temperatures for 1 h and at 25 °C for 2 h. The solvent was removed under reduced pressure followed by coevaporation (4×) with 95% ethanol. The residue was purified by using silica gel chromatography with 9:1 chloroform:methanol as the developing solvent. The band at R_f 0.65 upon elution yielded 0.522 g (1.01 mmol, 84%) of **5** as off-white crystals: mp 78–80 °C; ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 20.9, 63.1, 70.6, 73.4, 80.5, 86.1, 119.7, 120.1, 138.33, 149.9, 155.4, 169.4, 169.5, 170.3; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.13 (s, 3 H), 2.16 (s, 3 H), 4.41 (m, 3 H), 5.30 (t, 1 H), 5.79 (t, 1 H), 6.13 (d, 1 H), 6.40 (br s, 2 H), 7.87 (s, 1 H); UV (EtOH) λ_{max} 222 nm (ε 1.97 × 10^4), 264.5 (ε 1.32 × 10^4); mass spectrum, m/z (relative intensity) 519 (M^+, 2.1), 262 (15.3), 261 (4.6), 260 (Pur^+, 4.3), 259 ($sugar^+$, 30.5), 157 (11.8), 139 (100), 135 (6.4), 134 (12.8), 133 (Pur^+ − I, 1.4).

2,6-Diiodo-9β-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)purine (6). A mixture of 0.320 g (0.616 mmol) of **5**, 5.4 mL (40 mmol) of *n*-pentyl nitrite, and 16 mL of diiodomethane was protected from moisture and stirred for 7 h and 80 °C. The solvent was then removed under reduced pressure and the residue was chromatographed on silica gel plates. After elution with 20:1 chloroform:methanol, the band at R_f 0.68 afforded 0.198 g (0.314 mmol, 51%) of **6** as light yellow crystals: mp 160–162 °C; ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 20.8, 62.9, 70.6, 73.3, 80.8, 86.6, 117.1, 122.2, 139.3, 142.5, 148.2, 169.3, 169.5, 170.1; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.14 (s, 3 H), 2.17 (s, 3 H), 4.42 (m, 3 H), 5.60 (t, 1 H), 5.80 (t, 1 H), 6.19 (d, 1 H), 8.24 (s, 1 H); UV (EtOH) λ_{max} 290 nm (ε 8.17 × 10^3), 252 (ε 8.76 × 10^3), 226 (ε 1.70 × 10^4); mass spectrum, m/z (relative intensity) 630 (M^+, 0.8), 415 (4.4), 401 (1.2), 373 (12.4), 372 (Pur^+ + H, 1.3), 259 ($sugar^+$, 40.4), 246 (1.4), 245 [(Pur^+ − I) + H, 4.1], 157 (12.6), 139 (100.0).

Acknowledgment is made to the NSF for support of our investigations.

Registry No. **1**, 1818-71-9; **2**, 16321-99-6; **3**, 5987-76-8; **4**, 35109-88-7; **5**, 94042-04-3; **6**, 94042-05-4; guanosine, 118-00-3.

Synthesis of 2,6-Dihalo-DL-tyrosines

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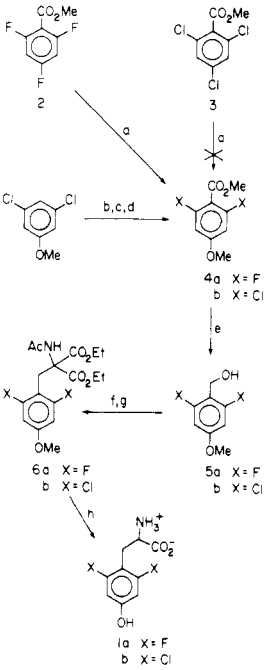
As part of a program of research on the mechanisms of catalysis by α-keto acid dioxygenases, it has been necessary for us to synthesize a variety of unusual α-keto acids for use as alternate substrates or inhibitors of these enzymes. It is convenient to prepare these compounds by the action of commercially available D- and L-amino acid oxidases on the corresponding α-amino acids,[1] and since an enormous number of α-amino acids have been chemically synthesized or isolated from natural sources, the acquisition of these synthetic precursors is usually a simple matter. However, when we required 2,6-difluoro-DL-tyrosine (**1a**) for our studies, we soon discovered not only that this particular amino acid was unknown but that there were no literature examples of any 2,6-dihalotyrosines.[2] This was especially surprising in view of the enormous chemical and biological literature concerning the 3,5-dihalotyrosines, which are of interest by virtue of their structural relationship to thyroxine. Several 2-halotyrosines have been prepared[5,6] and shown to have significant antibacterial activity,[6] but the 2,6-dihalo derivatives have not been made, perhaps due to the more severe synthetic challenge presented by the three mutually meta-oriented ortho,para-directing substituents on the aromatic ring. We report herein short syntheses (Scheme I) of 2,6-difluoro-DL-tyrosine (**1a**) and 2,6-dichloro-DL-tyrosine (**1b**).

