Cyanohydrin Synthesis: Studies with [^{13}C]Cyanide[1a]

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The classical Kiliani (cyanohydrin) reaction was studied by ^{13}C NMR and GLC. ^{13}C NMR studies were facilitated by the use of [^{13}C]cyanide and/or ^{13}C-enriched aldoses. The effects of aldose configuration, carbon-chain length, and derivatization on the rate and extent of cyanide reaction and on the overall rate of aldononitrile disappearance were investigated. For the condensation of cyanide with D-erythrose, the reaction sequence at pH 10.5 or 12.7 appears to be cyanide + D-erythrose → aldononitriles → imido-1,4-lactones → carbinolamines → aldonamides. Aldonamides hydrolyze via carbinolamines and aldonolactones to aldonates. At pH 7 or 8.5, the direct conversion of imido-1,4-lactones to aldono-1,4-lactones becomes appreciable. Ammonia, which is released in this reaction, can react with imido-1,4-lactones to yield amidines. A reaction between imidolactones and aldononitriles is proposed. ^{13}C NMR parameters (δ and J) and GLC retention times for the reactants, intermediates, and products are tabulated.

The condensation of cyanide with an aldose in aqueous solution to produce 2-epimeric aldononitriles (cyanohydrins) was first reported by Kiliani in 1885.[2] Cyanohydrins were hydrolyzed in situ to 2-epimeric aldonic acid salts (aldonates). Kiliani also demonstrated that aldonic acids could lose water to form aldonolactones.

The utility of the Kiliani reaction was extended when Fischer[3] demonstrated that aldonolactones could be reduced with sodium amalgam to aldoses, providing a convenient route for the preparation of aldoses from parent aldoses having one less carbon atom. Since that time, the Kiliani–Fischer reaction has been used to prepare a wide variety of aldoses. During the preparation of ^{14}C-labeled aldoses,[4] Isbell observed that the ratio of epimeric aldonates depended on reaction conditions. For example, the reaction of cyanide with D-arabinose at pH 11 yielded 73% D-gluconate, while at pH <9, 70% D-mannonate was formed.[4a] Militzer[5] studied the effects of parent aldose structure, temperature, and pH, and showed that lowering the temperature or pH of the reaction mixture significantly lowered the rate of cyanide consumption (aldonate formation).

The mechanism of cyanohydrin hydrolysis at pH ~11.5 was studied by Varma and French[6] with cyanohydrins formed from α-D-arabinose. Using paper and gas–liquid chromatography, they concluded that cyanohydrins cyclize to imido-1,5-lactones, which react with water to form cyclic carbinolamines. The carbinolamines rearrange to acyclic aldonamides. They proposed that aldonamides, in basic media, hydrolyze to aldonates via carbinolamine and lactone intermediates.

The present investigation of the Kiliani reaction resulted from the desire to prepare ^{13}C-enriched aldoses and their derivatives in high yield based on ^{13}C-enriched cyanide.[7] The effects of pH, temperature, and concentration of reactants were examined by using ^{13}C nuclear magnetic resonance spectroscopy (^{13}C NMR) and gas–liquid chromatography (GLC). In addition, the effects of aldose configuration, carbon-chain length, and derivatization on the rate and extent of cyanide condensation and on the rate of aldononitrile hydrolysis were investigated. The ^{13}C NMR study was facilitated by use of [^{13}C]cyanide and ^{13}C-enriched aldoses, which simplified characterization and quantitation of reaction intermediates.

Experimental Section

Materials. Glycolaldehyde, DL-glyceraldehyde, calcium DL-glycerate, D-arabinose, D-lyxose, D-ribose, D-xylose, D-ribono-1,4-lactone, sodium DL-2-hydroxybutyrate, D-gulono-1,4-lactone, 2-deoxy-D-glucose, ion-exchange resins, potato acid phosphatase (EC 3.1.3.2) and palladium barium sulfate (5%) were purchased from Sigma Chemical Co. and used without further purification. L-Threonine (allo free) was obtained from the United States Biochemical Corp. Calcium D-galactonate and calcium D-gluconate were purchased from Pfanstiehl Laboratories, Inc.

Potassium [^{13}C]cyanide (K^{13}CN) was supplied by the Los Alamos Scientific Laboratory, University of California, New Mexico, with 99.6% purity and 90.7 atom % ^{13}C enrichment. Potassium [^{14}C]cyanide (K^{14}CN) was purchased from New England Nuclear with a specific activity of 46 mCi/mmol. *N,O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) with 1% chloromethylsilane (TMCS) was obtained from Pierce Chemical Co. Pyridine for GLC was distilled from barium oxide and stored over 4-Å molecular sieves. Other chemicals and solvents were reagent grade and were used without further purification.

Preparations. D-Glyceraldehyde was prepared by oxidation of D-fructose with lead tetraacetate.[8] D-Lactaldehyde was prepared from L-threonine.[9] 2,4-*O*-Ethylidene-D-erythrose was prepared by the method of Perlin.[10] D-Erythrose was prepared by hydrolysis of 2,4-*O*-ethylidene-D-erythrose monomer.[11] Dilute aqueous solutions (0.1–0.5 M) contained approximately 5% dimers and/or higher order structures.[12] 2,4-*O*-Ethylidene-D-threose was prepared according to Ball[13] and was hydrolyzed as described for 2,4-*O*-ethylidene-D-erythrose.[11] Tetroses were estimated to be greater than 95% pure by ^{13}C NMR.[12] Sodium D-xylonate was prepared by hypoiodite oxidation of D-xylose.[14]

D-[1-^{13}C]Arabinonamide and D-[1-^{13}C]ribonamide were prepared from the respective [1-^{13}C]lactones.[15]

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DL-[1-^{13}C]Glyceronitrile and mixtures of D-[1-^{13}C]arabinono- and -ribononitriles and 3,5-*O*-ethylidene-D-[1-^{13}C]arabinono- and -ribononitriles were prepared as described previously.[11]

D-[1-^{13}C]Arabinono-, -ribono-, -lyxono-, and -xylononitrile 5-phosphates were prepared and purified as described previously.[16] The aldononitrile 5-phosphates were dephosphorylated by incubation for 18 h at 34 °C with potato acid phosphatase (5–10 mg) at pH 4.0. When inorganic phosphate (P) was greater than 90% of the total P present, the reaction mixture was treated with an equal volume of hot ethanol, incubated for 15 min at 34 °C, and centrifuged at 12 000 rpm to remove protein. The supernatant was treated with Dowex 1-X8 (OAc^-) and Dowex 50-X8 (H^+) to remove organic and inorganic P. The pH of the nitrile solution was maintained below 5 to prevent epimerization. The final solution was concentrated in vacuo at 30 °C and assayed by ^{13}C NMR. Epimeric purity was greater than 95% by ^{13}C NMR.

