

Ethyl 3-Butenoate, 7. *trans*-Ethyl 2-butenoate, 6, (2.33 g) and 1,2-dimethylimidazole (76.6 mg) were dissolved in ether (50 mL) and irradiated as for 16. After 6 days the reaction was judged complete by GC (SE 30, 50 °C). The ether was evaporated and the residue distilled (90 °C (100 mm)) to give 1.62 g of 7 (70%): ¹H NMR (60 MHz, CDCl₃) 6.0 (1 H, doublet of doublets of triplets, *J* = 18, 9, 7 Hz), 5.1 (2 H, broad doublet, *J* = 18), 4.15 (2 H, quartet, *J* = 7), 3.1 (2 H, doublet, *J* = 7), 1.3 (3 H, triplet, *J* = 7) ppm.

A small scale reaction was carried out as follows. The ester 6 (0.4 g) and 1,2-dimethylimidazole (16.7 mg) were dissolved in ether (10 mL) and irradiated as for 16. Complete conversion, as indicated by GC (5% SE 30, 70-200 °C at 10 °C/min.), required 26 h. The solvent was removed and the residue was purified by preparative GC (20% Carbowax, 90 °C) to give 0.148 g of 7 (37%).

Ethyl 2,3-Dimethyl-3-butenoate, 3. Ethyl 2,3-dimethyl-2-butenoate, 2 (2.30 g), and 1,2-dimethylimidazole (79.5 mg) were dissolved in ether (50 mL) and irradiated as for 16. After 16 days the reaction was judged to be complete by GC (OV 351, 80 °C). The ether was evaporated and the residue distilled (55-60 °C (15 mm)) to give 1.18 g (51%): ¹H NMR (60 MHz, CDCl₃) 4.85 (2 H, broadened singlet), 4.15 (2 H, quartet, *J* = 7), 3.10 (1 H, broadened quartet, *J* = 7), 1.79 (3 H, triplet, *J* = 1), 1.27 (3 H, doublet, *J* = 7), 1.26 (3 H, triplet, *J* = 7) ppm.

A small scale reaction was carried out as follows. The ester 2 (0.50 g) and 1,2-dimethylimidazole (15.7 mg) were dissolved in ether (10 mL) and irradiated as for 16. Complete conversion (as judged by GC on 10% OV101, 100 °C) required 20 h. Evaporation of the solvent gave an oil which was purified by preparative GC (20% DEGS, 104 °C) to give 0.25 g of 3 (50%).

Ethyl (1-Cycloheptenyl)acetate, 20. Ethyl cycloheptylideneacetate, 5 (0.7 g), and 1,2-dimethylimidazole (17.8 mg) were dissolved in ether (10 mL) and irradiated as for 16. After 26 h GC (5% SE 30, 70-200 °C at 10 °C/min.) indicated complete conversion. The solvent was removed and the residual oil was purified by preparative GC (20% Carbowax, 146 °C) to give 0.41 g of 20 (58%): ¹H NMR (60 MHz, CDCl₃) 5.70 (1 H, triplet, *J* = 7), 4.10 (2 H, quartet, *J* = 7), 3.02 (2 H, singlet), 2.18 (4 H, broad

multiplet), 1.68 (6 H, multiplet), 1.30 (3 H, triplet, *J* = 7) ppm.

Ethyl (1-Cyclopentenyl)acetate, 19. Ethyl cyclopentylideneacetate, 4 (0.141 g), and 1,2-dimethylimidazole (0.022 g) were dissolved in ether (20 mL) and irradiated as for 16. After 43 h GC (OV 351, 150 °C) indicated that no starting material remained. The ether was evaporated and the residue separated by using preparative GC (10% UCON LB 550 X, 140 °C) to give 19 (0.056 g, 40%): ¹H NMR (200 MHz, CDCl₃) 5.64 (1 H, broad singlet), 4.15 (2 H, quartet, *J* = 7), 3.11 (2 H, singlet), 2.34 (4 H, triplet, *J* = 7.5), 1.90 (2 H, quintuplet, *J* = 7.5), 1.27 (3 H, triplet, *J* = 7) ppm.