Scheme I[a]



[a] (a) NaOMe/MeOH/reflux; (b) *n*-BuLi/TMEDA/THF/−78 °C, then CO_2; (c) $SOCl_2$/reflux; (d) MeOH/pyridine; (e) $LiAlH_4/Et_2O$; (f) HBr/HOAc; (g) diethyl acetamidomalonate/NaOEt/EtOH; (h) HBr/H_2O/reflux.

The key intermediates in these syntheses were the trisubstituted benzyl alcohols **5a** and **5b**. A very convenient preparation of 2,6-difluoro-4-methoxybenzyl alcohol (**5a**) has been described recently in the patent literature.[7] 1,3,5-Trifluorobenzene was deprotonated and carboxylated, and the resulting acid was esterified to give methyl 2,4,6-trifluorobenzoate (**2**). Treatment of **2** with 1 equiv of sodium methoxide in refluxing methanol yielded a mixture of esters from which pure methyl 2,6-difluoro-4-methoxybenzoate (**4a**) crystallized upon concentration. Reduction of compound **4a** with Red-Al (Aldrich) or $LiAlH_4$ gave the desired benzyl alcohol **5a**. In our hands the overall yield of **5a** from the trifluorobenzene was approximately 15%.

We attempted to prepare 2,6-dichloro-4-methoxybenzyl alcohol (**5b**) using similar methodology, but the methoxide treatment of methyl 2,4,6-trichlorobenzoate (**3**) was without effect. When more vigorous conditions were employed for the substitution reaction—treatment of **3** with sodium *n*-butoxide in refluxing *n*-butanol—only *n*-butyl 2,4-di-

(1) Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321–358, and references cited therein.

(2) An extensive literature search uncovered only two apparent reports of the preparation of 2,6-dihalotyrosines. Mantescu et al.[3] treated tyrosine with iodine monochloride to give 3,5-diiodotyrosine which was in turn converted to 3,5-[$^{18}F_2$]difluorotyrosine by treatment with postassium [^{18}F]fluoride in acetic acid. However, these compounds were not characterized (in the latter case because of the short half-life of the radioisotope ^{18}F), and the illustrations in their paper incorrectly depict the products as 2,6-dihalotyrosines. Subsequent repetition of this synthesis by Donnerhack and Sattler[4] was accompanied by a repetition of the error in nomenclature.

(3) Mantescu, C.; Genunche, A.; Simionescu, L. *Radiopharm. Labelled Compds., Proc. Symp.* **1973**, *1*, 395–404.

(4) Donnerhack, A.; Sattler, E. L. *Int. J. Appl. Radiat. Isot.* **1980**, *31*, 279–285.

(5) Bennett, E. L.; Niemann, C. *J. Am. Chem. Soc.* **1950**, *72*, 1806–1807.

(6) McCord, T. J.; Smith, D. R.; Winters, D. W.; Grimes, J. F.; Hulme, K. L.; Robinson, L. Q.; Gage, L. D.; Davis, A. L. *J. Med. Chem.* **1975**, *18*, 26–29.

(7) Punja, N. Eur. Pat. Appl. 80 304 158.1, 1981.

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chloro-6-(*n*-butoxy)benzoate was obtained; no trace of the desired 4-butoxy isomer was observed.[8]

The successful synthesis of 2,6-dichloro-4-methoxybenzyl alcohol (**5b**) is outlined in Scheme I. Deprotonation and carboxylation of 3,5-dichloroanisole in the presence of TMEDA yielded a mixture of trisubstituted benzoic acids. These acids were esterified and separated by silica gel chromatography to give methyl 2,4-dichloro-6-methoxybenzoate and methyl 2,6-dichloro-4-methoxybenzoate (**4b**) in low overall yield. Reduction of the latter ester with $LiAlH_4$ gave alcohol **5b**.