Mixtures of D-[1-^{13}C]ribonate and -arabinonate (5 mmol) were purified by chromatography at 25 °C on a 2.2 × 51 cm column packed with Dowex 1-X8 (200–400 mesh) resin in the acetate form. Aldonates were applied at pH 9–10, and the column was developed with 0.5 M acetic acid. Fractions (5 mL) were collected at 0.5 mL/min; D-[1-^{13}C]ribonic acid eluted between fractions 200 and 215, and D-[1-^{13}C]arabinonic acid eluted between fractions 80 and 120 after changing the eluent to 1 M acetic acid. Aldonic acids were detected by radioactivity[17] or by chromotropic acid assay.[18]

Mixtures of D-[1-^{13}C]xylonate and -lyxonate (2 mmol) were separated on a similar column at 4 °C. The column was developed with a linear gradient of acetic acid (0.3–0.5 M, 4 L) at 7.5 mL/15-min fraction, followed by 0.5 M acetic acid. D-[1-^{13}C]-Xylonic acid eluted between fractions 475 and 520 and D-[1-^{13}C]lyxonic acid between fractions 545 and 620.

D-[1-^{13}C]Ribono-1,4-lactone and D-[1-^{13}C]arabinono-1,4-lactone were prepared from the respective [1-^{13}C]aldonates by deionization on columns containing a tenfold excess of Dowex 50-X8 (H^+) and elution with deionized water. Solutions of the free acids were concentrated at 30 °C in vacuo and stored in vacuo at 25 °C over $MgClO_4$. Lactonization, estimated by ^{13}C NMR, was complete in 2–5 days.

D-[1-^{13}C]Arabinono-1,5-lactone and D-[1-^{13}C]ribono-1,5-lactone were prepared by oxidation of the respective [1-^{13}C]aldoses with Pt/O_2.[19]

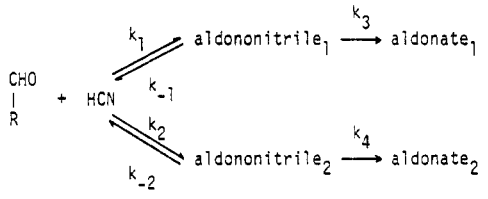
erythro,threo-2,3-Dihydroxy-D-[1-^{13}C]butanal was prepared by addition of K^{13}CN to D-lactaldehyde (pH 8.0, 18 °C, and 0.3 M). The resulting aldononitriles were catalytically reduced[12] at atmospheric pressure and pH 1.7 with palladium barium sulfate, and the mixture of aldoses (40% yield) was deionized. D-[1-^{13}C]Erythrose, DL-[2-^{13}C]erythrose, and DL-[3-^{13}C]erythrose were prepared as described previously.[12]

Instrumentation and Methods. ^{13}C NMR spectra were obtained by using a Bruker WP-60 Fourier transform spectrometer operating at 15.08 MHz for carbon and equipped with quadrature detection. Spectra were obtained with 3000-Hz spectral widths, 6000-Hz filter widths, and 4K real data points. The spectrometer was locked externally to the resonance of ^2H_2O in a capillary.

GLC analyses were performed on a Varian Aerograph 1200 gas chromatograph equipped with flame-ionization detection. A 2 m × 2 mm column of OV-17 (3%) on high-performance Chromosorb W-AW (100–120 mesh) from Applied Science was used with a temperature program of 100–230 °C at 4 °C/min. For derivatization, aqueous samples (6 μL) were added rapidly to a mixture of 150 μL of BSTFA with 1% TMCS and 150 μL of dry pyridine, and the mixtures were analyzed after 25 min at 60 °C. Retention data are reported relative to the pertrimethylsilylated derivative of D-gluconate.

Radioactivity was measured by scintillation counting using a cocktail described previously.[11] pH measurements were made with a Corning Digital 110 pH meter equipped with a Corning semimicro combination electrode. Phosphate was determined by the method of Leloir and Cardini.[20]

Scheme I



Tetrose solutions were standardized as follows. Aliquots (1–4 mL containing 0.1–1.0 mmol of aldose) taken from a stock tetrose solution were added at 4 °C to 5-mL solutions containing 1 mmol of KCN, and reaction mixtures were adjusted to 10 mL with water. After 1 h at 4 °C, the reaction mixtures were incubated at 25 °C for 50 h, and excess cyanide was determined.[21] Stock solutions of the tetroses standardized in this fashion were used to prepare standard curves for the Nelson reducing-sugar assay.[22] Glyceraldehyde was estimated by the Nelson assay with standard solutions prepared from crystalline DL-glyceraldehyde.

GLC Analysis of Reaction Intermediates. Reactions were carried out at 18 ± 1 °C (water bath) in 15-mL centrifuge tubes with magnetic stirring. For reactions without pH control (pH 12.7), the tube was charged with KCN (0.6 mmol in 1.2 mL of H_2O), followed by the aldose solution (0.6 mmol in 0.8 mL of H_2O).