Deconjugation of Ethyl 3-Methylpentenoate, 26. The ester 26 (0.383 g) and 1,2-dimethylimidazole (0.022 g) were dissolved in methanol (35 mL) and irradiated as described for 16 until GC (SE 30, 90 °C) indicated almost complete conversion to a mixture of 27, 28, and 29 in 17%, 41%, and 37% yield, respectively. A portion of the mixture was separated by preparative GC (10% SE 30, 90 °C) to give samples of the deconjugated isomers for characterization and GC calibration. For 27: ¹H NMR (100 MHz, CDCl₃) 5.45 (1 H, quartet, *J* = 7), 4.14 (2 H, quartet, *J* = 7), 3.04 (2 H, singlet), 1.77 (3 H, singlet), 1.62 (3 H, doublet, *J* = 7), 1.26 (3 H, triplet, *J* = 7) ppm. For 28: ¹H NMR (100 MHz, CDCl₃) 5.37 (1 H, quartet, *J* = 7), 4.13 (2 H, quartet, *J* = 7), 2.97 (2 H, singlet), 1.67 (3 H, singlet), 1.62 (3 H, doublet, *J* = 7), 1.26 (3 H, triplet, *J* = 7) ppm. For 29: ¹H NMR (100 MHz, CDCl₃) 4.89 (1 H, broad singlet), 4.14 (2 H, *J* = 7), 3.04 (2 H, singlet), 2.12 (2 H, quartet, *J* = 7), 1.26 (3 H, triplet, *J* = 7), 1.05 (3 H, triplet, *J* = 7) ppm. The separated samples were used for GC calibration against isoamyl acetate as internal standard. The irradiation was also performed in the absence of base but otherwise under identical conditions. The products yields (Table II) were determined by GC (5% SE30, 90 °C).

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Effect of Water on the Extraction and Reactions of Fluoride Anion by Quaternary Ammonium Phase-Transfer Catalysts

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The maximum conversion of the fluoride-chloride exchange reaction $\text{RCl} + \text{KF} \rightarrow \text{RF} + \text{KCl}$ catalyzed by quaternary onium salts was found to be strongly dependent on the water content of the inorganic salt. A maximum conversion was obtained when the potassium fluoride contained 0.33 mol of water per mol of KF. This phenomenon is due to better extraction of the fluoride anion when the KF is drier, offset by decomposition of the catalyst in the absence of water. It was shown that the selectivity constant $K_{\text{Cl/F}}^{\text{sol}}$ is dependent on composition of the inorganic salt and on temperature. Rate measurements indicate that the mechanism proposed by Starks for liquid-liquid exchange reactions is valid also in a solid-liquid process which is also chemically controlled.

A major synthetic application of phase-transfer catalysis (PTC) by onium salts is in the two-phase nucleophilic substitution of the general type (eq 1)^{1,2}



where RX is usually an alkyl or aryl halide in organic phase and Y⁻ is a nucleophilic anion in aqueous solution or in

a solid state. The catalysis takes place in the presence of quaternary ammonium or phosphonium salts functioning as liquid anion exchanger which transport the reacting anions across the interphase.

The reaction of type 1 when applied to the fluorination process, i.e., when the extracted nucleophile Y⁻ is a fluoride anion, suffers from several unique difficulties:³

(a) The extraction coefficient⁴ of the fluoride anion by lipophilic quaternary cations is extremely low. Conse-

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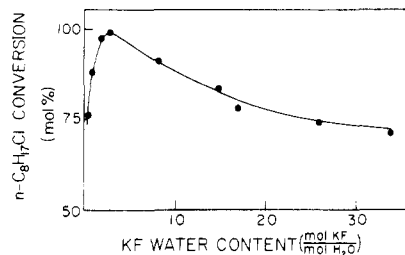


Figure 1. Maximum conversion of octyl chloride according to reaction 2 as function of water content of potassium fluoride. Reaction conditions: 1.485 g of *n*-octylchloride (10 mmol) 0.928 g of freeze-dried potassium fluoride (16 mmol), 0.2 g of Aliquat 336 (0.5 mmol) with varying amounts of water at 120 °C for 120 h in sealed tubes with magnetic stirring.

quently, the selectivity constants⁵ K^{sel} of the relevant anion pairs, e.g., Cl^-/F^- or Br^-/F^- , are also very small. As a result a very large excess of the fluoride salt is required in reaction 1, in order to obtain reasonable rates and to avoid catalyst poisoning effects.⁵ In addition, foreign anions, which may be introduced with the catalyst, can also act as a poison.⁶ This is particularly true if this foreign anion is bromide or iodide, mainly in cases when large amounts of catalyst are used.

