of inhibition by m-dinitrobenzene, initiation by AIBN, and polarity of the solvents.

GLPC analyses were carried out with a HP 402 gas chromatograph coupled to an HP 3388A integrator and the HPLC with a Varian 5000 liquid chromatograph coupled to a Vista 402 data handling system. The area ratios were converted to mole ratios for quantitative determinations by using standard calibration curves. ^{1}H NMR high-resolution spectra were obtained with a Brucker WH 200 high-field spectrometer. GLPC/IR data obtained by using a Nicolet 7199 FT/IR spectrometer interfaced to a Varian 3700 gas chromatograph. GLPC/MS data were obtained by using a low-resolution, KRATOS MS 12, mass spectrometer coupled to a Varian 400 gas chromatograph.

Competitive Reduction between α-Halo Ketones. An aliquot solution of two of the α-halo ketones (0.02 M in each of the ketones), 0.02 M tin hydride, and the internal standard (0.02 M) was placed in a NMR tube, degassed, sealed, thermostated (61 °C), and allowed to react for 18 h. The relative reactivity determined as 1:3.2:21 for the reaction of the fluoro- to chloro- to bromoacetophenones reduced in solvent acetonitrile and 1:2.5:54 when the reductions were carried out in benzene. The ratio of k_{Br}/k_F was determined indirectly. The indirect value was obtained from the direct measurement of k_{Cl}/k_F and k_{Br}/k_{Cl}. All the relative reactivities are the mean values of two sets of individual experiments (see Table IV).

Secondary Deuterium Isotope Effects. An examination of the secondary deuterium isotope effect for the reduction of the α-halo ketones was carried out by investigating the competitive reduction of an acetonitrile solution of α-halo-α,α-dideuterioacetophenone (0.05 M) and undeuterated α-haloacetophenone (0.05 M) with triphenyltin hydride (0.1 M). Aliquot samples of the reaction mixtures were placed in reaction ampoules, degassed, sealed, thermostated (61 °C) and allowed to react for 1 h (bromo ketones) or 48 hr (chloro ketones).

The product mixtures of the bromo ketones were isolated by removing the acetonitrile by rotary evaporation. The resultant residue was dissolved in ether. The ethereal solution was treated with excess KF in water (10 g in 100 mL).[18] The precipitated triphenyltin fluoride was removed by filtration, and the ether layer of the filtrate was separated and dried (anhydrous $MgSO_4$). Removal of the solvent yielded a solid which was analyzed by using a KRATOS MS 12 mass spectrometer. The intensity of the ratio of mass peaks m/e 198 (C_8H, OBr^{79}) and 202 ($C_8H_5D_2OBr^{81}$) in the starting material was compared with the same ratio in the unreacted starting material after the reduction had been partially completed. The products acetophenone and α,α-dideuterioacetophenone, m/e 120 (C_8H_8O) and 122 ($C_8H_6D_2O$) were also compared to the starting material for the ratio of protium to deuterium.

In the case of the α-chloroaceophenones the reaction mixture was concentrated, and the mixture of products was collected by preparative GLPC. The protium to deuterium ratio was determined using an AEI MS-50 mass spectrometer at high resolution. The ratio was determined by examining the mass peaks at m/e 158.0289 ($C_8H_5D_2O^{37}Cl$) and 154.0185 ($C_8H_7O^{35}Cl$) in the starting material and m/e 120.0579 (C_8H_8O) and 122.0701 ($C_8H_6D_2O$) in the products. The ratio of m/e mass peaks containing chlorine were corrected for natural abundance $^{35}Cl/^{37}Cl$ = 75.53/24.47.

The percentage reaction for the α-bromoacetophenones acetophenone reaction was determined by NMR.

Polarographic Reduction of Ketones. The current–voltage curves for the polarographic reductions of acetophenone, α-chloroacetophenone, α-fluoroacetophenone, α-bromoacetophenone, and α,α,α-trifluoroacetophenone were obtained on a Princeton Applied Research (PAR) Model 174A polarograph interfaced with a PAR 303 DME.

The solutions were anhydrous acetonitrile containing $(Bu)_4N^+ClO_4^-$ (0.1 M) and the appropriate ketone (0.005 M). The $E_{1/2}$ values relative to $Ag/AgClO_4$ (0.1 M) are listed in Table IV.

Registry No. $PhCOCH_2Cl$, 532-27-4; $PhCOCH_2Br$, 70-11-1; Ph_3SnH, 892-20-6.