For reactions at controlled pH, the tube containing the cyanide solution (1.1 mL) was sealed with a stopper fitted with a pH electrode and three polyethylene tubing inlets for adding 4 M HCl, 1 M NaOH, and the aldose solution. The pH of the solution (~11) was adjusted to the desired value with 4 M HCl and the aldose solution (0.8 mL) added during 0.5 min with efficient stirring. The pH was controlled to ±0.2 unit by the addition of 4 M HCl and/or 1 M NaOH.

Samples were withdrawn at various times, derivatized with BSTFA, and analyzed by GLC.

^{13}C NMR Analysis of Reaction Intermediates. Reaction mixtures were prepared as described above except that K^{13}CN was used. Reactions without pH control (pH 12.7) were studied by mixing 1-mL samples of equimolar solutions of K^{13}CN and aldose in a 10-mm NMR tube. Reaction mixtures at controlled pH were assayed at various times by transferring samples to a 0.5-mL coaxial insert tube. The probe temperature was maintained at 18 ± 1 °C.

To improve detection and quantitation, 55° pulses and 5-s delay times were employed. Computer-integrated peak areas were used for quantitation.

Results

Aldonic Acid Formation. An aqueous solution containing stoichiometric amounts of cyanide salt and C_4 or C_5 aldose (0.1–0.3 M) at 25 °C is sufficiently basic (pH 12–13) to cause rapid hydrolysis of the initially formed 2-epimeric C_5 and C_6 aldononitriles to the corresponding aldonates. Hydrolysis is complete in 3–4 h except for the aldononitriles derived for D-xylose, which require 11 h for complete hydrolysis. In contrast, the production of aldonates from the C_4 nitriles derived from D-glyceraldehyde (0.1–0.3 M) at pH 12–13 requires 6–10 days.

At lower pH values (8.5–10.5), hydrolysis of C_5 and C_6 aldononitriles depends on the rate of hydrolysis of intermediate aldonamides and typically requires several days (see below). In weakly basic solution (pH 8.0), C_3 and C_4 aldononitriles are stable for extended periods at −15 °C.[12]

The addition of KCN to glycolaldehyde (0.1–0.3 M) at pH 12–13 yields reaction mixtures of unexpected com-

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Table I. Aldonate Formation: Effect of pH and Reactant Concentration on the Distribution of Epimers[a]

parent aldose	concn, M	pH[b] (± 0.2)	% yield GLC (± 3%)	% yield NMR (± 3%)	predominant epimer
D-glyceraldehyde	0.1	u	61	60	threo
	0.3[c]	u		59	threo
D-threose	0.1	u	58		lyxo
	0.3[d]	8.5		61	lyxo
D-erythrose	0.1	u	62		arabino
	0.3[c]	u		68	arabino
	0.3[d]	10.5		79	arabino
	0.3[d]	8.5		74	arabino
D-arabinose	0.1	u	75	76	gluco
	0.5	u	69	66	gluco
	0.1	9.0	65	70	manno
D-lyxose	0.1	u		72	galacto
D-ribose	0.1	u	57	56	allo
	0.5	u	53	52	allo
	0.1	9.0	57	61	allo
D-xylose	0.1	u	78	75	gulo
	0.5	u	69		gulo
	0.1	9.0	59	59	gulo

[a] Reactions were carried out at room temperature. NMR ratios were determined by examination of the peak areas of the hydroxymethyl groups (CH_2OH) in unenriched compounds and/or the carboxylate groups (COO^-) in 1-^{13}C-enriched compounds. [b] u = uncontrolled pH; for pH-controlled reactions, HOAc and NaOH were employed. [c] Conducted at 18 °C. [d] pH was controlled with HCl instead of HOAc.

plexity. At 0.3 M, 5% DL-glycerate is formed. The major products are C_5 aldonates formed by the addition of cyanide to C_4 aldoses produced by aldol condensation of glycolaldehyde.

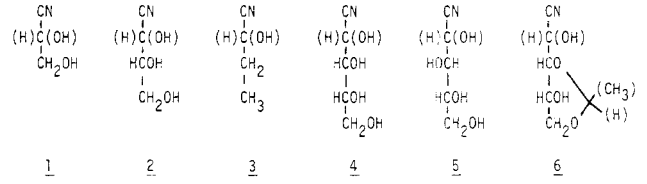
The ratio of 2-epimeric aldonates found after the addition of cyanide to an aldose depends on the values of the rate constants indicated in Scheme I. In this simple scheme, it is assumed that, after aldononitriles are formed, no intermediate exists that can epimerize at C-2. All of the rates are pH dependent (see below), and the ratio of aldonates produced depends on reaction conditions (Table I). At pH 12–13, the addition of cyanide to D-arabinose (0.1 M) yields 75% D-gluconate, whereas, at pH 9.0, 68% D-mannonate is formed (Table I). In the case of D-xylose (pH 12–13, 0.1 M), 77% of the product is D-gulonate. At pH 9.0 and a 0.1 M concentration, 59% D-gulo epimer is formed. It has been proposed[23] that the predominant aldonate has OH-2 trans to OH-4. At pH 12.7, neither D-arabinose nor D-ribose meet this expectation, while, at pH 9.0, D-ribose gives the OH-2/OH-4 cis product predominantly (Table I).

Aldononitrile Formation. The equilibrium between starting aldose and aldononitrile depends on the concentration of the reactants, the structure of the parent aldose, and pH.

The condensation of 0.3 M [^{13}C]cyanide and 0.3 M D-erythrose at 18 °C can be followed by ^{13}C NMR as a function of pH. Starting at pH 2, aldononitrile formation is not observed until the pH of the reaction mixture is raised to 5.1 ± 0.2. At this pH, the ratio of nitriles to unreacted cyanide is ~0.7. At pH 6.5 ± 0.2, aldononitrile formation is complete (ribo/arabino ratio of 54:46). The absence of unreacted aldose was verified by GLC. As the pH of the reaction mixture is raised above 11, both the concentration of free aldose and the rate of aldononitrile hydrolysis increase.

