We attribute the dramatic change in the extraction of fluoride ion as a function of water to the behavior of the phase diagram of the system KF-KCl-H_2O in regions of very high concentrations. It is apparent that when sufficient water is present both chloride and fluoride anions are in aqueous solution and they compete freely for extraction by the quaternary cation. In this case the extraction of the chloride is by far higher than the extraction of the fluoride. However, when a limited amount of water is available, the potassium chloride is rejected from the solution by the more soluble potassium fluoride. The precipitated solid potassium chloride *cannot be extracted* and thus eq 3 is shifted to the right.

The less water present in the system, the better the extraction of the fluoride relative to the chloride until the point where the solubility limit of potassium fluoride is achieved. At this point and up the aqueous solution is invariant and the solid contains both potassium fluoride and potassium chloride. At this "critical" point 28% of the quaternary ammonium cation is in the fluoride form. This fraction remains constant until almost dry potassium fluoride is obtained. In the region where the inorganic salt is dryer, a new phenomenon takes place, namely, decomposition of the quaternary salt according to reaction 4. The decomposition is a relatively slow process and could be observed only in the long-run experiments presented in Figures 1 and 2.

The phase diagram of the system KCl-KF-H_2O is naturally temperature dependent and thus the Cl^-/F^- ratio in the aqueous solution increases with increasing temperature. As a result, the chloride anion competes more effectively for the quat at higher temperatues and $K^{sel}_{Cl/F}$ decreases. This temperature dependency is in contrast to the behavior of anion extraction in liquid-liquid systems which is known to be almost independent of temperature.[4]

Despite these differences between liquid-liquid and liquid-solid systems our rate measurements of reaction 5 indicate that the accepted mechanism of phase-transfer-catalyzed exchange reactions (eq 1) as proposed by Starks[11,12] is valid in this case as well. The reaction mechanism is therefore solid-liquid anion extraction (eq 3) followed by a rate-determining chemical step in the organic phase (eq 5).

Further work in the behavior of the solid-liquid system is now in progress.

Experimental Section

Materials. *n*-Octyl chloride, Aliquat 336, and tetra-*n*-butylammonium bromide were purchased from Aldrich and were used without further purification.

When required Aliquat 336 was freeze dried prior to use.

Potassium fluoride was purchased from Merck and was freeze dried for 48 h prior to use.

Lanthanum triacetate was purchased from BDH. The synthesis of trioctylmethylammonium fluoride will be published separately.

Analysis. Organic components (1-octene, 1-octanol, *n*-octyl chloride, *n*-octyl fluoride, and tri-*n*-octylamine) were analyzed by direct sampling from the organic phase, addition of a known amount of mesitylene as an internal standard, and then gas chromatographic analysis [HP-5790 gas chromatograph equipped with 6 ft × 1/8 in. stainless steel packed column, 10% Carbowax, 20 M on Chromosorb W, 120 °C (5 min) to 220 °C at 10°/min, nitrogen carrier gas FID detector].

Inorganic components (KF-KCl-KHF_2) were separated from the mixture after being cooled by filtration, wahsed with chloroform, dried, and weighed.

Fluoride analysis was carried out by dissolving 0.1 g of the sample in 30 mL of 40% methanol in a water solution which was titrated conductometrically with 0.1 M lanthanum triacetate. The end point was determined graphically.

Chloride anion was determined by titration with silver nitrate; bifluoride was finally determined by mass balance on the salt phase.

Quaternary ammonium fluoride in the organic phase was determined by dissolving a 0.1-g sample in 30 mL of 40% methanol in water solution, followed by conductometric titration with 0.1 M lanthanum triacetate.

Reactions were carried out in sealed tubes equipped with magnetic stirrers which were placed in a thermostated bath with percision of ±1.0 °.

Experiments presented in Table I and Figure 1: 1.485 g of *n*-octyl chloride (10 mmol), 0.928 g of freeze-dried potassium fluoride (16 mmol), 0.2 g of freeze-dried Aliquat 336 (0.5 mmol) with varying amounts of added water at 120 °C for 120 h.

Experiments presented in Figure 2: 1.1 g of freeze-dried potassium fluoride (19 mmol) and 5 g of Aliquat 336 (9.1 mmol) were mixed in the presence of varying amounts of water in the absence of solvent for 12 h at 60 °C.