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Effects of Solvents and Additives on the Reaction of *N*-Benzyloxycarbonyl-L-aspartic Anhydride with L-Phenylalanine Methyl Ester (Synthesis of Aspartame)

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Received December 6, 1985

N-Benzyloxycarbonyl-L-aspartic anhydride (Z-L-aspartic anhydride) was reacted with L-phenylalanine methyl ester. The nature of the ring-opening reaction was affected by the organic solvent. In Me_2SO, DMF, and dimethylacetamide the β-isomer of Z-L-aspartyl-L-phenylalanine methyl ester (ZAPM) was predominant while in glacial acetic acid, esters, ketones, ethers, chlorohydrocarbons, acetonitrile, toluene, etc. the α-isomer of ZAPM prevailed. Especially in glacial acetic acid, the yield of α-form ZAPM reached more than 85%. The results of reactions in mixed solvents like acetonitrile–Me_2SO and ethyl acetate–acetonitrile showed that the yield of α-ZAPM changed linearly with a change in the composition of the mixed two solvents. The reaction in acetonitrile–acetic acid and Me_2SO–acetic acid showed that the addition of acetic acid not only caused a solvent effect by itself, but that the acid also affected the reaction. Therefore, the yield of α-ZAPM was increased by use of a mixed solvent containing only a small amount of glacial acetic acid. A mechanism to explain these experimental phenomena is presented.

Introduction

The reaction of N-protected L-aspartic anhydride with L-phenylalanine methyl ester has long been regarded as an important method for producing aspartame—α-L-aspartyl-L-phenylalanine methyl ester—discovered by Mazur et al.[1] Due to different modes of ring-opening, two isomers, the α-form and the β-form, are produced; however, only the α-form has a sweet taste. There are essentially three different chemical methods for production of aspartame.[2-19] In the first method, the α-carbonyl group

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Table I. Effect of Different Single Solvents on the Yield of α- and β-ZAPM

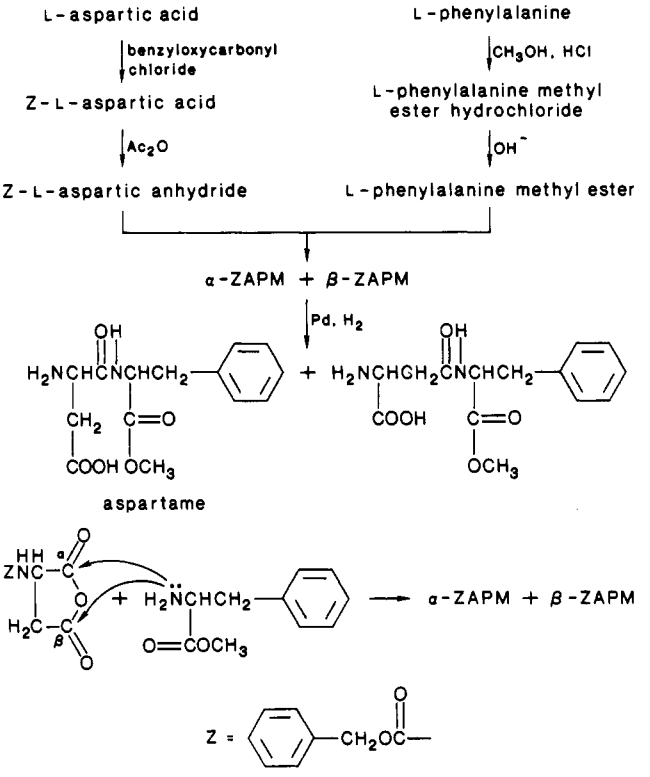
solvent	reaction[a] time, min	reaction[a] temp, °C	relative yield, % α-ZAPM	relative yield, % β-ZAPM	total yield, %	α/β, ratio	D^h
methanol	60	21.0	56.1	43.9	90	1.28	32.6
ethanol	58	21.0	57.8	42.2	90	1.37	24.3
acetone	61	21.0	71.0	29.0	Q[b]	2.45	20.7
methyl acetate	63	21.3	73.1	26.9	Q	2.72	6.5
ethyl acetate	71	21.3	81.0	19.0	Q	4.26	6.0
MEK[c]	80	21.3	76.1	23.9	Q	3.18	18.5
THF[d]	112	21.3	72.7	27.3	Q	2.66	–
1,4-dioxane	114	21.3	80.4	19.6	Q	4.10	2.2
ethyl ether	135	21.3	71.8	28.2	Q	2.55	–
acetonitrile	56	20.5	70.8	29.2	Q	2.42	37.5
chloroform	60	20.5	80.1	19.9	Q	4.03	4.8
toluene	57	20.5	74.2	25.8	Q	2.88	2–3
ethylene dichloride	61	20.5	80.1	19.9	Q	4.03	10.5
DMF[e]	67	23.0	10.2	89.8	Q	0.11	37
Me_2SO[f]	52	23.0	4.0	96.0	Q	0.04	45
DMAC[g]	55	23.0	1.8	98.2	Q	0.02	37
glacial acetic acid	202	22.0	86.2	13.8	Q	6.25	–
propionic acid	188	22.0	85.5	14.5	Q	5.90	–
acetic acid	190	22.0	85.4	14.6	98	5.85	6.2