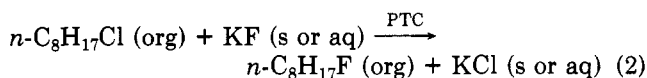
(b) The high basicity of the extracted "naked" fluoride anion results in several undesired side reactions,^{7,8} e.g., eliminations, hydrolysis, or decomposition of the catalyst.^{9,10}

(c) Attempts to improve the extractability of the fluoride anion by utilization of a polar solvent result in lower nucleophilicity of the extracted fluoride anion due to solvation and coextraction of water molecules with the fluoride ion pair.¹¹⁻¹³

In this article we present some new observations¹⁴ regarding the phase-transfer-catalyzed fluoride chloride exchange with particular emphasis on the role of the water in the system. We believe that our conclusions will assist in improving the synthetic utilization of this reaction.

Results

We have studied the exchange reaction between *n*-octyl chloride and potassium fluoride in the presence of 5 mol % of Aliquat 336 as phase-transfer catalyst (eq 2).



The reactions were carried out in sealed tubes equipped with magnetic stirrers which were placed in a thermostated bath at 120 °C. Initially the effect of the amount of water in the system on the conversion of *n*-octyl chloride after 120 h was examined. It was found that in the total absence of water no fluoride ion was extracted into the organic phase and consequently no exchange reaction took place. A similar phenomenon was observed in other phase-

Table I. Effect of Water on Product Distribution in Reaction 2

expt	reactants ^a		products, mol %		
	KF/C ₈ H ₁₇ Cl ratio	KF/H ₂ O ratio	1-octanol	<i>n</i> -octyl fluoride	1-octene
1	1.3	0.5	24.9	47.1	2.4
2	1.3	1.2	22.3	66.3	3.2
3	1.3	2.2	18.1	72.7	4.3
4	1.3	4.0	12.5	78.2	5.3
5	1.3	10.0	6.4	74.9	6.7
6	1.3	15.0	3.9	72.0	5.9
7	1.3	18.5	2.7	69.2	5.4
8	1.3	23.0	2.2	64.2	5.9
9	1.7	0.5	18.4	74.1	2.6
10	1.7	1.0	15.1	78.2	2.4
11	1.7	2.5	11.4	83.7	3.3
12	1.7	4.0	10.1	79.2	6.8
13	1.7	16.0	3.7	77.3	5.4

^a Reaction conditions: see Experimental Section.

transfer-catalyzed reactions.^{11,12} Upon addition of as little as 1 mol % of water to the potassium fluoride, immediate extraction of fluoride ion, as an ion pair with the quaternary ammonium cation takes place followed by substitution reaction to yield *n*-octyl fluoride.

Figure 1 presents the conversion of *n*-octyl chloride after 120 h (which were found to be practically final conversions) as a function of the initial KF/H₂O molar ratio using a KF/C₈H₁₇Cl molar ratio of 1.7 and a C₈H₁₇Cl/Aliquat 336 molar ratio of 20 at 120 °C. It can be seen that the final conversion is very sensitive to the amount of water present.^{15,16} Maximum conversion is obtained with KF/H₂O ratio of 3:1 while both higher or lower ratios gave lower conversions. Identical behavior was observed when smaller amounts of potassium fluoride were used except that the maximum conversion was lower. The substitution reaction 2 was accompanied by side reactions, namely, hydrolysis and elimination, which yielded *n*-octanol and 1-octene, respectively. These side reactions also depend on the amount of water in the system. Octanol yield increases and octene formation decreases with lower KF/H₂O ratio. The complete mass balance of reaction 2 with various amounts of water with KF/C₈H₁₇Cl molar ratios of 1.3 and 1.7 is presented in Table I. It should be kept in mind that the formation of octanol consumes a certain amount of water and that the final amount of water in the mixtures is thus lower than the initial amount.