With the benzyl alcohols **5** in hand, the syntheses of the dihalotyrosines were swiftly completed. Brief treatment of compounds **5** with 30% HBr in acetic acid gave the corresponding benzyl bromides, which were used immediately for the alkylation of diethyl acetamidomalonate. The resulting diesters **6** were carefully purified and then hydrolyzed in refluxing 48% hydrobromic acid to yield the desired 2,6-dihalo-DL-tyrosines.

Experimental Section

Melting points were recorded on an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded by using tetramethylsilane (Me_4Si) and sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) as internal references. Gas–liquid chromatography (GC) was carried out on columns (6 ft × 1/4 in.) packed with 20% QF-1 on Gas Chrom Q. Relative retentions (RR) were calculated with respect to methyl benzoate. Thin layer chromatography (TLC) was performed on plates (2.5 × 10 cm) of silica gel GF.

2,6-Difluoro-4-methoxybenzyl alcohol [**5a**; ^1H NMR ($CDCl_3$) δ 1.81 (br s, 1 H, OH), 3.79 (s, 3 H, Ar OCH_3), 4.70 (s, 2 H, CH_2), 6.45 (m, 2 H, Ar H_2)] was prepared as described previously.[7]

Diethyl 2-Acetamido-2-(2,6-difluoro-4-methoxybenzyl)-malonate (6a). A solution of 2,6-difluoro-4-methoxybenzyl alcohol (**5a**, 2.5 g, 14.4 mmol) in 30% HBr in acetic acid (15 mL) was stirred for 45 min at room temperature. The solution was poured into 100 mL of water and the resulting mixture was extracted with pentane. The pentane layer was separated, washed 3 times with water, and dried over anhydrous magnesium sulfate:sodium bicarbonate (1:1). Evaporation of the solvent under reduced pressure gave white crystals of the crude 2,6-difluoro-4-methoxybenzyl bromide (2.38 g, 10.1 mmol). Diethyl acetamidomalonate (2.17 g, 10 mmol) was added to a solution of sodium (0.29 g, 12.6 mmol) in ethanol (120 mL). After 5 min, the benzyl bromide was added and the solution was stirred overnight. The reaction mixture was acidified and then poured into water and chloroform. After shaking, the chloroform layer was separated and dried over magnesium sulfate. Evaporation of the solvent gave a yellow oil which was purified by passage through a short column of silica gel (eluting solvent: chloroform). Concentration of the eluate gave crystals of diester **6a**. Recrystallization of this material from ether–hexane gave 2.64 g (7.08 mmol, 71%) of the analytically pure product, mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz, ester CH_3s), 1.99 (s, 3 H, amide CH_3), 3.65 (s, 2 H, benzyl CH_2), 3.77 (s, 3 H, OCH_3), 4.26 (m, 4 H, ester CH_2s), 6.40 (m, 2 H, Ar H_2), 6.48 (br s, 1 H, NH); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 13.9, 22.7, 26.0, 55.7, 62.6, 65.8, 97.8 (d, J = 29 Hz), 103.0 (t, J = 11 Hz), 160.4 (t, J = 14 Hz), 162.7 (dd, J = 246 Hz, 11 Hz), 167.7, 169.0; MS, m/z (relative intensity) 373 (M^+, 2), 314 (M – CH_3CONH_2, 15), 258 (M – CH_3CO – $CO_2CH_2CH_3$, 13), 174 (20), 157 (100).

Anal. Found: C, 54.69; H, 5.67; N, 3.75. Calcd for $C_{17}H_{21}F_2NO_6$: C, 55.02; H, 5.62; N, 3.71.

(8) The low reactivity of **3** with respect to nucleophilic aromatic substitution is attributable to the twisting of the carboxyl group out of plane and therefore out of conjugation with the aromatic ring due to the steric bulk of the ortho chlorine atoms. The exclusive preference of **3** for ortho substitution by alkoxide is probably due to the relief of carboxyl–chlorine nonbonded interactions in the developing transition state for the substitution reaction. On the other hand, alkoxide addition to trifluorobenzoate **2** is more rapid and less regiospecific due to the much lower steric demands of the fluorine substituents.