[a] Reaction concentration = 6% w/v. [b] Quantitative. [c] Methyl ethyl ketone. [d] Tetrahydrofuran. [e] Dimethylformamide. [f] Dimethyl sulfoxide. [g] Dimethylacetamide. [h] Dielectric constant.

of L-aspartic acid whose amino and β-carboxyl groups are both protected is converted first to a very reactive ester, the ester is then condensed with L-phenylalanine methyl ester, and the protecting groups are finally removed. However, this method is not suitable for industrial production because too many reaction steps are involved and expensive reagents are needed. In the second method, amino-protected L-aspartic acid is dehydrated to an anhydride, the anhydride is then reacted with L-phenylalanine methyl ester, and the protecting group is finally removed.[3-10] Two kinds of isomers (α- and β-form) are produced by this method. The third method is similar to second one, but the amino group of aspartic acid is protected as a salt by strong acid[11-16] instead of a covalent bond linkage. The defect of the third method is that the β-form and byproducts are abundantly formed.

As a result of the rapid development of enzymatic techniques in recent years, an enzyme called thermolysin has been discovered which can condense *N*-benzyloxycarbonyl-L-aspartic acid with L-phenylalanine methyl ester to form only the α-isomer.[20-23] However, because the enzyme is still very expensive, it has not yet been applied to industrial production of aspartame. Thus, at this date the most feasible method for producing the sweetener on an industrial scale is still the ring-opening reaction of N-protected L-aspartic anhydride with L-phenylalanine methyl ester. The purpose of this study was to achieve a higher yield of the α-isomer from the ring-opening reaction. The effects of solvents, additives, and concentration on the reaction are enumerated, and possible reasons to account for these effects are given and discussed.

Scheme I. Reaction Involved in Synthesis of α-ZAPM



Results and Discussion

The reactions used for chemical synthesis of N-benzyloxycarbonyl-L-phenylalanine methyl ester (ZAPM) are shown in Scheme I. The fresh pure L-phenylalanine methyl ester easily forms a dimer of diketopiperazine ring;

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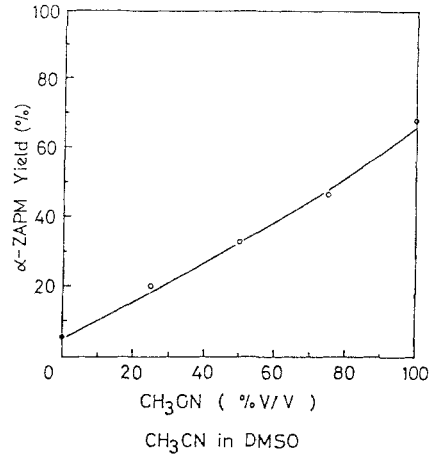

Figure 1. Effects of CH_3CN in Me_2SO on the yield of α-ZAPM.

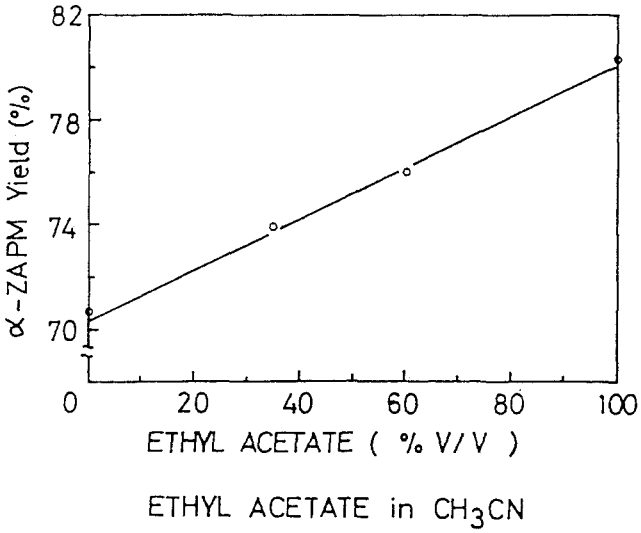

Figure 2. Effects of ethyl acetate in CH_3CN on the yield of α-ZAPM.

it should be used within 1 day to ensure its purity. Though Z-L-aspartic anhydride is more stable than L-phenylalanine methyl ester, it should be stored away from moisture to prevent hydrolysis.

