was adjusted to the desired value by using the pH-stat. The resulting suspension was stirred at 100 rpm by a magnetic stirrer during the kinetic procedures. Two samples were taken out at suitable intevals. One sample was dissolved in 0.001 N HCl to give a solution of measurable concentration (0.5×10^{-4}—5.0×10^{-4} M), followed by the assay of total penicillins by I_2-colorimetry. The other was filtered immediately with 0.45 μm filter and then the dissolved total penicillins and ABPC in the resultant filtrate were determined simultaneously by I_2-colorimetry and the HPLC method, respectively.

Apparent Partition Coefficients The apparent partition coefficient of BAPC with or without Alg between toluene and water was measured as follows. Bacampicillin hydrochloride was dissolved in 0.15 M phosphate buffer ($\mu = 0.5$ with the addition of KCl) with or without 1.0% Alg at pH 4.00, 5.00 and 6.00. The BAPC solution with Alg was shaken for 20 min at 25 °C, then the precipitate was removed by centrifugation at 2000 rpm for 20 min. The resulting aqueous solution of BAPC and Alg was used for the measurement of partition coefficient. A suitable volume of the solution was transferred into a separatory funnel together with 5 fold (at pH 4.00), a half (at pH 5.00), and one tenth (at pH 6.00) volume of toluene. Then, the funnel was shaken vigorously for 10 min at 25 °C. After equilibrium had been reached, the clear aqueous layer was obtained by centrifugation at 2000 rpm for 20 min, and the concentration of BAPC in the aqueous layer was measured by I_2-colorimetry.

The apparent partition coefficients of BAPC in toluene/water were calculated from the observed concentration of BAPC in the aqueous layer before and after the extraction with toluene.

Infrared (IR) Measurement The spectrum was measured with a JASCO DS-701G spectrometer by the KBr method.

Data Analysis The amounts of BAPC and/or ABPC were calculated by an NEC PC-8800 microcomputer using the MULTI[7] program according to the appropriate reaction scheme.

Results and Discussion

Formation of Adduct between BAPC and Alg As mentioned in the experimental section, when an Alg solution was added dropwise into BAPC·HCl solution, a white precipitate was produced. The pH of this resulting solution, to which AlgNa was added until there was no further increase of the precipitate, was about 5.0. However, no precipitate was obtained by the addition of HPC, MC and PEG under the same conditions. Therefore, this precipitate was thought to be slightly water-soluble BAPC–Alg adduct produced from the interaction between BAPC and Alg. The BAPC content in this adduct was determined to be 69.9 ± 1.1%, while the content of Alg was 27.6 ± 2.4%. The ratio of BAPC to Alg was 71.7/28.3. This ratio was in good agreement with the value (70.6/29.4) which was calculated from the molecular weights of both substances by assuming the binding of a molecule of BAPC to a molecule of the constituent sugar of Alg.

We have already found that BAPC base itself precipitates from a concentrated solution of BAPC·HCl with time.[4] Therefore, BAPC base may separate out together with the adduct upon the precipitation of the adduct. However,