Addition of an aldose to a cyanide salt (KCN, NaCN; 0.3 M) at 18 °C in the absence of pH control is followed by an increase in pH from 11.3 to 12.7 during the first 5 min of reaction. This increase results from the condensation of cyanide ion ($pK_a = 9.2$)[24] with the aldose to form

Chart I



1 2 3 4 5 6

an O-2 alkoxide intermediate, which abstracts a proton from water to produce OH^-. A gradual rise in pH is noted during the next 50 min as the remaining aldose reacts. A subsequent slow decrease in pH reflects the rate of aldononitrile hydrolysis to yield aldonates and ammonium ion.

The extent of aldononitrile formation is reduced when the parent aldose can form a pyranose ring. The C_2 and C_3 aldoses, which are extensively hydrated in aqueous solution,[12,25] and the C_4 aldoses,[12] which are 88% furanose, 11% hydrate, and 1% aldehyde, react with cyanide stoichiometrically and essentially quantitatively at pH 7.5–9.0. On the other hand, pentoses, which are predominantly in pyranose forms, do not react quantitatively at pH 7.5–9.0, and equilibrated reaction mixtures contain ~15% unreacted aldose. Complete conversion can be accomplished at pH 8.0 by using a threefold excess of cyanide.[11]

The formation of aldononitriles is rapidly reversible at pH 7.0 or above, whereas below pH 4 they are stable. This stability permits epimeric mixtures of aldononitrile phosphates to be separated at pH 3.9 by chromatography on ion-exchange resins.[16] Aldononitrile phosphates, separated in this fashion, rapidly revert to epimeric mixtures at pH 7 or above.

Rates of Aldononitrile Disappearance. The rate of disappearance of aldononitriles depends on pH and the structure of the aldononitrile.

The rate of aldononitrile disappearance at pH >11 is difficult to measure since aldononitrile concentration is determined by two rates, the rate of formation from aldose and the rate of hydrolysis to aldonamides and other products. The rates of aldonamide formation and disap-

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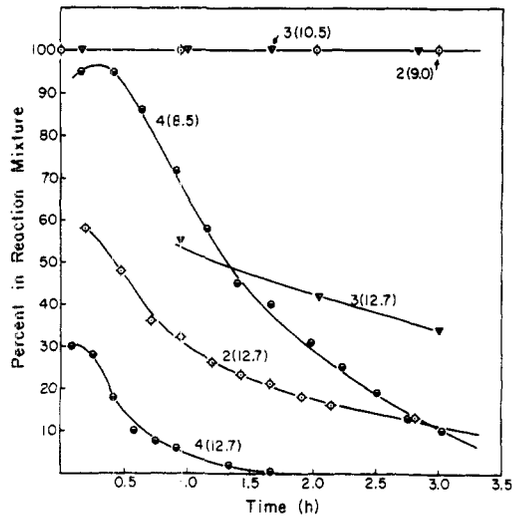


Figure 1. Disappearance of aldononitriles in cyanohydrin reaction mixtures. Reaction mixtures were incubated at 18 ± 1 °C, and data were obtained from ^{13}C NMR spectra as described in Instrumentation and Methods. Concentrations of reactants were 0.3 M except for reactions involving **3**, which were conducted at 0.4 M. Experiments were conducted at the pH values in parentheses. **2** = D-[1-^{13}C]erythrono- and D-[1-^{13}C]threononitriles; **3** = DL-2-hydroxy[1-^{13}C]butyronitrile; **4** = D-[1-^{13}C]arabinono- and D-[1-^{13}C]ribononitriles. Data for **3** at pH 12.7 were obtained over a 16-h period (partial data shown).

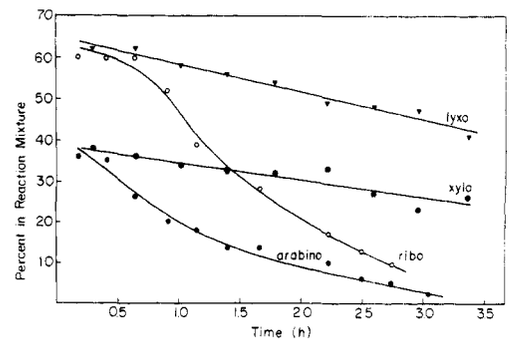


Figure 2. Differences in the rates of aldononitrile disappearance between C_5 diastereomers during the cyanohydrin reaction at pH 8.5 ± 0.2. Reaction mixtures were incubated at 18 ± 1 °C and were 0.3 M in aldose and [^{13}C]cyanide. Data were obtained from ^{13}C NMR spectra obtained as described in Instrumentation and Methods.

pearance are both high at high pH values. The disappearance of aldononitriles at 18 °C was measured by ^{13}C NMR for the [1-^{13}C]aldononitriles **1**–**6** (Chart I, Figure 1). At pH 8.5, the rate of DL-glyceronitrile (**1**) disappearance is negligible (not shown). However, **1** (0.3 M) disappears slowly at pH 12.7 ($t_{1/2} \simeq 25$ h). The reaction is complete in ~125 h, at which time the ^{13}C NMR spectrum of the products shows resonances for DL-[1-^{13}C]glycerate (5%) and for DL-[1-^{13}C]lyxonate (40%), DL-[1-^{13}C]xylonate (17%), DL-[1-^{13}C]arabinonate (28%), and DL-[1-^{13}C]ribonate (10%) (confirmed by GLC). The formation of DL-[1-^{13}C]pentonates is due to aldol condensation of glycolaldehyde to form the DL-tetroses. DL-Pentonates derived from the trans (DL-threose) and cis (DL-erythrose) aldol products compose about 60 and 40% of the mixture, respectively. Clearly, aldol condensation is favored over the hydrolysis of **1** at pH 12.7. Although the hydrolysis of the C_5 nitriles derived from erythrose is more rapid than hydrolysis of those derived from threose (Figure 2), the preponderance of C_5 aldonates derived from threose indicates that aldol condensation of glycolaldehyde favors threose formation.[26]

The rate of disappearance of C_4 aldononitriles **2** is negligible at pH 9.0 and 18 °C (Figure 1). At pH 12.7 and 18 °C, **2** disappears more rapidly ($t_{1/2} \simeq 1$ h) than the C_3 homologue **1** ($t_{1/2} \simeq 25$ h) or DL-2-hydroxybutyronitrile (**3**, $t_{1/2} \simeq 5$ h). DL-2-Hydroxybutyrate (75%) and other aldonates (25%) are produced from the total hydrolysis of **3**. These differences in rates suggest that cyclization may facilitate hydrolysis.