Effects of Solvents on the Synthesis of ZAPM. Equal moles of Z-L-aspartic anhydride and L-phenylalanine methyl ester were reacted in different solvents (6% w/v) at room temperature. The results (as shown in Table I) seem to indicate that the solvents used in the reaction can be brought into three categories: the first type, which characteristically produces more β-ZAPM, includes Me_2SO, DMAC, and DMF; the second type, which produces more α-ZAPM, includes ethyl acetate, dioxane, chloroform, ethylene dichloride, glacial acetic acid, acetic acid, propionic acid, etc.; the third type, which produces an almost equal amount of both α- and β-ZAPM, includes methanol and ethanol. That the reactions at the same temperature and concentration produce different yield isomers in different solvents must be attributed to the effects of solvents.

A comparison of the α/β ratio with the dielectric constant revealed that the solvents that rendered the α/β ratio higher than 4 all had a D value lower than 11, except for methyl acetate and toluene. According to the results of Table I, the products of the ring-opening reaction in ethyl acetate, dioxane, chloroform, ethylene dichloride, acetic acid, glacial acetic acid, propionic acid, etc. contain over 80% of α-ZAPM. Especially in the case of glacial acetic acid and propionic acid, the α-ZAPM in the product ex-

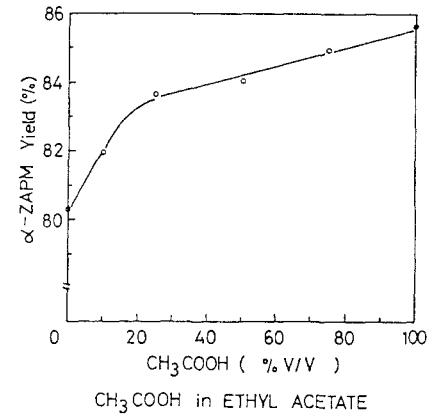

Figure 3. Effects of glacial acetic acid in ethyl acetate on the yield of α-ZAPM.

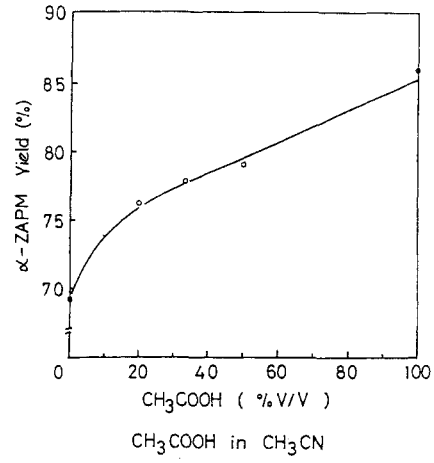

Figure 4. Effects of glacial acetic acid in CH_3CN on the yield of α-ZAPM.

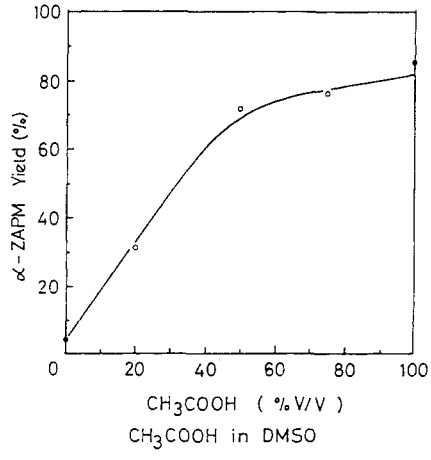

Figure 5. Effects of glacial acetic acid in Me_2SO on the yield of α-ZAPM.

ceeded 85%. Therefore, the two acids are better solvents for producing α-ZAPM. On the other hand, the β-isomer is predominant in DMAC, Me_2SO, and DMF. To explain this phenomenon, a further study was taken up.

Effects of Mixed Solvents on the Synthesis of ZAPM. The results of reaction in the following five mediums of mixed solvents that include acetonitrile–Me_2SO, ethyl acetate–acetonitrile, ethyl acetate–acetic acid, acetonitrile–acetic acid, Me_2SO–acetic acid are shown in Figures 1 to 5. It was found that in the first two systems, as shown in Figure 1 and Figure 2, the yield of α-ZAPM was linearly related to the volume percentage of solvents

Table II. Effect of Glacial Acetic Acid in Various Solvents on the Yield of α- and β-ZAPM

solvent[a]	reaction[b] time, min	reaction[b] temp, °C	relative yield, % α-ZAPM	relative yield, % β-ZAPM	increase of α-ZAPM, %[e] linear	increase of α-ZAPM, %[e] actual
methanol	75	19.0	62.2	37.8	1.51	6.1
ethanol	76	19.0	65.5	34.5	1.42	7.7
acetone	78	19.0	77.2	22.8	0.76	6.2
methyl acetate	54	19.0	82.6	17.4	0.66	9.5
ethyl acetate	77	19.0	82.6	17.4	0.26	1.6
THF[c]	50	19.0	80.6	19.4	0.67	7.9
ethylene dichloride	61	19.0	81.8	18.2	0.31	1.7
chloroform	230	15.0	81.9	18.1	0.31	1.8
DMF[d]	217	15.0	27.9	72.1	3.80	17.7