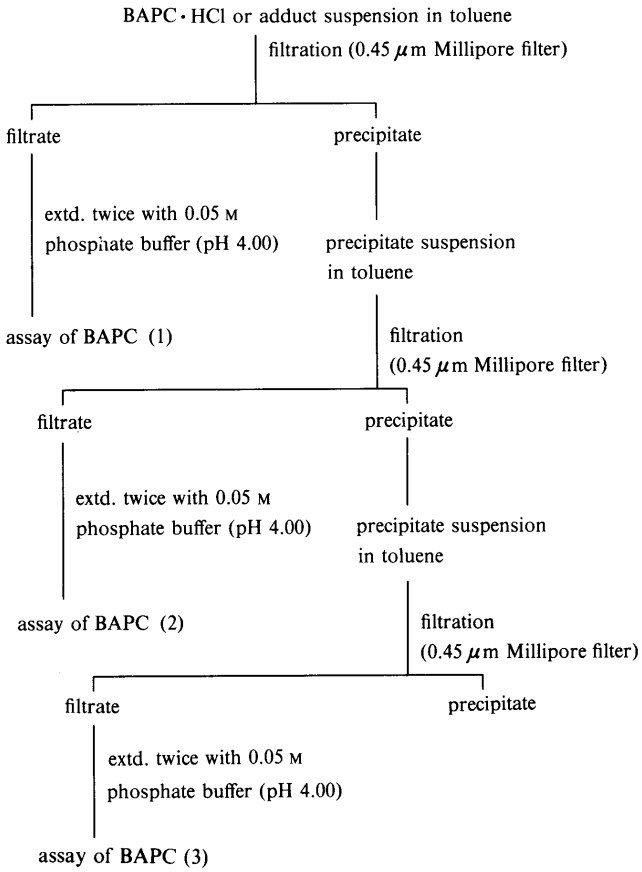

Chart 1

TABLE II. BAPC Base Content in BAPC·HCl and Adduct

No. of BAPC assay in Chart 1	BAPC base content (%)			
	In BAPC·HCl	In the mixture[a]		In adduct
		1:2	1:1	
1	n.d.	33.0	50.2	n.d.
2	n.d.	n.d.	n.d.	n.d.
3	n.d.	n.d.	n.d.	n.d.

a) BAPC base content was measured in the mixture of BAPC base/BAPC·HCl (1/2 or 1/1). n.d.: not detected.

substances other than BAPC and Alg seem not to be contained in this adduct because the sum of their individual contents is almost 100%. To confirm the purity of the adduct, extraction of BAPC into toluene was examined as shown in Chart 1, resulting in Table II. Table II shows that the adduct was apparently free form BAPC base. Since BAPC·HCl or the adduct was sieved to obtain fine powder by using a 200 mesh screen and the suspension in toluene was allowed to stand for at least 5 h with stirring, toluene should have penetrated sufficiently into the adduct, similarly to BAPC·HCl. This method of determining BAPC base was proved to be useful because BAPC base in the mixture with BAPC·HCl could be separated and determined as shown in Table II.

In order to evaluate the binding in this adduct, its IR spectrum was measured (Fig. 2). As shown in Fig. 2, specific absorption bands such as ammonium ion due to BAPC at 2600, 1550 cm^{-1} and carboxylate due to Alg at

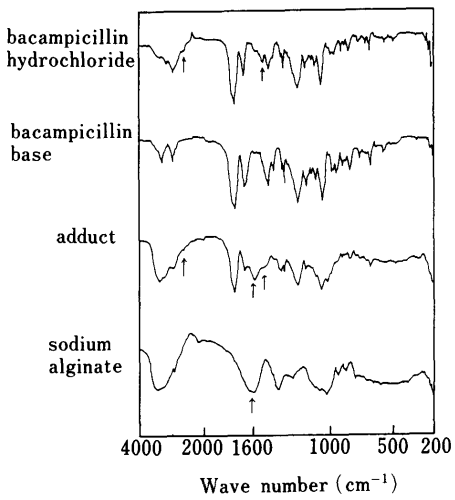

Fig. 2. IR Spectra of BAPC, Adduct and Alg

TABLE III. Apparent Partition Coefficient of BAPC between Toluene and Water with or without Alg at 25 °C

pH	Initial BAPC concn. ($\times 10^{-3}$ M)	With Alg	Without Alg
4.00	1.47	0.226	0.216
	4.02	0.220	0.228
5.00	0.73	2.53	2.51
	1.50	2.52	2.53
6.00	0.12	26.5	26.3
	0.14	26.1	26.6

Each value represents the mean of two experiments.

1620 cm^{-1} were observed for the adduct. From the IR spectrum, the adduct is supposed to be contain ions of both BAPC and Alg. Chlorine ions were not detected in the adduct by the silver nitrate test. Therefore, the adduct can be assumed not to be a mixture of BAPC·HCl and AlgNa, but to be physicochemically bonded complex of both substances.

Interrelation of BAPC and Alg in Aqueous Solution Partition experiments were carried out in order to investigate the interaction involved in the adduct formation in aqueous solution. Partition coefficients of BAPC between toluene and water were constant at each pH of 4.00—6.00 regardless of the concentration of BAPC and the addition of Alg (Table III). If the dissolved adduct is present to some extent in the aqueous solution of BAPC and Alg, the apparent partition coefficient of BAPC should decrease because the adduct is insoluble in toluene and only BAPC base can pass into toluene.[4] The lowest limit of detection of BAPC by the I_2-colorimetry method used is 6.0×10^{-6} M (this concentration almost corresponds to the solubility of BAPC base). Therefore, the results shown in Table III suggest that the BAPC–Alg adduct is not present as a solute in the solution consisting of BAPC and Alg.