An important observation is that when the KF/H₂O molar ratio is smaller than 2 the aqueous phase is a clear homogeneous solution under the reaction conditions. At larger ratios the KF-H₂O phase exists initially as a slurry. As the reaction proceeds, more solid precipitates, which was found to be practically pure potassium chloride.

Interestingly, when reaction 2 was carried out in the presence of an optimal quantity of water at 120 °C but in an open system the reaction stopped completely after 50 h with only 50% conversion. Addition of water to the dried-out mixture immediately resumed the exchange process. The amount of water added at this point clearly effected the increase in the conversion measured 20 h after the addition. The maximum increase in yield (up to almost complete conversion) is observed for addition of 0.5 mol of water for each initial mole of potassium fluoride. Both lower and higher quantities of added water resulted in lower conversions.

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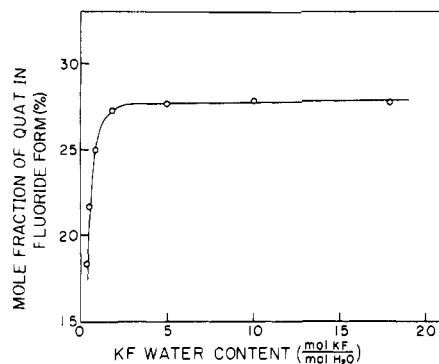
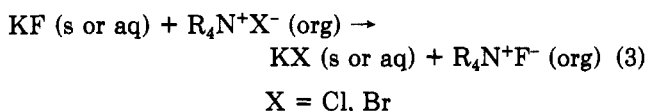


Figure 2. Extraction of fluoride anion by Aliquat 336. Reaction conditions: 1.1 g of freeze-dried potassium fluoride (19 mmol) and 5 g of Aliquat 336 (9.1 mol) were mixed for 12 h at 60 °C. Analysis by titration of both phases for Cl^- and F^- .

For a better understanding of the displacement process 2, we have examined the direct exchange reaction between potassium fluoride and quaternary ammonium chlorides or bromides in the presence or in the absence of *o*-dichlorobenzene as a solvent (eq 3) (this solvent is inert under the reaction conditions).



This exchange was studied at various temperatures from 60 to 130 °C. It was again found that the amount of fluoride extracted into the organic phase was strongly dependent on the amount of water in the system. In the absence of water no extraction took place at all while maximum extraction was observed when the amount of water in the system was less than 0.5 mol for each mol of potassium fluoride.

Figure 2 presents the fraction of the quaternary ammonium ion (quat) paired with fluoride when 2 equiv of potassium fluoride and 1 equiv of Aliquat 336 are contacted at 60 °C for 12 h as a function of the amount of water in the system. The same results were obtained after 24 h. It can be seen that below a certain amount of water up to 28% of the quat can be found in fluoride form. This figure is much higher than could be expected on the basis of the published K^{sel} for the Cl^-/F^- pair.^{1,5} With increasing quantities of water in the mixture the fluoride in the organic phase drops sharply.

The equilibrium conversion of eq 3 is also strongly dependent on the temperature. Thus at 120 °C a maximum of only 6.9% of the Aliquat 336 was found in the fluoride form. Surprisingly, when tetra-*n*-butylammonium bromide (TBAB) was exchanged with potassium fluoride containing the minimal amount of water at 120 °C, up to 11% of the quat were found to be in the fluoride form. This is again in contrast to the expectation based on the known selectivity constant $K^{\text{sel}}_{\text{Cl}/\text{F}}$ and $K^{\text{sel}}_{\text{Br}/\text{F}}$ ⁵ in homogeneous solutions.

As mentioned earlier, no extraction of fluoride anion is observed if water is absent. However, if the fluoride ion pair already exists in the organic phase, e.g., if the water evaporated while the exchange process is in progress, the quaternary ammonium fluoride salt decomposes according to eq 4 where R^{2-} is an olefin.