[a] Containing 5.0% v/v glacial acetic acid. [b] Reactant concentration = 6% w/v. [c] Tetrahydrofuran. [d] Dimethylformamide. [e] The yield of α-ZAPM was compared with the yield obtained in pure single solvent without adding acetic acid, and the linear increase of yield was calculated from comparing the yields between pure single solvent and acetic acid.

Table III. Effect of Adding Formic Acid in Acetonitrile on the Yield of α- and β-ZAPM[a]

HCOOH concn, M	yield, % α-ZAPM	yield, % β-ZAPM	α/β, relative ratio
0.00	67.5	32.5	2.077
2.65	66.0	24.0	2.750
5.30	61.5	20.5	3.000
7.96	52.2	15.8	3.304

[a] The reaction was performed at 20 °C for 4 h.

mixed. In the solvents of acetic acid mixed, as shown in Figures 3–5, the curves bend upwards. The increased yield of α-ZAPM is higher than the value calculated from a linear relation. Thus, it is obvious that glacial acetic acid can give a higher yield of α-ZAPM than that calculated from the linear relation of solvent effects as shown in Figures 1 and 2.

Effects of Acids on the Synthesis of ZAPM. Table II shows the effects of acetic acid in various organic solvents on the yield of α- and β-ZAPM. It was found that the yield of α-ZAPM increased when a small amount of glacial acetic acid was added to the reaction solvent. When the actual increase with that estimated by linear relation of solvent effect is compared, the former is about 5 to 15 times more than the latter.

The effects of formic acid added to acetonitrile on the yield of α- and β-ZAPM are shown in Table III. It was found that the yields of both α- and β-ZAPM decreased, but the α/β ratio increased. The change may be due to the fact that formic acid formed a salt with the amino group of L-phenylalanine methyl ester when it was added in acetonitrile and the ring-opening reaction between Z-L-aspartic anhydride and L-phenylalanine methyl ester was retarded by this salt; therefore, the yield of ZAPM decreased.

Table IV shows the effects of trichloroacetic acid added in acetonitrile on the yields of α- and β-ZAPM. It was found that the yields of both α- and β-ZAPM decreased, but the ratio of α- to β-ZAPM obviously increased when the amount of trichloroacetic acid added increased. The ratio of α- to β-ZAPM increased rapidly when the concentration of trichloroacetic acid in acetonitrile reached 0.2 M. As the concentration of trichloroacetic acid in acetonitrile reached 1.213 M, α-ZAPM stood out while only a small amount of β-ZAPM was formed.

It may be explained that trichloroacetic acid forms a salt with the free amino group of L-phenylalanine methyl ester, and the salt slows down the ring-opening reaction as in the formic acid case. These phenomena could be observed from the change of NMR spectrum during reaction. More than 4 h are required to complete the reaction of 0.2 M Z-L-aspartic anhydride and L-phenylalanine methyl ester

Table IV. Effect of Adding Trichloroacetic Acid in Acetonitrile on the Yield of α- and β-ZAPM[a]

CCl_3COOH concn, M	yield, % α-ZAPM	yield, % β-ZAPM	yield, ratio α/β
0.000	68.7	31.3	2.195
0.024	57.5	25.8	2.226
0.061	59.1	23.8	2.483
0.121	58.2	22.4	2.598
0.243	42.0	7.6	5.526
0.606	34.2	2.4	14.250
1.213	26.4	0.7	37.714

[a] The reaction mixture containing 2% w/v of reactant was kept at 20 °C for 4 h.

Table V. Effect of Reactant Concentration on the Yield of α- and β-ZAPM[a]

solvent	anhydride/amine[b] concn, M/M	yield, % α-ZAPM	yield, % β-ZAPM
Me_2SO	0.01/0.01	6.8	93.2
Me_2SO	2.50/2.50	20.6	79.4
glacial acetic acid	0.10/0.10	85.6	14.4
glacial acetic acid	2.50/2.50	82.7	17.3

[a] The reaction mixture was kept at 20 °C for 1 night. [b] Z-L-aspartic anhydride/L-phenylalanine methyl ester.

in acetonitrile containing 0.04 M of trichloroacetic acid but only 10 min is needed in acetonitrile containing glacial acetic acid and 1–2 min is needed in acetonitrile containing no acid. The changes of the absorption of methoxy group in the ^1H NMR spectra during the reaction are shown in Figure 6.