Experiments presented in Figure 3: 9.28 g of potassium fluoride (0.1 mol) were mixed with 20 g of Aliquat 336 (0.05 mol) or with 13.7 g of tetra-*n*-butylammonium bromide (0.05 mol) at 120 °C.

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Registry No. KF, 7789-23-3; *n*-$C_8H_{17}Cl$, 111-85-3; F_2, 7782-41-4.

β-Methylene-D,L-asparagine

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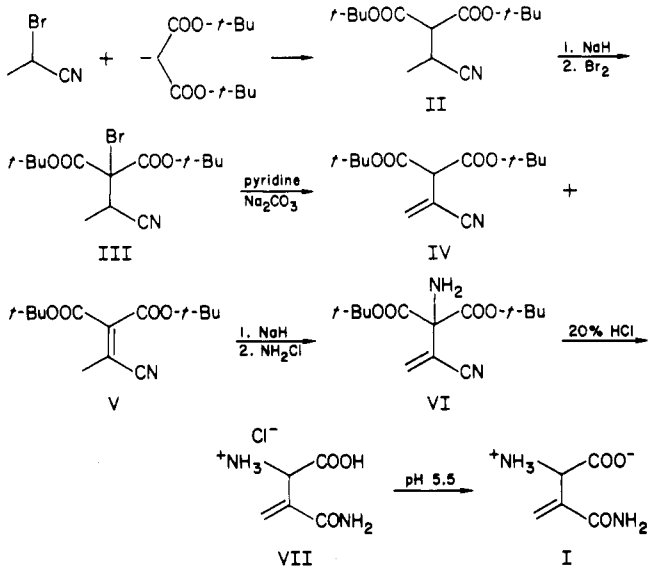
The synthesis of β-methylene-D,L-asparagine (I) was carried out as follows. 2-Bromopropionitrile was condensed with the anion of di-*tert*-butyl malonate yielding *tert*-butyl 3-cyano-2-((*tert*-butyloxy)carbonyl)butyrate (II). Formation of the anion of II with sodium hydride followed by reaction with bromine yielded *tert*-butyl 3-cyano-2-bromo-2-((*tert*-butyloxy)carbonyl)butyrate (III). Elimination of hydrogen bromide was effected by gently heating III with potassium carbonate in pyridine. The product was a 90:10 mixture of *tert*-butyl 3-cyano-2-((*tert*-butyloxy)carbonyl)but-2-enoate (V) and *tert*-butyl 3-cyano-2-((*tert*-butyloxy)carbonyl)but-3-enoate (IV). Isomer V is readily converted to IV by reaction with sodium hydride followed by quenching with hydrochloric acid. Treatment of the mixture of IV and V with sodium hydride followed by reaction with chloramine yielded *tert*-butyl 3-cyano-2-amino-2-((*tert*-butyloxy)carbonyl)but-3-enoate (VI). The latter was hydrolyzed to the desired β-methylene-D,L-asparagine (I) by heating at 40 °C for 12 h with 20% hydrochloric acid. Acetylation of I with acetic anhydride yielded *N*-acetyl-β-methylene-D,L-asparagine (VIII).

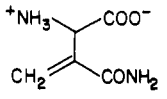
Many β,γ-unsaturated amino acids[1,2] are active-site directed suicide inhibitors of pyridoxal phosphate-dependent enzymes. Upon finding that β-methylene-D,L-aspartic acid[3] is a specific inhibitor of glutamate-aspartate

0022-3263/85/1950-0882$01.50/0

Scheme I



transaminase,[4,5] it appeared worthwhile to synthesize and explore the inhibitory activity of β-methylene-D,L-asparagine (I).



I

Asparagine is a special metabolic requirement of some forms of leukemic cells.[6] Accordingly, asparaginase,[6] which converts asparagine to aspartate, has been used in the treatment of certain leukemias. Unfortunately, asparaginase therapy has serious drawbacks. It starves the system of asparagine, and it can, as a consequence, give rise to severe toxicity. Asparaginase treatment also carries the threat of serious antigenic reaction. Development of inhibitors of enzymes for which asparagine is a substrate might constitute a useful alternative approach. This provided part of the rationale for the synthesis of β-methylene-D,L-asparagine (I) which follows.

The synthesis of β-methylene-D,L-asparagine (I) was based on that used for β-methylene-D,L-aspartic acid[3] with appropriate modification to differentiate the carboxylic acid groups. The synthesis is outlined in Scheme I.