C_5 cyanohydrins **4** ($t_{1/2} \simeq 1.5$ h) and **5** ($t_{1/2} \simeq 4.5$ h) hydrolyze more readily than **1**, **2**, and **3** at pH 8.5 and 18 °C. In contrast, compound **6** is stable under these conditions. Pentoses[11] produced from **6** are predominantly hydrated (*gem*-diols) in aqueous solution ($\delta_{C\text{-}1}$ 90.7),[12] demonstrating that OH-4 is unavailable for cyclic hemiacetal formation. Thus, **6** probably cannot form cyclic intermediates, which accounts for its slower rate of hydrolysis relative to the underivatized homologue **4**. Data in Figure 1 suggest that aldononitriles capable of cyclization react faster and that cyclization to form six-membered rings facilitates hydrolysis better than cyclization to form five-membered rings. The latter conclusion is not valid, however, and will be discussed later.

Configuration also affects the rate of aldononitrile disappearance (Figure 2). The overall rate of disappearance of C_5 cyanohydrins derived from D-erythrose (ribo, arabino; **4**) is ~3 times faster than that of the C_5 aldononitriles derived from D-threose (lyxo, xylo; **5**) at pH 8.5.

The epimeric ratio of C_5 aldononitriles observed at pH 8.5 may not equal the epimeric ratio of aldonates after hydrolysis. The ratio of lyxono- to xylononitrile is 3:2, and, because their rates of disappearance are similar (Figure 2), the aldonates are formed in the same ratio (Table I). On the other hand, arabinono- and ribononitriles are formed in a 2:3 ratio, but hydrolysis yields arabinonate and ribonate in a 7:3 ratio. Clearly, the arabinononitrile hydrolyzes more rapidly than the ribo epimer. Data in Figure 2 do not reflect these differences accurately, since rapid equilibration of the epimeric aldononitriles by reversal of cyanide condensation will increase the apparent rate of disappearance of ribononitrile and decrease the apparent rate of disappearance of the arabino epimer.

Characterization of Reactants, Intermediates, and Products. GLC and ^{13}C NMR parameters of the compounds involved in this study are listed in Tables II and III.

Aldoses, epimeric aldononitriles, aldonolactones, aldonates, and aldonamides are resolved by GLC. However, derivatization alters the structure and distribution of intermediates, making GLC unreliable for examining changes in the concentrations of intermediates as a function of time.

^{13}C NMR spectroscopy with ^{13}C-enriched compounds was employed to increase sensitivity and decrease acquisition times. 1-^{13}C intermediates observed by ^{13}C NMR in the reaction of K^{13}CN with D-erythrose are shown in Figure 3. The assignments of resonances to aldononitriles, aldono-1,4-lactones, aldonamides, and aldonates were made by comparison with spectra of 1-^{13}C-enriched standards prepared by alternate routes.

The chemical shift of cyanide is pH dependent; HCN has δ 113 and CN^- has δ 166.4. The short-chain aldoses that exist principally as hydrates have $\delta_{C\text{-}1}$ ~90.[12] Aldononitriles have $\delta_{C\text{-}1}$ ~120 ppm at pH 8.5 that shift down-

(26) (a) Stanêk, J.; Cerný, M.; Kocourek, J.; Pacák, J. "The Monosaccharides"; Academic Press: New York, **1963**; pp 171–173. (b) Berl, W. G.; Feazel, C. E. *J. Am. Chem. Soc.* **1951**, *73*, 2054. (c) Gutsche, C. D.; Redmore, D.; Buriks, R. S.; Nowotny, K.; Grassner, H.; Armbruster, C. W. *Ibid.* **1967**, *89*, 1235.

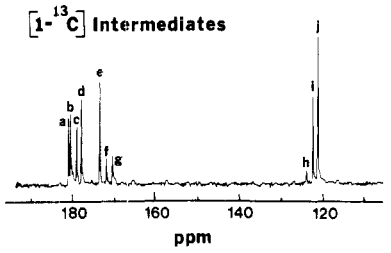


Figure 3. ^{1}H-decoupled, 15.08-MHz ^{13}C NMR spectrum of cyanohydrin reaction intermediates with 90.7 atom % ^{13}C enrichment at C-1. The spectrum shows only the enriched carbons (2536 scans). Reaction conditions: 0.3 M in D-erythrose and [^{13}C]cyanide; pH 7.0 ± 0.4; total reaction time, 11 h; 18 ± 1 °C. a, D-[1-^{13}C]arabinonate; b, D-[1-^{13}C]arabinonamide; c, D-[1-^{13}C]-ribonamide; d, D-[1-^{13}C]arabinono-1,4-lactone; e, D-[1-^{13}C]-arabinonoamidine; f, D-[1-^{13}C]ribonoamidine; g, U1; h, U2; i, D-[1-^{13}C]arabinononitrile; j, D-[1-^{13}C]ribononitrile. Shoulder and minor resonance between peaks b and c are D-[1-^{13}C]ribono-1,4-lactone and D-[1-^{13}C]ribonate, respectively.

field ~5 ppm as the pH is increased to 12.7.