The solubility of BAPC in water was measured with the addition of Alg. As shown in Chart 2, when the suspension of BAPC·HCl was prepared at pH 4.00—6.00, it was found that nonionized species of BAPC (BAPC base) were separated out as suspended particles and that the resultant particles degraded because they were very labile.[4] The

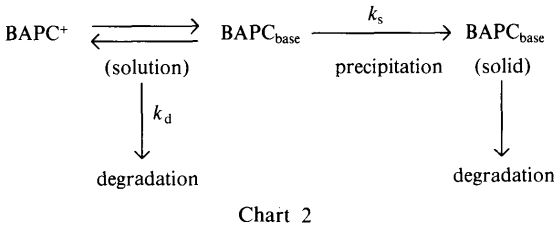

Chart 2

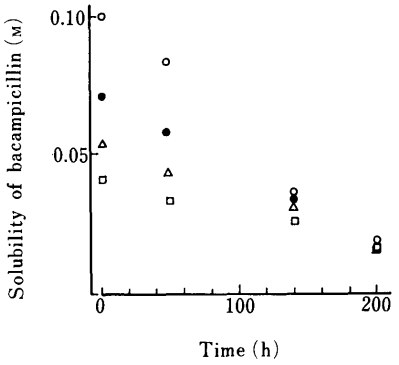

Fig. 3. Changes of the Concentration of BAPC in BAPC·HCl Suspension with or without Alg at pH 4.00 and 0 °C

○, without Alg; ●, with 0.5% Alg; △, with 1.0% Alg; □, with 1.8% Alg.

degradation of the dissolved BAPC and the solid BAPC, however, was not observed for 240 h at 0 °C after the reaction was initiated. Thus, the determination of the solubility of BAPC carried out at 0 °C in order to prevent the degradation of BAPC. The time courses of the concentration of BAPC in solution with or without Alg at pH 4.00 are shown in Fig. 3. The concentration of BAPC was affected by the addition of Alg and decreased with an increase of the concentration of Alg. If the adduct is present to some extent as a solute, the solubility of BAPC at a constant pH and temperature should be higher than that of BAPC alone under the same conditions. Therefore, this result supports the concept that the equilibrium state between BAPC and Alg, in which the adduct is not present as a solute, is similar to that of an extremely slighly soluble salt, as shown in Chart 3. However, the solubility product relation recognized in a general slightly soluble salt could not be obtained. This may be because Alg has a heterogeneous molecular weight and changes its three dimensional structure in solution dependently upon pH and concentration. On the other hand, after 200 h, the concentration of BAPC decreased in a similar concentration range. This seems to be due to the precipitation of BAPC base as discussed below in connection with the IR spectrum. Similar changes of the concentration of BAPC were observed at other pH values (5.00 and 6.00).

Particles in a BAPC·HCl suspension without Alg were identified as BAPC base from their IR spectrum.[4] On the other hand, particles in the suspension with Alg at 140 h were found to be a mixture of BAPC–Alg adduct and BAPC base (Table IV).

The ratio (BAPC base/BAPC–Alg adduct) in these particles decreased with an increase of Alg concentration as shown in Table IV. In 1.8% Alg solution, particles were all BAPC–Alg adduct. The solubility of BAPC in Alg solution above this Alg concentration, however, could not be determined owing to the high viscosity of the solution. The

Table IV. BAPC Base Content in the Particles of BAPC·HCl Suspension with Various Concentrations of Alg Buffered Solution at 140 h and 0 °C

Alg concn. (%)	BAPC base content (%)		
	pH		
	4.00	5.00	6.00
0	100.0	100.0	100.0
0.5	21.5	40.0	69.3
1.0	9.8	20.7	32.1
1.8	0.0	0.0	0.0

Each value represents the mean of two experiments.