We have studied reaction 4 by carrying out the exchange process 3 at 120 °C followed by drying out of the system which resulted in decomposition 4. The degree of the

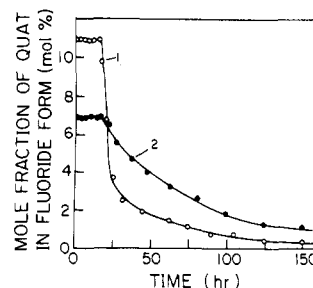
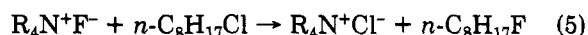


Figure 3. Formation and decomposition of quaternary ammonium fluorides: (1) tetra-*n*-butylammonium fluoride; (2) tri-octylmethylammonium fluoride. Reaction conditions: 9.28 g of potassium fluoride (0.1 mol) with 20 g of Aliquat 336 (0.05 mol) or with 13.7 g of tetra-*n*-butylammonium bromide (0.05 mol) at 120 °C.

decomposition was calculated on the basis of the quantitative determination of the tertiary amine and the potassium bifluoride. The decomposition of type 4 is probably accompanied by the intermolecular decomposition of the quaternary fluorides as reported by Harman et al.⁹ and later by Sharma and Fry.¹⁰

Figure 3 shows the exchange of Aliquat 336 and of TBAB with KF at 120 °C followed by the decomposition of the formed quaternary fluoride. The decomposition is practically complete after 120 h and is even faster for the tetra-*n*-butylammonium fluoride. It should be noted that both Aliquat 336 and tetra-*n*-butylammonium bromide are stable under the above conditions.

Finally, the homogeneous exchange reaction of quaternary ammonium fluoride with *n*-octyl chloride was examined (eq 5).



We synthesized tri-*n*-octylmethylammonium fluoride and reacted it with a large excess of *n*-octyl chloride in a homogeneous solution. The reaction was followed by analysis of samples by gas chromatography. It was found that reaction 5 under the above conditions at 80–120 °C is irreversible and follows pseudo-first-order kinetics. The first-order rate constants were calculated to be 1.58×10^{-3} , 3.15×10^{-3} , and $6.61 \times 10^{-3} \text{ min}^{-1}$ at 80 °C, 90 °C, and 100 °C, respectively. The calculated activation energy is 19.0 kcal/mol. These constants are in good agreement with our kinetic measurements for the overall reaction 2 at 120 °C,¹⁴ indicating that reaction 5 is the rate-determining step in the consecutive extraction–substitution (eq 3–5) process which is the classical mechanism of reaction 2.¹

Discussion

The main conclusion from the above observations is that the extraction of fluoride ion into the organic phase by quaternary ammonium cation is strongly dependent on the composition of the inorganic phase and on the temperature. The extraction is most efficient at lower temperature and in the presence of 0.33 mol of water for each mol of potassium fluoride applied. Surprisingly, high extraction constants are obtained under such conditions (up to $K^{\text{sel}}_{\text{Cl}/\text{F}} = 0.195$), even higher selectivity constants were calculated for $K^{\text{sel}}_{\text{Br}/\text{F}}$ (0.31) under these conditions. These results suggest that the behavior of solid–liquid extraction systems is quite different from the behavior of liquid–liquid systems. In liquid–liquid systems the extraction is not effected by temperature⁴ and the measured selectivity constant $K^{\text{sel}}_{\text{Cl}/\text{F}}$ is very low. $K^{\text{sel}}_{\text{Br}/\text{F}}$ is even smaller. Figures given by Starks¹ for similar quaternary cations in toluene are 0.02 and 0.0012, respectively.

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 $\text{KF-KCl-H}_2\text{O}$ 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 $\text{KCl-KF-H}_2\text{O}$ 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 temperatures and $K^{\text{sel}}_{\text{Cl/F}}$ 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 \times 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, washed 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 precision 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*-C₈H₁₇Cl, 111-85-3; F₂, 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-de-

pendent enzymes. Upon finding that β -methylene-D,L-aspartic acid³ is a specific inhibitor of glutamate-aspartate