Chemical shifts of 4 were assigned by preparing and separating the 2-epimeric [1-^{13}C]aldononitrile phosphates[16] and removing the phosphate group with acid phosphatase. Assignments are also based on observed differences in the magnitude of $^3J_{C\text{-}1,C\text{-}4}$ for standard linear ribo compounds (<0.7 Hz) and arabino compounds (~2.5 Hz) (Table III).[27]

Chemical shifts at 175.4 and 177.3 ppm are assigned to C-1 of imido-1,4-lactones having the arabino and ribo configurations, respectively. These assignments are based on a comparison of NMR parameters (δ and J) of these compounds with structurally related 1,4-lactones of known configuration, on their time of appearance during the hydrolysis of aldononitriles, and on the structure and proportion of products (aldono-1,4-lactones) found after their hydrolysis in acid (pH <4).[31] The C-2, C-3, and C-4 chemical shifts of D-ribono- and D-arabinono-1,4-lactones and the corresponding imido-1,4-lactones are similar (Table III), while C-1 of the 1,4-lactones is 2.2–2.7 ppm downfield from C-1 in the corresponding imido-1,4-lactones. Ring formation involving OH-4 causes downfield shifts (>10 ppm) in $\delta_{C\text{-}4}$ from 71–73 to 83–88 ppm.[30]

$J_{C\text{-}1,C\text{-}3}$ and $J_{C\text{-}1,C\text{-}4}$ are ~7 and <1 Hz, respectively, for arabinono-1,4-lactone and arabinonoimido-1,4-lactone. $J_{C\text{-}1,C\text{-}3}$ and $J_{C\text{-}1,C\text{-}4}$ for the ribo isomers are ~2.0 and ~1.0 Hz, respectively (Table III).

Chemical shifts at 171.6 and 173.2 ppm are assigned to C-1 of amidines having the ribo and arabino configurations, respectively. These assignments of structure and configuration are based on reactions of separated, and epimeric mixtures of, D-[1-^{13}C]ribono- and -arabinononitriles with NH$_4$Cl at pH 9.5 that yield products with C-1 chemical shifts at 171.6 and 173.2 ppm, respectively. Amidines are reported to form readily from imidates under these conditions,[32] and cyclic analogues of the latter (imidolactones) are observed during aldononitrile hydrolysis between pH 8.5 and 10.5 (see below). ^{1}H-coupled ^{13}C NMR spectra of the [1-^{13}C]amidines show that C-1 does not have a directly bound proton(s).

C-1 resonances at 170 ppm (U1) and 122 ppm (U2) appear in reaction mixtures between pH 7.0 and 10.5. These resonances are pH dependent (Table III). Acidification to pH <4 causes upfield shifts and splitting (~4 Hz) of both resonances. Gated ^{1}H-decoupling experiments show that these carbons are not directly bound to proton(s). From the reaction of K^{13}CN with D-[1-^{13}C]erythrose, at pH 9.5, C-2 resonances corresponding to U1 and U2 were observed at 81.8 and 72.3 ppm, respectively, and $^1J_{C\text{-}1,C\text{-}2}$ values of 41.8 and 54.3 Hz, respectively, were calculated. The intermediate(s) having these chemical shifts binds to

Table II. GLC Retention Times of Pertrimethylsilylated Carbohydrates and Derivatives

compd	t_R,[a] min
D-gluconate	1.00
glycolaldehyde	0.25, 0.26, 0.27
D-glyceraldehyde	0.36, 0.83, 0.85, 0.87, 0.90
2,4-*O*-ethylidene-D-erythrose	0.50, 1.32
D-erythrose	0.37
D-threose	0.33, 0.36
D-arabinose	0.59, 0.64, 0.67
D-lyxose	0.60, 0.65, 0.68
D-ribose	0.60, 0.64
D-xylose	0.57, 0.66, 0.72
D-glycerate	0.41
D-erythronate	0.52
D-threonate	0.56
D-arabinonate	0.77
D-ribonate	0.73
D-lyxonate	0.75
D-xylonate	0.75
D-allonate	0.94
D-altronate	0.99
D-gulonate	0.93
D-idonate	1.02
D-mannonate	0.94
D-galactonate	0.99
D-talonate	0.99
D-glyceronitrile	0.17
D-erythrononitrile	0.41
D-threononitrile	0.41
3,5-*O*-ethylidene-D-arabinononitrile	0.63
3,5-*O*-ethylidene-D-ribononitrile	0.63
D-arabinononitrile	0.63
D-ribononitrile	0.66
D-lyxononitrile	0.65
D-xylononitrile	0.65
D-gluconononitrile	0.92
D-mannononitrile	0.89
D-galactononitrile, D-talononitrile	0.87, 0.91[b]
D-allononitrile, D-altrononitrile	0.89, 0.90[b]
D-gulononitrile	0.90
D-idononitrile	0.92
D-arabinono-1,4-lactone	0.68
D-ribono-1,4-lactone	0.75
D-arabinonamide	0.85
D-ribonamide	0.80

[a] Retention times are relative to the $(CH_3)_3Si$ derivative of D-gluconate; column conditions are described in Instrument and Methods. [b] Retention times were not assigned.

(27) This difference probably reflects the preferred conformations of these compounds in solution.[28] Linear compounds having the arabino configuration are expected to have a planar, extended conformation where C-1 and C-4 are antiplanar (180°), and maximal coupling occurs based on the Karplus relationship.[29] Linear compounds having the ribo configuration are expected to have preferred C-1 to C-4 dihedral angles of approximately 90°, where ^{13}C–^{13}C three-bond coupling is at, or close to, a minimum.

(28) Horton, D.; Wander, J. D. *Carbohydr. Res.* **1970**, *15*, 271.

(29) Marshall, J. L.; Müller, D. E. *J. Am. Chem. Soc.* **1973**, *95*, 8305.

(30) For example, the C-4 chemical shifts of D-ribono-1,4-lactone and D-ribonoimido-1,4-lactone are 88.2 ppm, while those for D-ribononitrile, D-ribonamide, D-ribonic acid, and D-ribonate lie between 71.9 and 72.9 ppm (Table III). Although the C-4 chemical shifts of the pentose phosphates[16] and tetroses[12] are relatively insensitive to configuration at C-2 and C-3, the C-4 resonances of 1,4-lactones and imido-1,4-lactones having the ribo configuration (OH-2 and OH-3 cis) are downfield (88.2 ppm) from those having the arabino configuration (OH-2 and OH-3 trans; 82.6 ppm).