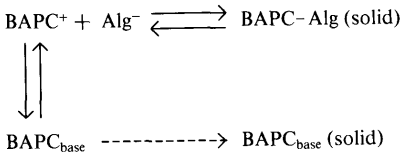

Chart 3

results shown in Table IV indicate that the fast precipitation of the adduct and the slow separation of BAPC base particles proceed simultaneously in the case of low Alg concentration (below 1.0% in the range studied), as shown in Chrat 3. In addition, it is suggested that the equilibrium between the adduct and free BAPC is shifted to the adduct formation in preference to the precipitation of BAPC base particles under the condition of high Alg concentration because the rate of the adduct formation is faster than that of BAPC base precipitation. That is to say, the addition of AlgNa increases the concentration of Alg ions so that some BAPC–Alg adduct precipitates from the solution until the equilibrium (Chart 3) is re-established. In contrast, BAPC concentration in these various concentrations of Alg solution converged to a similar concentration at about 200 h and each pH as shown in Fig. 3. Each resultant concentration may represent the solubility of BAPC at each pH and 0 °C, that is, the solubility BAPC at pH 4.0 and 0 °C is about 1.0×10^{-2} M, and the adduct is not produced below this BAPC concentration even if about 1% Alg is added, because the relationship of the solubility product fails. This speculation is supported by the BAPC concentration found when the adduct was prepared as described in Experimental.

Stability of BAPC with Alg Aqueous Solution The effects of Alg addition on the stability of BAPC were studied in a solution. Time courses of BAPC degradation, when BAPC·HCl or adduct was dissolved in water at pH 5.00, are shown in Fig. 4. BAPC degradation in the solution showed an apparent first-order reaction regardless of the presence of Alg, and the obtained first-order rate constants were in good agreement with each other and with those reported previously[2] (Table V). As Table V shows, similar results were obtained at other pHs as well as at pH 5.00. Furthermore, no effect of the concentration of Alg on the degradation was observed as also summarized in Table V. From these results, it was proved that Alg did not affect the stability of BAPC in aqueous solution. Further, it was found that BAPC degradation in a solution, in which the adduct was dissolved, obeyed the same first order kinetics

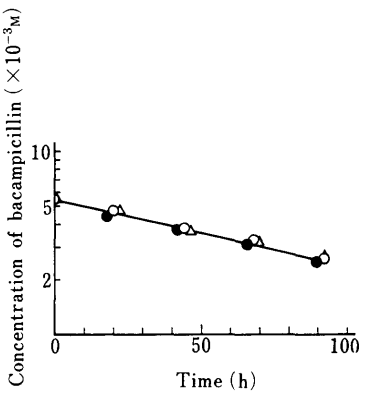

Fig. 4. Time Courses for the Degradation of BAPC in BAPC·HCl or Adduct Solution with or without Alg at pH 5.00, $\mu = 0.5$ and 35 °C

△, BAPC·HCl without Alg; ○, adduct without Alg; ●, BAPC·HCl with 0.5% Alg. A solid line represents the calculated values obtained by the least-squares method from data on BAPC·HCl.

Table V. Rate Constants (h^{-1}) of the Degradation of BAPC and Adduct in Aqueous Solution ($\mu = 0.5$) with or without Alg at 35 °C

		pH			
		5.00	5.50	6.00	7.00
BAPC·HCl	without Alg	0.0080	0.0081	0.0069	0.050
	with 0.1% Alg	0.0079	0.0083	0.0070	—
	with 0.2% Alg	—	—	0.0067	—
	with 0.3% Alg	—	—	0.0060	—
	with 0.5% Alg	0.0091	0.0079	0.0073	0.044
Adduct	without Alg	0.0084	—	0.0061	0.041

Each value represents the mean of two experiments.

as well. This is due to the degradation of BAPC itself dissociated from the adduct; the adduct dissociates completely into BAPC and Alg in solution, in which BAPC and Alg concentrations are very low (5.5×10^{-3} M and 0.1% as shown in Fig. 4) with respect to those for the adduct formation.