Summing up the above effects of acids as additives on the nature of the ring-opening reaction, we may conclude that the yield ratio of α-ZAPM to β-ZAPM increases when acid is added to the organic solvents used in this study. Liquid weak organic acid can be used as a solvent, and the reaction rate is closely related to the K_a value of the acid. The time required to complete the reactions in weak acids such as acetic acid ($K_a = 1.8 \times 10^{-5}$) and propionic acid ($K_a = 1.3 \times 10^{-5}$) is about 10 min. The reaction rate in acetonitrile containing acetic acid is relative to the amount of acid added, but the reaction is still completed within 10 min. The reaction in stronger acids like formic acid ($K_a = 1.8 \times 10^{-4}$) and trichloroacetic acid ($K_a = 2 \times 10^{-1}$) were very slow because the salt formed is too stable to react with anhydride. Therefore, though there are more chances to produce α-ZAPM, the total yield decreases.

Effects of Reactant Concentration on the Synthesis of ZAPM. Table V shows the results of ring-opening reaction at lower and higher concentrations of reactant in Me_2SO and glacial acetic acid. In Me_2SO, the yield of β-ZAPM at 0.01 M reactant concentration was 93.2%,

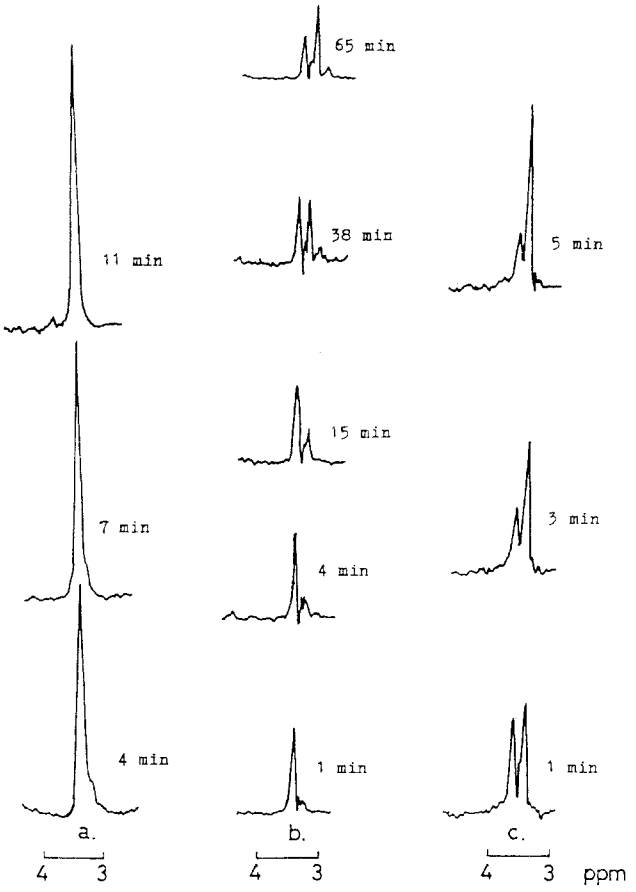

Figure 6. Change of absorption of $-OCH_3$ group in NMR spectrum during reaction: (a) in CH_3CN; (b) in 1/100 (v/v) of CCl_3COOH/CH_3CN; (c) in 3/1 (v/v) of CH_3COOH/CH_3CN. 10% w/v of reactants were reacted in NMR tubes at 30 °C.

which was 13.8% higher than the yield obtained at 2.5 M concentration (79.4%). In glacial acetic acid, the yield of α-ZAPM at 0.1 M reactant concentration was 85.6%, which was 2.9% higher than the yield obtained at 2.5 M concentration (82.6%). These results show again that this ring-opening reaction is actually affected by the solvent. At a higher reactant concentration, the directed nucleophilic attack is hindered in the absence of an adequate solvent; therefore, the yield of β-ZAPM is decreased while reacting in a solvent like Me_2SO, which provides more attack possibilities of β-position. Similarly, the reaction in a solvent like glacial acetic acid, which provides more attack possibilities of α-position, will produce a lower yield of α-ZAPM when the concentration of reactant is increased.

Assumptions of Mechanism. According to the experimental results mentioned above, the reaction mechanisms taking place between Z-L-aspartic anhydride and L-phenylalanine methyl ester in organic solvents, weak organic acids, and organic solvents containing organic acids are suggested below: The –NH– group of Z-L-aspartic anhydride seems to form a five-membered ring[24] easily with the α-carbonyl group through intramolecular hydrogen bonding. As a result, the positive charge (+ δ) of carbon atom in the α-carbonyl group increases. If Z-L-aspartic anhydride reacts with nucleophilic agents such as an amine, nucleophilic attack is prone to occur on the α-carbonyl group which has a larger positive charge (+ δ). Therefore, in the absence of a solvent or in the presence of a solvent with a small polarity of solvation, the reaction produces more α-ZAPM than β-ZAPM.