(31) (a) Schmir, G. L.; Cunningham, B. A. *J. Am. Chem. Soc.* **1965**, *87*, 5692. (b) Cunningham, B. A.; Schmir, G. *Ibid.* **1966**, *88*, 551.

(32) Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 3505.

Table III. ^{13}C NMR Parameters of Reactants, Intermediates, and Products of the Cyanohydrin Reaction[a]

compd	pH (± 0.2)	^{13}C chemical shifts, ppm					^{13}C–^{13}C coupling constants, Hz			
		C-1	C-2	C-3	C-4	C-5	$^{1}J_{C\text{-}1,C\text{-}2}$	$J_{C\text{-}1,C\text{-}3}$	$J_{C\text{-}1,C\text{-}4}$	$J_{C\text{-}1,C\text{-}5}$
HCN	3.6	113.4								
KCN	11.5	166.4								
D-lactaldehyde, hydrate	6.0	94.3	71.5	18.1						
D-*threo,erythro*-2,3-dihydroxybutanal, hydrate	6.0	91.3								
DL-glyceronitrile	12.5	125.7								
	8.5	121.0	63.2	64.6						
DL-2-hydroxybutyronitrile	3.7	122.2								
	10.5	122.8								
	12.5	126.9								
D-*threo,erythro*-2,3-dihydroxybutyronitrile[h]	7.5	120.7, 120.4								
D-threono- and D-erythrononitriles[h]	12.5	125.6, 124.9								
D-lyxononitrile	8.5	121.5								
D-xylononitrile	8.5	120.6								
DL-2-hydroxybutyrate		182.8	74.6	28.3	9.9					
D-lyxono-1,4-lactone		179.6	71.9	71.0	83.0	61.2	56.5	br	1.5	br
D-xylono-1,4-lactone		178.8	73.9		82.1	60.7	56.5			
D-lyxonic acid	1.2	177.6	72.7			64.0	59.4			
D-xylonic acid	1.0	177.4	72.7			63.7	59.4			
D-lyxonate	10.8	180.4	75.2	72.7[b]	73.1[b]	64.3	54.3		*c, d*	
D-xylonate	9.8	180.1	74.1	73.9[b]	74.3[b]	63.9	54.3		2.9[d]	
D-threono- and D-erythronoamidines[h]	9.5	172.2, 171.6								
D-erythrose[e]	6.0									
α		96.8	72.4	70.6	72.9		43.3			
β		102.4	77.7	71.7	72.4		46.9			
hydrate		90.8	74.9	73.0	64.0		48.4			
D-arabinononitrile	8.5	121.4	62.8	72.6	71.2		61.6	*i*	2.9	
	12.5	125.2								
D-arabinonoimido-1,4-lactone	10.5	175.4	75.2	74.3	82.6		51.3	6.6	*i*	
D-arabinonamide	8.1	180.3	72.2	72.9	72.0	62.4	53.5	*i*	2.9	*i*
	13.3	181.8								
D-arabinono-1,4-lactone		177.6	75.2	73.8	82.6	60.7	55.7	7.3	*i*	br
D-arabinono-1,5-lactone	3.0	176.2								
D-arabinonic acid	2.0	178.4	71.7	73.2	71.9	64.4	60.1	*i*	2.2	*i*
D-arabinonate	8.5	180.8	73.0	73.6	72.6	64.6	54.2	*i*	2.9	*i*
	13.3	181.0								
D-arabinonoamidine	9.6	173.2					48.4			
D-ribononitrile	8.5	120.1	64.2	73.0	72.9		60.1	*i*	*i*	*i*
	12.5	125.2								
D-ribonoimido-1,4-lactone	10.5	177.3	70.6	71.3	88.2		51.3	2.2	br	
D-ribonamide	8.2	178.7	73.9	74.1	72.3	64.4	52.8	*i*	*i*	*i*
	13.3	181.2								

D-ribono-1,4-lactone		180.0	70.4	71.0	88.2	62.0	55.7	2.2	1.5	*i*
D-ribono-1,5-lactone	2.6	179.3								
D-ribonic acid	1.7	176.9	73.3	74.2	71.9	64.5	59.4	*i*	*i*	*i*
D-ribonate	8.5	179.7	75.0	74.7	72.9	64.3	53.5	*i*	*i*	*i*
	13.3	179.9								
D-ribonoamidine	9.6	171.6					41.8			
U1	9.5	170.0	81.8				45.3			
	3.0	169.5[f]	81.5				54.3			
U2	9.5	122.9	72.3				50.6			
	3.0	115.7[g]	70.6							
D-5-deoxyarabinonoimido-1,4-lactone	10.5		75.3							
D-5-deoxyribonoimido-1,4-lactone	10.5		70.3							
D-5-deoxylyxonoimido-1,4-lactone	10.5		72.5							
D-5-deoxyxylonoimido-1,4-lactone	10.5		74.7							
D-5-deoxyarabinonamide	10.5		71.8							
D-5-deoxyribonamide	10.5		73.8							

[a] Determined at 18 ± 1 °C. Chemical shifts are accurate to ±0.1 ppm and coupling constants to ±0.7 Hz; br = broadened resonance. Couplings and chemical shifts for cases with no entry were not determined. [b] Assignments of C-3 and C-4 may be reversed. [c] Coupling could not be measured at 15.08 MHz due to resonance overlap. [d] May be from $^2J_{C\text{-}1,C\text{-}3}$. [e] Values for D-erythrose were taken from ref 12 and are included here for completeness. [f] Split by 4.4 Hz. [g] Split by 3.7 Hz. [h] Chemical shifts were not assigned. [i] Coupling constant is less than 0.7 Hz.

Dowex 50 (H^+) resin at pH 1–2 and elute with 1 M triethylammonium bicarbonate at pH 7.5; it hydrolyzes in alkali (pH 12.6) to aldonates and in acid (pH 0.6) to lactones at 50 °C. Addition of KCN to the [1-^{13}C]derivative at pH 8.5 and 9.0 does not cause isotope exchange of the enriched nuclei.