Thus, 2-bromopropionitrile was condensed with di-*tert*-butyl malonate yielding the diester nitrile II. Sodium hydride reacted with II yielding the corresponding malonate anion, which was then brominated yielding the bromide III. It was advantageous to crystallize the bromide III before proceeding to the subsequent steps. Elimination of HBr was effected by heating for 3 h with sodium carbonate in pyridine. The product was a 90:10 mixture of α,β- and β,γ-unsaturated malonates V and IV. The mixture of IV and V can be converted to their common anion by treatment with sodium hydride. Quenching the anion with HCl yielded exclusively IV by kinetic protonation. The anion was converted to the amino diester nitrile VI by treatment with chloramine. Hydrolysis of VI with 20% hydrochloric acid at 40 °C for 12 h accomplished in one step the cleavage of the *tert*-butyl esters, decarboxylation of the resulting malonic acid and hydrolysis of the nitrile to the amide VII. Neutralization to pH 5.5 then yielded the desired amino acid I.

The most crucial part of the structural assignment required establishing whether the product was the nitrile or the amide. The infrared spectrum showed no nitrile band, but such absorption bands can be weak. Infrared absorption in the N—H and C=O region was broad, and bands which might be ascribed to the amide group did not stand out. An EI mass spectrum of the *N*-acetyl amino acid VIII exhibited a peak at m/z 170 corresponding to the nitrile. However, this result was recognized to be ambiguous because loss of water is expected to be a facile fragmentation pathway. An LD mass spectrum[7] of I showed a molecular ion for the amide in the negative ion spectrum and the molecular ion plus sodium in the positive ion spectrum, thereby supporting the formulation I. The carbon-13 NMR spectrum provided the strongest evidence demonstrating that the product must be the amide I. The proton decoupled carbon-13 NMR spectrum shows five lines at 56.3, 131.3, 135.8, 170.9, and 171.6 ppm. Had the nitrile group survived the acidic hydrolysis conditions, the line at 170.9 ppm would not be present, but instead a nitrile band at ca. 120 ppm[8] would have been observed. The proton-coupled carbon-13 NMR spectrum confirmed the structural assignment showing a methine doublet of quartets (^1J = 144.0, ^3J = 7.3 and 12.2 Hz) at δ 56.3, a vinyl methylene triplet of doublets (^1J = 161.1, ^3J = 4.9 Hz) at δ 131.2, a quaternary vinyl singlet (broadened and very slightly split) at δ 135.7, an amide carbonyl multiplet at δ 170.7 and a carboxyl doublet (^2J = 4.9 Hz) at δ 171.6.

To confirm the spectroscopic structural assignment, the amide I was hydrolyzed by heating in 20% hydrochloric acid at 70 °C for 60 h. The hydrolysis reaction was readily monitored by using NMR spectroscopy. The product obtained in 70% yield was β-methylene-D,L-aspartic acid identical with an authentic sample.[3]

Experimental Section

Melting points are uncorrected and were carried out on Fisher-Johns or Meltemp melting point apparatuses. Infrared spectra were recorded by using a Perkin-Elmer Model 249 grating infrared spectrophotometer on neat samples for liquids and as KBr pellets or in $CHCl_3$ solution for solids. Proton NMR spectra were recorded in $CDCl_3$ or D_2O at 60 and 300 MHz on Varian T60A and Bruker WH-300 spectrometers with tetramethylsilane as internal standard. Low-resolution mass spectra were determined at 70 and 15 eV on an LKB 9000A gas chromatograph–mass spectrometer using a direct insert probe. High-resolution mass spectra were recorded on a Varian MAT CH-5 mass spectrometer and were calibrated by peak matching. Precoated silica gel sheets

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(60F-254, 0.2-mm thick) were used for analytical TLC. Silica gel (70–230 mesh, particle size 0.063–0.2 mm) was used for column chromatography. All solvents were distilled and dried according to literature procedures.