When Z-L-aspartic anhydride is in an aprotic solvent with a large polarity (or a higher *D* value) such as Me_2SO, DMF, and DMAC, there will be a solvation phenomenon and the five-atom ring of hydrogen bonding in the α-carbonyl group will be destroyed by the solvation effect. Therefore, the positive charge (+ δ) of α-carbon is not increased, and Me_2SO forms hydrogen bonds with the –NH– group of Z-L-aspartic anhydride. Hydrogen bonding with solvents to the α-carbonyl group results in steric hindrance that prevents the nucleophile from attacking the α-carbon, so the reaction produces more β-ZAPM than α-ZAPM in Me_2SO.

When Z-L-aspartic anhydride is in glacial acetic acid, the carbonyl group will be protonated by the proton (H^+) of glacial acetic acid. Therefore, it is easier for α-carbonyl group to hydrogen bond with the neighboring –NH– group of the amide group, thus increasing the positive charge on the α-carbon. Also the amine is converted to a salt, which slows down the rate of nucleophilic attack and increases the attack selectivity. As a result, the reaction of Z-L-aspartic anhydride with amine in glacial acetic acid or solvents containing organic acid will produce more α-ZAPM. As concentration decreases, the reaction slows down, the selectivity increases, and the effect of the solvent becomes more obvious.

Experimental Section

Instruments and Analysis. HPLC (Shimadzu LC-3A) and Integrator (Shimadzu C-RIA) were used in analyzing the products. The column used was Toyo-gel ODS-120T purchased from Toyo Soda Co., Japan. IR and NMR spectrometer (Jeol FX 90Q and JNM-PMX 60) were used for identifying the samples.

The analysis conditions for HPLC were pressure 70 kg/cm^2, flow rate 1.0 mL/min, detecting wavelength 210 nm, mobile phase and carrier liquid mixtures of equal volume of acetonitrile and 0.01 M, pH 4.15 sodium dihydrogen phosphate aqueous solution. Quantitative analysis of α-ZAPM and β-ZAPM products was obtained by comparing with the standard α-ZAPM prepared from enzymatic synthesis[20] by thermolysin and the standard β-ZAPM prepared from chemical synthesis in Me_2SO.

NMR Analysis. L-Phenylalanine methyl ester (20 mg) was dissolved in 0.3 mL of solvent in a NMR test tube, and kept at 30 °C. After 27.8 mg of Z-L-aspartic anhydride was added, the mixture was shaken immediately. The change of NMR spectrum during reaction was observed at intervals after 1 min of reaction.

Materials. *N*-Benzyloxycarbonyl-L-aspartic acid (Z-L-aspartic acid) and L-phenylalanine were purchased from Sigma Co. All the organic solvents used in the experiments were reagent grade. L-Phenylalanine methyl ester (L-Phe–OMe) was prepared by the standard Fisher esterification method: The hydrochloride salts ($[\alpha]^{25}_D$ –4.7) were neutralized by sodium bicarbonate. The solution was extracted with ethylene dichloride, and a light-colored liquid of L-Phe-OMe was obtained after removing the solvent by reduced pressure, which should be used within 1 day.

Z-L-aspartic anhydride was prepared by treating Z-L-aspartic acid (15 mmol) with acetic anhydride (22 mmol) in ethyl acetate (6 mL) at 50–60 °C for 2 h. The solvent was removed by reduced pressure, and 10 mL of ethyl ether was added 3 times to wash out the remaining acetic acid and anhydride, yield 95%, mp 103 °C. The crude product was recrystallized from ethyl acetate, mp 109 °C (lit.,[25] 109 °C).

Experimental Procedures. (1) Effects of Solvents on the Synthesis of ZAPM. Equimolar amounts of Z-L-aspartic anhydride and L-Phe-OMe were reacted in different solvents at about 6% w/v concentration. The latter was dissolved in a solvent, then the former was added at 1 time, and the reaction was allowed to proceed at room temperature for 4 h. If the solvent was volatile, the reaction mixture was analyzed by HPLC after removing the solvent under reduced pressure. If the solvent was involatile but

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soluble in water, the reaction mixture was poured into water 20 times the volume of the mixture after reaction; then 1–2 drops of 5 N HCl was added to precipitate the products. The precipitate was collected by filtration after several hours and analyzed.