Kinetic Behavior of BAPC–Alg Adduct in Aqueous Suspension In order to obtain a good suspension, nonionic surfactant, Tween 80, which did not affect the degradation of BAPC,[4] was added. No effect of Tween 80 addition on the adduct formation was observed in the pH region studied. The resulting suspension was confirmed to be a homogenous system. The time courses of the total, dissolved and precipitated BAPC concentration at pH 5.00, 6.00 and 7.00 are shown in Fig. 5. In each case, both the total and dissolved BAPC in suspension decreased with time. The amount of the suspended particle of BAPC, however, showed unusual behavior at pH 5.00 and 6.00, that is, it increased initially and then decreased slowly. This change is similar to that of BAPC·HCl suspension[4] as shown in Chart 2. That is to say, when BAPC·HCl is taken up in water in order to make a suspension, a high BAPC concentration is produced by the fast dissolution of BAPC·HCl, followed by precipitation of the supersaturated BAPC base. In this suspension, the particles of BAPC increase with time and the decrease slowly because of the simultaneous degradation of the precipitated and the dissolved BAPC. In this case, the concentration of dissolved BAPC changes according to Eq. 1.[4]

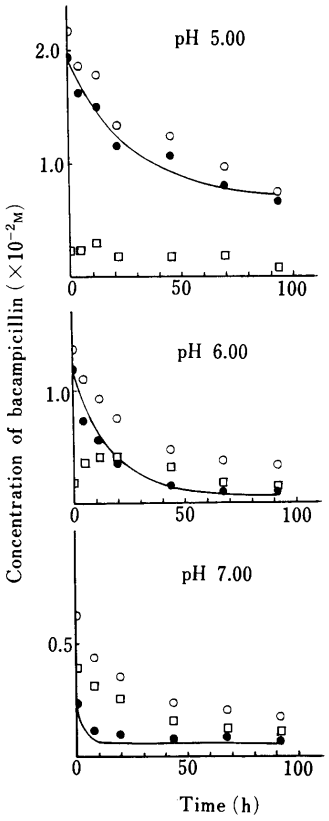

Fig. 5. Time Courses of the Concentration of BAPC in Adduct Aqueous Suspension at Various pH Values, $\mu=0.5$ and 35 °C

○, total BAPC; ●, dissolved BAPC; □, precipitated BAPC. The solid line represents a simulation curve calculated for the dissolved BAPC by using parameters taken from ref. 4 and Eq. 1.

$$[B]_{sol}=\left\{[B]_{sol.0}-\frac{k_s}{k_s+k_d}[B]_{sat}\right\}e^{-(k_s+k_d)t}+\frac{k_s}{k_s+k_d}[B]_{sat} \quad (1)$$

where $[B]_{sol.0}$ is the initial concentration of the dissolved BAPC, $[B]_{sol}$ is the concentration of the dissolved BAPC at time t, $[B]_{sat}$ is the solubility of BAPC, and k_s and k_d are apparent first-order rate constants of the precipitation and the degradation, respectively.

According to Charts 2 and 3, the time courses for the suspension of BAPC–Alg adduct can be regarded as follows. At the beginning of preparation of this suspension, free BAPC (dissociated from the adduct) is present as a solute, whereas the adduct itself forms suspended particles. BAPC base begins to precipitate as particles from the solution after that, and therefore an increase of the suspended BAPC particles occurs with time, similarly to the results of Fig. 3 and Table IV. This precipitation of BAPC base seems to arise owing to the low Alg concentration in the suspension; the Alg concentrations are presumed to be about 0.4, 0.2 and 0.04% at pH 5.00, 6.00 and 7.00, respectively (these values can be calculated from the BAPC concentrations shown in Fig. 5 and the Alg content in the adduct). The amount of the suspended particles, however, decreases little by little because of the simultaneous degradation of the precipitated unstable BAPC base and the dissolved free BAPC (shown in Chart 2), followed by additional dissociation of the adduct into BAPC and Alg ions.