2-Bromopropionitrile.[9] 2-Bromopropionamide (25.0 g, 0.16 mol) and phosphorus pentoxide (23.0 g, 0.21 mol) were placed in a 250-mL, three-necked, round-bottom flask fitted with a mechanical stirrer and a distillation apparatus. The two solids were mixed vigorously for 1 h. The reaction mixture was slowly (ca. 1 h) heated to 110 °C under reduced pressure (25 mm). The product, a colorless liquid, bp 68–71 °C (25 mm), weighing 14.28 g (65%), distilled into a collection flask. The 60-MHz proton NMR ($CDCl_3$) showed a one-proton quartet (J = 7.0 Hz) at δ 4.3 and a three-proton doublet (J = 7.0 Hz) at δ 2.0. The IR spectrum (neat) showed bands at 2950 cm^{-1} (s, C—H) and 2450 cm^{-1} (w, C≡N).

***tert*-Butyl 3-Cyano-2-((*tert*-butyloxy)carbonyl)butyrate (II).** Under an atmosphere of nitrogen, a solution of 37.5 g (0.173 mol) of di-*tert*-butyl malonate in 100 mL of dry THF was added dropwise to a stirred suspension of 10.83 g (0.226 mol, 50% dispersion in mineral oil) of NaH in 50 mL of THF and was allowed to stir for 1 h at room temperature. A solution of 22.92 g (0.171 mol) of 2-bromopropionitrile in 100 mL of dry THF was added dropwise to the stirred reaction mixture. After stirring overnight at room temperature, the reaction was cooled to 0 °C and extracted with two 50-mL portions of ice-cold 1% sodium carbonate solution. The combined aqueous layers were washed with two 50-mL portions of ether. The combined organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure to a light green oil. Distillation yielded 34.67 g (89%) of II as a colorless oil, bp 110–115 °C (0.5 mmHg). The 300-MHz proton NMR ($CDCl_3$) showed a one-proton doublet (J = 8.3 Hz) at δ 3.3, a one-proton doublet of quartets (J = 8.3 Hz, J = 6.9 Hz) at δ 3.2, a nine-proton singlet at δ 1.50, a nine-proton singlet at δ 1.49, and a three-proton doublet (J = 6.9 Hz) at δ 1.3. The IR spectrum (neat) showed bands at 2975 cm^{-1} (m, CH), 2240 cm^{-1} (w, C≡N) and 1720 cm^{-1} (s, CO). The mass spectrum (15 eV) showed peaks at m/z (relative intensity): 254 (2, $M^+ - 15$), 214 (5, $C_{11}H_{18}O_4^+$), 196 (13, $M^+ - C_4H_9O$), 158 (20, $C_7H_{10}O_4^+$), 113 (17, $C_6H_9O_2^+$), 57 (100, $C_4H_8^+$). Exact mass calcd for $C_{13}H_{20}NO_4$: 254.1392. Found: 254.1392.

***tert*-Butyl 3-Cyano-2-bromo-2-((*tert*-butyloxy)carbonyl)butyrate (III).** At 0 °C, under an atmosphere of nitrogen, a solution of 34 g (0.126 mol) of diester II in 200 mL of dry tetrahydrofuran was added to a stirring suspension of 7.2 g (0.15 mol, 50% dispersion in mineral oil) of NaH in 150 mL of dry tetrahydrofuran. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was then cooled to 0 °C and bromine was added dropwise until the bromine color persisted. The reaction mixture was then washed with 200 mL of ice-cold, saturated sodium thiosulfate solution followed by 250 mL of ice-cold 5% sodium bicarbonate solution. The aqueous layers were combined and washed with three 100-mL portions of ether. The combined organic layers were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The resulting milky oil was taken up in 75 mL of pentane. Upon cooling to 0 °C, 31.0 g (71%) of colorless crystals, mp 76–78 °C, were obtained. Recrystallization from hexane yielded product III with mp 80.5–81.5 °C. The 300-MHz proton NMR spectrum showed a one-proton quartet (J = 7.07 Hz) at δ 3.53, a nine-proton singlet at δ 1.53, a nine-proton singlet at δ 1.51, and a three-proton doublet at δ 1.47 (J = 7.07 Hz). The IR spectrum showed bands at 3005 cm^{-1} (m, C–H), 2240 cm^{-1} (w, CN), and 1725 cm^{-1} (s, CO). The mass spectrum (70 eV) showed peaks at m/z (relative intensity) 334 (5, M^+ – Me), 278 and 276 (7, $C_{10}H_{15}O_3NBr^+$), 249 and 247 (7, $C_9H_{14}O_2NBr^+$), 193 and 191 (24, $C_5H_6O_2NBr^+$), 57 (100, $C_4H_9^+$). Exact mass calcd for $C_{13}H_{19}NO_4{}^{81}Br$: 334.0477. Found: 334.0469.