2,6-Difluoro-DL-tyrosine (1a). The diester **6a** (1.00 g, 2.68 mmol) was refluxed in 48% hydrobromic acid for 24 h. After cooling, the acid was evaporated under reduced pressure, and the residue was dissolved in water. The solution was neutralized with 1 N sodium hydroxide, and it was applied to a column of Dowex-50 (H^+). The column was washed with water, and it was eluted with 1 N ammonium hydroxide. The eluate was concentrated to dryness, and the residue was recrystallized from water to give pure **1a** (0.389 g, 1.79 mmol, 67%): mp 313–315 °C dec; ^1H NMR (D_2O–NaOD) δ 2.71 (dd, 1 H, J = 14 Hz, 8 Hz, β-CH_2), 2.88 (dd, 1 H, J = 14 Hz, 6 Hz, β-CH_2), 3.39 (dd, 1 H, J = 8 Hz, 6 Hz, α-CH), 6.13 (m, 2 H, Ar H_2); $^{13}C\{^1H\}$ NMR (D_2O–NaOD) δ 28.8, 57.4, 99.1 (t, J = 11 Hz), 101.9 (d, J = 23 Hz), 163.4 (dd, J = 240 Hz, 15 Hz), 168.7 (t, J = 5 Hz), 183.0; IR ν_{max} 2925, 1610, 1580, 1320, 1140, 695 cm^{-1}.

Anal. Found: C, 50.02; H, 4.24; N, 6.38. Calcd for $C_9H_9F_2NO_3$: C, 49.77; H, 4.18; N, 6.45.

Methyl 2,6-Dichloro-4-methoxybenzoate (4b). *n*-Butyllithium (1.55 M in hexane, 34 mL, 53 mmol) and TMEDA (8.5 mL, 56 mmol) were added to dry THF (40 mL), and the solution was stirred for 30 min at –78 °C. A solution of 3,5-dichloroanisole (6.9 g, 39 mmol) in THF (15 mL) was added slowly, and the reaction mixture was stirred for an additional 1.5 h. Dry carbon dioxide was bubbled into the solution for 30 min at –78 °C and then the reaction mixture was allowed to warm to room temperature while CO_2 addition continued. The reaction mixture was poured into 1 N HCl, the resulting mixture was extracted twice with methylene chloride, and the combined organic layers were washed with water. The organic acids were extracted into 1 N NaOH, and the basic extracts were washed once with methylene chloride. The aqueous layer was acidified and extracted with methylene chloride. The organic extract was concentrated to give crude trisubstituted benzoic acids (5.9 g). The acid mixture was refluxed for 2 h in thionyl chloride (30 mL). The excess $SOCl_2$ was distilled away, methanol (30 mL) and pyridine (2.5 mL) were added, and the solution was stirred overnight. The reaction mixture was poured into 1 N HCl and methylene chloride; the organic phase was separated and washed once with water. Concentration of the organic layer gave a yellow oil (3.7 g). Analysis by TLC (hexane:benzene 4:1) showed two major components with R_f s of 0.15 and 0.09. These compounds were separated by silica gel column chromatography (hexane:benzene 3:1). The less polar component proved to be the desired methyl 2,6-dichloro-4-methoxybenzoate (**4b**, 1.49 g, 6.3 mmol, 16%): mp 39–40 °C (recrystallized from methanol); ^1H NMR ($CDCl_3$) δ 3.81 (s, 3 H, Ar OCH_3), 3.95 (s, 3 H, $COOCH_3$), 6.86 (s, 2 H, Ar H); MS, m/z (relative intensity) 234 (M^+, 36), 203 (M – CH_3O), 100). Analysis by GC (20% QF-1, 180 °C) indicated a purity in excess of 99% (RR = 10.2). Exact mass 233.9844, calcd for $C_9H_8{}^{35}Cl_2O_3$ 233.9850.

The more polar component was methyl 2,4-dichloro-6-methoxybenzoate (1.24 g, 5.3 mmol, 14%): mp 55–56 °C (recrystallized from methanol); ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H, Ar OCH_3), 3.93 (s, 3 H, $COOCH_3$), 6.83 (d, 1 H, J = 2 Hz, C-5-H), 7.02 (d, 1 H, J = 2 Hz, C-3-H); MS, m/z (relative intensity) 234 (M^+, 25), 203 (M – CH_3O, 100). Analysis by GC indicated a purity in excess of 99% (RR = 8.5). Exact mass 233.9835, calcd for $C_9H_8{}^{35}Cl_2O_3$ 233.9850.