If the time courses of BAPC in the adduct suspension proceed according to this mechanism, the behavior of the dissolved BAPC seems to be similar to that of BAPC·HCl suspension and therefore, the BAPC concentration appears to be changed according to Eq. 1. As shown in Fig. 5, the calculated values of the dissolved BAPC by using Eq. 1 were in good agreement with the observed values at every pH. From the above results, it was revealed that the suspension of the adduct alone was also unstable because the Alg concentration was too low to precipitate the adduct. Hence, the BAPC in this suspension should be stabilized with increasing concentration of Alg because the equilibrium between the adduct and free BAPC lies so far toward adduct formation with Alg addition. The kinetic behavior of the adduct suspension in 1.0% Alg solution was examined at the same pH region and temperature (Fig. 6). The total and dissolved BAPC decreased with time in a similar manner to that of the above suspension of the adduct alone, whereas the amount of the suspended solid BAPC was constant at the pH 5.00—6.00 region. This can be explained as follows. Because the adduct formation proceeds with an increase in concentration of Alg, the dissociation of the adduct into BAPC and Alg ions and the precipitation of BAPC base were depressed even if the dissolved BAPC was degraded with time. This may be due to the large rate constants of BAPC degradation compared to the rate constant of the adduct dissociation and due to the participation of some degradation products in the equilibrium state. Thus, the amount of the solid BAPC (the adduct) was not altered in spite of the decrease of the dissolved BAPC. Furthermore, the adduct was ascertained to be chemically stable from this result. If this assumption is valid, the time courses of the dissolved BAPC should obey the degradation process of BAPC in solution, that is, apparent first-order kinetics as shown in Eq. 2.

$$[B]_{sol}=[B]_{sol.0}e^{-k_d t} \quad (2)$$

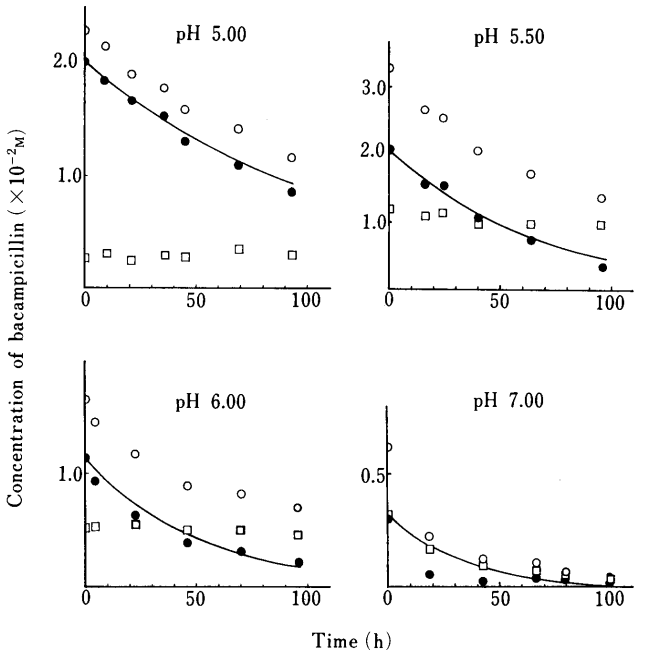

Fig. 6. Time Courses of the Concentration of BAPC in Adduct Aqueous Suspension with 1.0% Alg at Various pH Values, $\mu=0.5$ and 35 °C

○, total BAPC; ●, dissolved BAPC; □, BAPC. The solid line represents a simulation curve calculated for the dissolved BAPC by using parameters taken from ref. 4 and Eq. 2.

TABLE VI. Half Lives (h) of the Degradation of BAPC in Aqueous Adduct Suspension at 35 °C and $\mu=0.5$

Alg concn. (%)	pH			
	5.00	5.50	6.00	7.00
0	58	30	27	28
0.5	96	66	55	14

Each value represents the mean of two experiments.

The solid lines shown in Fig. 6, which were obtained by using Eq. 2 with the k_d values reported previously[4] and $[B]_{sol.0}$ in Fig. 6, were all in good agreement with the found values. In contrast, the suspension of the adduct could not be stabilized at pH 7.00, no matter how much Alg was added. This seems to be due to not only the rapid degradation of BAPC itself and the increase of the ratio of free BAPC, but also the decrease of binding of BAPC to Alg owing to a change of the three dimensional structure of Alg at pH 7.00. The stability of BAPC in a suspension of the adduct in terms of half life is summarized in Table VI. The fact that half life with Alg is about a half of that without Alg at pH 7.00 may be due to the fast precipitation and the subsequent fast degradation of free BAPC by the Alg addition.

Consequently, the BAPC suspension was found to be stabilized by the addition of a large enough amount of Alg because the precipitation of BAPC base was depressed.

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References and Notes

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