***tert*-Butyl 3-Cyano-2-((*tert*-butyloxy)carbonyl)but-3-enoate (IV) and *tert*-Butyl 3-Cyano-2-((*tert*-butyloxy)carbonyl)but-2-enoate (V).** In a 250-mL round-bottom flask, 31.0 g (0.089 mol) of the bromide III, 5.66 g (0.053 mol) of sodium carbonate, and 86 mL of pyridine were heated under an atmosphere of nitrogen at 50–55 °C for 3 h. After cooling to 0 °C, the reaction mixture was taken up in 175 mL of ice-cold ether and washed with 175 mL of ice-cold water. The layers were separated, and the aqueous layer was washed with four 100-mL portions of ether. The combined ether layers were dried with sodium sulfate and filtered. Upon evaporation of the solvent, 27.5 g of dark reddish oil was obtained. This was placed on 400 g of silica gel and eluted with 8:2 hexane–ethyl acetate affording 22.2 g (93%) of a 10:90 mixture of the two double bond isomers IV and V. The two isomers may be separated by using the above chromatography scheme by taking small fractions and following the course of the chromatography using thin-layer chromatography in which, with 75:25 hexane–ethyl acetate, IV has R_f 0.55 and V has R_f 0.66. The major product V (>90%) showed in its 60-MHz proton NMR spectrum ($CDCl_3$) a 3-proton methyl singlet at δ 1.56 and an 18-proton singlet at δ 2.10. The IR spectrum (neat) showed 3000 cm^{-1} (m, CH) and 1690 cm^{-1} (s, CO). The mass spectrum (15 eV) showed m/z (relative intensity) 252 (12, M^+ – Me), 196 (84, $C_9H_{10}O_4N^+$), 194 (100, $M^+ - C_4H_9O$), 156 (61, $C_7H_8O_4^+$), 138 (51, $C_6H_4O_3N^+$, and 112 (71, $C_6H_8O_2^+$).

The β-methylene isomer IV is a crystalline compound, mp 40–41 °C. The 60-MHz proton NMR spectrum of IV ($CDCl_3$) showed a 1-proton vinyl singlet at δ 6.18, a 1-proton vinyl singlet at δ 5.98, and an 18-proton *tert*-butyl singlet at δ 1.50. The IR spectrum of IV ($CHCl_3$) showed bands at 2975 cm^{-1} (m, CH) and 1725 cm^{-1} (s, CO). The coupled ^{13}C NMR spectrum of IV ($CDCl_3$) showed a carbonyl singlet at δ 164.5, a vinyl triplet (J = 151 Hz) at δ 135.0, a vinyl singlet at δ 117.1, a nitrile singlet at δ 117.8, a quaternary carbon singlet at δ 83.6, a methine doublet (J = 143 Hz) at δ 58.5, and a methyl quartet (J = 132 Hz) at δ 27.8. The mass spectrum (15 eV) of IV showed m/z (relative intensity) 252 (36, M^+ – Me), 212 (24, $C^{10}H_{14}O_4N^+$), 196 (86, $C_9H_{10}O_4N^+$), 194 (100, $M^+ - C_4H_9O$), 167 (40, $C_9H_{13}O_2N^+$), 138 (36, $C_6H_4O_3N^+$), and 101 (87, $C_5H_9O_2^+$). Exact mass calcd for $C_{13}H_{18}NO_4$: 252.1236. Found: 252.1234.

***tert*-Butyl 3-Cyano-2-((*tert*-butyloxy)carbonyl)but-3-enoate (IV).** To a suspension of 4.57 g (0.095 mol, 50% suspension in mineral oil) of NaH in 300 mL of dry tetrahydrofuran stirred at 0 °C under an atmosphere of nitrogen was added 19.54 g (0.073 mol) of a mixture of the two isomers IV and V. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then cooled to 0 °C and 100 mL of ice-cold 5% HCl solution was added slowly. The resulting mixture was poured into a separatory funnel which contained 200 g of an ice–water slush and 200 mL of ether. The layers were separated, and the aqueous layer was washed with two 100-mL portions of ice-cold ether. The organic layers were combined, dried with sodium sulfate, filtered, and concentrated under reduced pressure, yielding a light brown oil. The oil was placed on 1 kg of silica gel and was eluated with 4:1 hexane–ethyl acetate yielding, after recrystallization from hexane, 14.45 g (73%) of colorless crystals, mp 40–41 °C, of IV.