2,6-Dichloro-4-methoxybenzyl Alcohol (5b). Lithium aluminum hydride (0.486 g, 12.8 mmol) was added to a solution of ester **4b** (1.49 g, 6.34 mmol) in ether (40 mL) at 0 °C. After 3 h, ice, water, and 1 N HCl were added, and the resulting mixture was extracted 3 times with methylene chloride. The organic extracts were dried and concentrated to give crystalline alcohol **5b** (1.18 g, 5.70 mmol, 90%): mp 78–79 °C (recrystallized from ether–hexane); ^1H NMR ($CDCl_3$) δ 1.96 (t, 1 H, J = 6 Hz, OH), 3.80 (s, 3 H, OCH_3), 4.88 (d, 2 H, J = 6 Hz, CH_2), 6.88 (s, 2 H, Ar H_2); MS, m/z (relative intensity) 206 (M^+, 100), 189 (M – OH, 26), 143 (M – CH_2OH – CH_3OH, 22). Analysis by GC (20% QF-1, 180 °C) indicated a purity of 99% (RR = 7.2). Exact mass 205.9912, calcd for $C_8H_8{}^{35}Cl_2O_2$ 205.9901.

Diethyl 2-Acetamido-2-(2,6-dichloro-4-methoxybenzyl)-malonate (6b). A solution of 2,6-dichloro-4-methoxybenzyl alcohol (**5b**, 1.13 g, 5.46 mmol) in 30% HBr in acetic acid (20 mL) was stirred for 90 min at room temperature. The solution was poured into 100 mL of water and the resulting mixture was ex-

tracted with pentane. The pentane layer was separated, washed 3 times with water, and dried over anhydrous magnesium sulfate:sodium bicarbonate (1:1). Evaporation of the solvent under reduced pressure gave white crystals of the crude 2,6-dichloro-4-methoxybenzyl bromide (1.41 g, 5.22 mmol). Diethyl acetamidomalonate (1.09 g, 5.0 mmol) was added to a solution of sodium (0.21 g, 9.1 mmol) in ethanol (40 mL). After 5 min, the benzyl bromide was added and the solution was stirred for 18 h. The reaction mixture was acidified and then poured into water and methylene chloride. After shaking, the organic layer was separated and dried over magnesium sulfate. Evaporation of the solvent gave compound **6b** as a yellow oil which was crystallized from ether (1.17 g, 2.88 mmol, 53%): mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6 H, J = 7 Hz, ester CH_3), 1.97 (s, 3 H, amide CH_3), 3.77 (s, 3 H, OCH_3), 3.91 (s, 2 H, Ar CH_2), 4.25 (m, 4 H, ester CH_2), 6.42 (br s, 1 H, NH), 6.84 (s, 2 H, Ar H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 13.9, 23.2, 33.5, 55.7, 62.5, 65.6, 114.6, 123.8, 137.4, 158.9, 167.9, 169.1; MS, m/z (relative intensity) 405 (M^+, 3), 370 (M – Cl, 3), 332 (M – $CO_2CH_2CH_3$, 3), 311 (M – Cl – CH_3CONH_2, 15), 290 (M – $CO_2CH_2CH_3$ – CH_2CO, 11), 189 (100). The compound showed a single component upon analysis by TLC in two solvents (chloroform, R_f 0.15; ether, R_f 0.85). Exact mass 405.0756, calcd for $C_{17}H_{21}{}^{35}Cl_2NO_6$ 405.0746.

2,6-Dichloro-DL-tyrosine (1b). The diester **6b** (0.79 g, 1.94 mmol) was refluxed in 48% hydrobromic acid for 24 h. After cooling, the acid was evaporated under reduced pressure, and the residue was dissolved in water. The solution was neutralized with 1 N sodium hydroxide, and it was applied to a column of Dowex-50 (H^+). The column was washed with water, and it was eluted with 1 N ammonium hydroxide. The eluate was concentrated to dryness, and the residue was recrystallized from water to give pure **1b** (0.288 g, 0.91 mmol, 47%), mp 272–274 °C dec; ^{1}H NMR (D_2O-NaOD) δ 2.95 (dd, 1 H, J = 14 Hz, 9 Hz, β-CH_2), 3.12 (dd, 1 H, J = 14 Hz, 6 Hz, β-CH_2), 3.53 (dd, 1 H, J = 9 Hz, 6 Hz, α-CH_2), 6.60 (s, 2 H, Ar-H_2); ^{13}C{^{1}H} NMR (D_2O-NaOD) δ 35.4, 56.2, 118.5, 118.6, 135.3, 166.3, 182.5.

Analysis: C, 40.60; H, 4.26; N, 5.38. Calcd for $C_9H_9Cl_2NO_3 \cdot H_2O$: C, 40.32; H, 4.14; N, 5.22.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM31801).