(2) Effects of Mixed Solvents on the Synthesis of ZAPM. Z-L-aspartic anhydride and L-Phe-OMe were reacted in five kinds of mixed solvents (5% w/v): acetonitrile–Me_2SO, ethyl acetate–acetonitrile, ethyl acetate–acetic acid, acetonitrile–acetic acid, and Me_2SO–acetic acid, respectively, according to the procedures described above (1).

(3) Effects of Acids as Additives in Organic Solvents on the Synthesis of ZAPM. (a) Effects of a fixed amount of glacial acetic acid as additive: Equimolar amounts of Z-L-aspartic anhydride and L-Phe-OMe were reacted in various solvents (5% w/v) containing 5% v/v of glacial acetic acid at room temperature. The products were analyzed after 4 h.

(b) Effects of formic acid and trichloroacetic acid as additives: Equimolar amounts of Z-L-aspartic anhydride and L-Phe-OMe were reacted in acetonitrile containing different amounts of formic acid or trichloroacetic acid under the same conditions described in (a).

(4) Effects of Reactant Concentration on the Synthesis of ZAPM. The reactions proceeded in glacial acetic acid and Me_2SO at different concentrations of reactants. The products were analyzed after 4 h.

Registry No. α-ZAPM, 33605-72-0; β-ZAPM, 35739-01-6; L-Phe-OMe, 2577-90-4; aspartame, 22839-47-0; Z-L-aspartic anhydride, 4515-23-5; Z-L-aspartic acid, 1152-61-0; acetic acid, 64-19-7; formic acid, 64-18-6; trichloroacetic acid, 76-03-9.

Hydrochlorination of Alkenes. 3.[1] Reaction of the Gases Hydrogen Chloride and (*E*)- and (*Z*)-2-Butene

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Received July 25, 1986

Mixtures of the gases hydrogen chloride and (*E*)-2-butene, hydrogen chloride and (*Z*)-2-butene, and hydrogen chloride and (*Z*)-[2,3-$^2H_2$]-2-butene at total pressures up to 7 atm and temperatures between 283 and 313 K react to yield, exclusively, 2-chlorobutane (*erythro*- and *threo*-[2,3-$^2H_2$]-2-chlorobutane in the case of the labeled alkene). Kinetic measurements for the reactions of all three gaseous alkenes with gaseous hydrogen chloride have been made by infrared spectroscopy. Elimination studies were performed on the [2,3-$^2H_2$]-2-chlorobutane formed. It is concluded that surface catalysis is required for product formation and that surface adsorption of both hydrogen chloride and butene is required to consummate the reaction.

Somewhat more than five decades ago, Maass and his co-workers[3] attempted an extensive study of the interaction between hydrogen chloride and alkenes. Much of their work was done in the gas phase, and for the set of alkenes including propene and the butene isomers, they concluded, among other things, the following: (1) The gases 2-methylpropene (then called γ-butylene) and hydrogen chloride readily reacted to form 2-chloro-2-methylpropane at subatmospheric pressures. This reaction, which did not lend itself to easy interpretation, has been subsequently analyzed in some detail by others[1,4] and, under the conditions utilized by Maass et al., is clearly a surface-catalyzed process. (2) The gases α-butylene (1-butene), β-butylene (a mixture of (*E*)- and (*Z*)-2-butene), and propene failed to react with hydrogen chloride gas, even at long reaction times, under conditions similar to those lending success to the reaction of gaseous 2-methylpropene with gaseous hydrogen chloride.

Subsequently, we have reported[5] that gaseous 2-chloropropane does not form in the gas-phase reaction between the gases hydrogen chloride and propene at appreciable rates at total pressures of 1 atm or less (as Maass correctly observed). However, 2-chloropropane does form in this gas-phase reaction at higher pressures in a process first order in alkene and about third order in hydrogen chloride.

Furthermore, at pressures less than 1 atm, the gases 2-methylpropene and hydrogen chloride yield gaseous 2-chloro-2-methylpropane by a different pathway, i.e. a surface-catalyzed process involving strongly adsorbed hydrogen chloride and weakly adsorbed 2-methylpropene—a classical Rideal–Eley pathway.[1]

The observations made by Maass and his co-workers with regard to (*E*)- and (*Z*)-2-butene, despite what has subsequently been learned about propene[5] and 2-methylpropene,[1] remain of interest for the following reasons:

First, Poutsma[6] and others[7] have shown for electrophilic addition reactions in solution in nonpolar solvents, where open carbocations are not formed,[8] that the rates of reactions correlate with Taft's σ* constants,[9] and thus "...no account need be taken of the *position* of the substituents, but only of their relative inductive electron-donating powers".[6] If, reasonably, carbocations are not involved in gas-phase addition reactions and, if perhaps not so rea-

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