***tert*-Butyl 3-Cyano-2-amino-2-((*tert*-butyloxy)carbonyl)but-3-enoate (VI).** Under an atmosphere of nitrogen 5.98 g (0.125 mol, 50% dispersion in mineral oil) of NaH was placed in 100 mL of tetrahydrofuran. The reaction mixture was cooled to 0 °C and a solution of 22.2 g (0.083 mol) of the two isomers IV and V in 100 mL of tetrahydrofuran was added slowly. After the addition was complete, the reaction mixture was stirred for 2 h at room temperature. The reaction was cooled to 0 °C and 108 mL (0.13 mol) of an ice-cold ethereal solution (1.2 M) of chloramine was added. After stirring 12 h at room temperature, the reaction mixture was cooled to 0 °C and washed with three 125-mL portions of 10% HCl solution. Maintaining the temperature at 0 °C, the combined aqueous layers were made basic with sodium carbonate and washed with four 125-mL portions of ether. The ether layers were combined, dried with sodium sulfate, and filtered. Upon evaporation of solvent, 19.0 g of red oil was obtained. The oil was placed on 400 g of silica gel and eluted with 75:25 hexane–ethyl acetate affording 16.1 g (68%) of slightly colored oil. The 60-MHz proton NMR spectrum ($CDCl_3$) showed a 1-proton vinyl singlet at δ 6.36, a 1-proton vinyl singlet at δ 6.10, a broad 2-proton amino singlet at δ 2.20, and an 18-proton *tert*-butyl singlet at δ 1.51. The IR spectrum ($CHCl_3$)

(9) Adapted from a procedure of Reisner et al. (Reisner, D. B.; Horning, E. C. "Organic Syntheses"; Wiley: New York, Collect. Vol. IV, 1963; p 144) for preparing chloroacetonitrile. Reaction of propionitrile with *N*-bromosuccinimide according to Couvreur et al. (Couvreur, P.; Bruylants, A. *J. Org. Chem.* **1953**, *18*, 501) was not satisfactory.

showed bands at 2990 cm^{-1} (s, CH), 2240 cm^{-1} (w, CN), and 1740 cm^{-1} (s, CO). The coupled ^{13}C NMR spectrum ($CDCl_3$) showed a carbonyl singlet at δ 167.4, a vinyl triplet (J = 166.0 Hz) at δ 132.7, a vinyl singlet at δ 122.4, a nitrile singlet at δ 117.1, a quaternary carbon singlet at δ 84.5, a quaternary carbon singlet at δ 68.8, and a methyl quartet (J = 126.0 Hz) at δ 28.2.

β-Methylene-D,L-asparagine (I). A solution of 10.00 g (0.035 mol) of amino diester nitrile VI in 400 mL of 20% hydrochloric acid was heated at 40 °C for 12 h. The reaction mixture was concentrated under vacuum yielding a solid residue weighing 8.72 g. The solid was taken up in water, treated with 500 mg of charcoal, and filtered, yielding 7.48 g of yellow-white solid. This substance was then cooled to 0 °C and treated with small portions of cold (0 °C) 2 N sodium hydroxide until the solid dissolved and the pH of the solution became 5.5. At this point 2.8 g of a white solid precipitated from the solution. The mother liquor was concentrated, yielding an additional 1.49 g of tan solid. Recrystallization of the second crop from 8 mL of hot water yielded 938 mg of white crystalline product. The total combined weight was 3.738 g (72%). The NMR spectrum (D_2O/TSP reference) was taken of the hydrochloride and showed three singlets at δ 4.81, 6.12, and 6.39, corresponding to the methine and two vinyl protons. The proton-coupled carbon-13 NMR spectrum (D_2O, DCl, TSP reference) showed a methine doublet of quartets (^1J = 144.0, ^3J = 7.3 and 12.2 Hz) at δ 56.3, a vinyl methylene triplet of doublets (^1J = 161.1, ^3J = 4.9 Hz) at δ 131.2, a quaternary vinyl singlet (broadened and very slightly split) at δ 135.7, an amide carbonyl multiplet at δ 170 .7, and carboxyl doublet (^2J = 4.9 Hz) at δ 171.6.