Registry No. **1a**, 94278-64-5; **1b**, 94294-08-3; **4b**, 94278-65-6; **5a**, 79538-27-5; **5b**, 86111-47-9; **6a**, 94278-66-7; **6b**, 94278-67-8; 2,6-difluoro-4-methoxybenzyl bromide, 94278-68-9; diethyl acetamidomalonate, 1068-90-2; 3,5-dichloroanisole, 33719-74-3; 2,6-dichloro-4-methoxybenzoic acid, 94278-69-0; 2,4-dichloro-6-methoxybenzoic acid, 94294-09-4; methyl 2,4-dichloro-6-methoxybenzoate, 94294-10-7; 2,6-dichloro-4-methoxybenzyl bromide, 94278-70-3.

The Structure of *N*-(2-Ammonioethyl)carbamate in Solution

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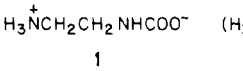
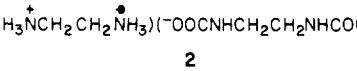
N-(2-Ammonioethyl)carbamate, the solid equimolar adduct of ethylenediamine and CO_2, has been known at least since 1900.[1] In 1951, Katchalski et al.[2] provided evidence that in solution the compound could exist as either a monomolecular zwitterion (**1**) or as a disalt (**2**).



1



2

Thus, diazomethane in ether was found to react with the solid carbamate to yield a solution containing the monomethyl ester from **1** as well as the dimethyl ester and free ethylenediamine from **2**; they also reported that calcium hydroxide added to an aqueous solution of the carbamate yielded a precipitate which was identified as the calcium salt of the dicarbamate anion.

Subsequent workers have confirmed that alkaline aqueous solutions contain both **1** and **2**. Jensen and Christensen[3] showed that amyl alcohol extracted free ethylenediamine (from **2**) from solutions of the carbamate in 1 M NaOH. Frahn and Mills[4] found two spots, corresponding to monocarbamate and dicarbamate anions, in paper electrophoresis of solutions of ethylenediamine in 0.1 M NaOH after exposure to CO_2. Frank[5] has used an NMR technique to demonstrate the existence of both **1** and **2** in aqueous solutions. The quantitative results of these measurements, however, have been discordant. Katchalsky et al. estimated that their solutions contained about equal weights of **1** and **2**, while Jensen and Christensen reported much smaller proportions of dicarbamate as determined by their procedure. Frank found amounts of **2** varying from 15 to 58 mol % in solutions of different preparations.

Recent X-ray crystallographic studies in this laboratory[6] have shown that solid *N*-(2-ammonioethyl)carbamate prepared in a variety of ways is always composed solely of **1** (although two crystalline polymorphs exist, with orthorhombic and monoclinic unit cells, respectively). Accordingly, it appears that **2** must be formed during or after dissolution of the solid. In the present work ^{13}C NMR has been used to study this process.

Obtaining satisfactory (natural abundance) ^{13}C NMR spectra of *N*-(2-ammonioethyl)carbamate required concentrated solutions in D_2O. Preliminary measurements showed that the number, position, and intensity of lines in the aliphatic carbon region varies with concentration and pH of solutions, presumably due to shifts in protonation equilibria. On addition of strong base (KOD), however, the shifts became reproducible and lines were fairly well resolved; Frank[5] found the same to be true for proton NMR spectra.

Four aliphatic C lines are observed. By comparison with spectra of ethylenediamine and dipotassium ethylenedicarbamate under the same conditions, those at 43.9 ppm (relative to tetramethylsilane) and 42.5 ppm can be assigned to the methylene carbons in ethylenediamine and the dicarbamate anion, respectively. Those at 41.8 and 44.5 ppm, therefore, are associated with the two different methylene carbons in the monocarbamate **1**.

When the solid carbamate was dissolved in ice-cold alkali solution, and the spectrum recorded immediately with the sample maintained at 0 °C, only the monocarbamate lines were present. Very slow conversion to the dicarbamate occurred on storage of the alkaline solution at 0 °C; thus after 46 h the relative line intensities indicated 3.6 mol % of dicarbamate. At room temperature, the reaction is much faster; after 4 h ca. 29 mol % of dicarbamate was observed. On the other hand, solutions of the carbamate in water at the "natural" pH (8.4), or made only slightly alkaline (0.5 M ethylenediamine, pH 9.0), showed no more than ca. 5% dicarbamate after room temperature storage for up to 1 week.

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