The infrared spectrum (KBr) showed bands at 3450–3100 cm^{-1} (-OH, NH), 1600 cm^{-1} (C=O), 1495 cm^{-1}, and 1385 cm^{-1}. The negative LD mass spectrum showed m/z (relative intensity) 144 (100, M^-), 100 (33, $M^- - CO_2$), 82 (80, $C_4H_4ON^-$), 43 (44, $CHON^-$), 37, 35 (17, 85, Cl^-), and 28 (25, CN^-). The positive LD mass spectrum showed m/z (relative intensity) 190 (67, MNa_2^+), 81 (14, $C_4H_3ON^+$), and 22 (100, Na^+).

The amino acid I does not have a sharp melting point; it begins to decompose at 160 °C, becoming progressively darker as the temperature is raised above this point.

***N*-Acetyl-β-methylene-D,L-asparagine (VIII).** A suspension of 30 mg (0.16 mmol) of the amino acid I in 175 μL of H_2O was treated with 48 mg (0.47 mmol) of acetic anhydride. After stirring for 10 min, the reaction mixture became homogeneous and was allowed to stir an additional 20 min. The reaction mixture was then evacuated under high vacuum, yielding 34 mg (93%) of white foamy acetylated amino acid VII. The 60-MHz proton NMR spectrum (D_2O) showed a one-proton vinyl snglet at δ 5.96, a one-proton vinyl singlet at δ 5.76, a one-proton methine singlet at δ 5.20, and a three-proton acetate singlet at δ 1.96. The IR spectrum (KBr) showed bands at 3300 cm^{-1} (s, OH) and 1740 cm^{-1} (s, CO). The mass spectrum (15 eV) showed peaks at m/z (relative intensity) 170 (100, $C_7H_8O_3N_2^+$), 128 (50, $C_5H_6O_3N^+$), 127 (47, $C_5H_7O_2N_2^+$), and 43 (33, $CHNO^+$).

Hydrolysis of I to β-Methylene-D,L-aspartic Acid. A solution of 500 mg (0.003 mol) of β-methylene-D,L-asparagine (I) in 20 mL of 20% hydrochloric acid was heated at 70 °C for 60 h. The reaction mixture was concentrated under vacuum, leaving a solid residue of off-white solid. The total recovered weight was 425 mg (82%). The NMR spectrum (D_2O/TSP reference) showed three singlets at δ 5.02, 6.37, and 6.73, identical with the spectrum of an authentic sample of β-methylene-D,L-aspartic acid.

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Registry No. I, 94859-90-2; II, 94859-91-3; III, 94859-92-4; IV, 94859-93-5; V, 94859-94-6; VI, 94859-95-7; VII, 94859-96-8; VIII, 94859-97-9; β-methylene-DL-aspartic acid, 71195-09-0; 2-bromopropionitrile, 19481-82-4; 2-bromopropionamide, 5875-25-2; di-*tert*-butyl malonate, 541-16-2.

Notes

Leaving Group Ability and pK_a in Elimination Reactions

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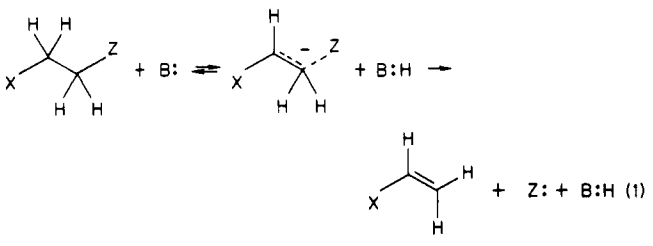
Alkene-forming elimination reactions are known to be sensitive to variations of the leaving group.[1] In the case of base-promoted, alkene-forming 1,2-eliminations, the rate of reaction depends primarily on the leaving group Z when the activating group X is constant. Rate data reported[2]



for a diverse set of Z groups when X = $PhSO_2$ span a range of at least 10^{16}. By comparing these rates to pK of the acid Z–H, C–Z bond strength, and the rate of reaction of the free leaving group with methyl iodide, Stirling et al. concluded that reactivity shows no correlation with these molecular properties for neutral leaving groups.[2] It has been emphasized repeatedly that there is no general correlation of the leaving group ability with pK_a of Z–H in water.[1-4] On the other hand, others have adopted the simple idea that the acidity of Z–H can parallel reactivity in mechanisms involving departure of a leaving group for a "related" series of structures.[5]

Recently, Stirling et al.[6] have pointed out that a corre-

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