The C-2 chemical shift at 81.8 ppm suggests that this carbon is part of a five-membered ring,[12,16] and $^1J_{C\text{-}1,C\text{-}2}$ (41.8 Hz) indicates that both C-1 and C-2 are sp^3 hybridized.[12] The C-1 resonance at 122 ppm is in the aldononitrile region and is nonexchangeable. The resonances, U1 and U2, are split by similar amounts at low pH, indicating that they are in the same molecule. The resonances appear simultaneously in reaction mixtures after imido-1,4-lactone formation. The behavior of this intermediate on Dowex 50 (H^+) suggests that it is cationic at low pH. Structure 7 is consistent with these properties.

7

U1 is the resonance of C-1 of the furanoid component, while U2 arises from the acyclic nitrile C-1 carbon. Dimer 7 probably forms by the addition of the cyanohydrin alkoxide to the protonated imido-1,4-lactone. The amount of 7 formed during the cyanohydrin reaction at pH 8.5 increases with the concentration of reactants, as expected for a bimolecular reaction (see below). A similar structure has been proposed by Kuhn and Weiser[33] to explain the formation of an ortho ester in the reaction of 3-phenylcoumarinimide with $CH_3OH/H_2O/HCl$. They proposed that the ortho ester arose from an intermediate 1-*O*-methylcarbinolamine.

Assignments of configurations to the 2-^{13}C labeled 5-deoxyimido-1,4-lactones from the addition of cyanide to *erythro,threo*-2,3-dihydroxy-D-[1-^{13}C]butanal are based on the effect of configuration at C-2 and C-3 on the chemical shift of C-2,[34] on similar ratios of epimeric imido-1,4-lactones found from the addition of cyanide to D-erythrose and D-threose under similar conditions, and on similar C-2 chemical shifts of the structurally related pentono-1,4-lactones (Table III).

$^1J_{C\text{-}1,C\text{-}2}$ was measured for several intermediates and products simultaneously by adding K^{13}CN to D-[1-^{13}C]-erythrose. $^1J_{C\text{-}1,C\text{-}2}$ increases as follows: 1-*O*-substituted carbinolamine (7) (42–45 Hz), amidines (48 Hz), imido-1,4-lactones (51 Hz), 2-*o*-substituted aldononitrile (7) (51–54 Hz), aldonamides (53 Hz), aldonates (54 Hz), aldono-1,4-lactones (56 Hz), aldonic acids and aldononitriles (60 Hz). A double-bonded nitrogen decreases $^1J_{C\text{-}1,C\text{-}2}$ relative to the oxygen analogue by ~5 Hz.

Cyanohydrin Reaction Applied to D-Erythrose: Intermediates in the Hydrolysis of D-Ribono- and D-Arabinononitriles at Several pH Values. D-Erythrose was selected because (a) D- or DL-erythrose enriched with ^{13}C at several positions was available,[12] (b) ^{13}C resonances of intermediates could be resolved, (c) the role of five- and six-membered rings in aldononitrile hydrolysis could be evaluated, (d) differences in the rates of hydrolysis of epimeric intermediates were observed, and (e) struc-

(33) Kuhn, R.; Weiser, D. *Angew. Chem.* **1957**, *69*, 371.
(34) Ritchie, R. G. S.; Cyr, N.; Korsch, B.; Koch, H. J.; Perlin, A. S. *Can. J. Chem.* **1975**, *53*, 1424.

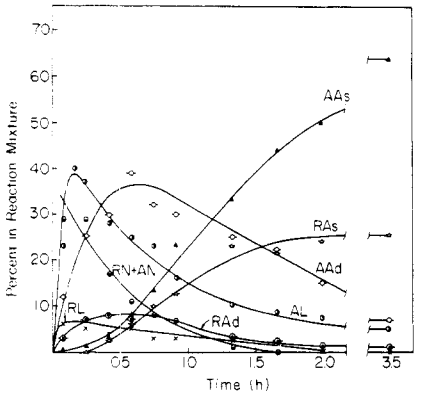


Figure 4. Profile of intermediates in pH-quenched aliquots from the reaction of 0.3 M K^{13}CN and 0.3 M D-erythrose at pH 12.7 and 18 ± 1 °C. Aliquots (0.5 mL) were quenched with 0.7 mL of HCl (0.3 M), incubated at 25 °C for 20–30 min, and analyzed by ^{13}C NMR (400 scans) after adjustment to pH 5. RN, D-[1-^{13}C]ribononitrile; AN, D-[1-^{13}C]arabinononitrile; AL, D-[1-^{13}C]-arabinono-1,4-lactone; RL, D-[1-^{13}C]ribono-1,4-lactone; RAd, D-[1-^{13}C]ribonamide; AAd, D-[1-^{13}C]arabinonamide; AAs, D-[1-^{13}C]arabinonate; RAs, D-[1-^{13}C]ribonate.

turally modified analogues of erythrose were available. Reactions were carried out at 18 ± 1 °C and 0.3 M with stoichiometric amounts of reactants. The overall reaction sequence, established by the following experiments, is shown in Scheme II.

At pH 12.7, several intermediates are observed (data not shown). Aldononitriles disappear in 1.7 h with the formation and subsequent hydrolysis of aldonamides. Aldonate formation is complete in 3.5 h. The apparent sequence of the reaction is nitrile → amide → aldonate.

Analyses at pH 12.7 are complicated by line broadening from chemical exchange and by overlap of C-1 resonances (Table III), and the reaction sequence appears deceptively simple. For example, the C-1 resonance of D-ribonamide coincides with that of an unidentified component that increases rapidly during the first 10 min and cannot be D-ribonamide itself. As shown below, amides do not epimerize or revert to early intermediates once they are formed. There cannot be more ribonamide than arabinonamide in the reaction mixture, since ribonate is the minor product (Table I).

For further examination of the reaction at pH 12.7, aliquots were taken at various times and quenched to pH 4 with HCl (Figure 4). At this pH, resonances are sharp, and the intermediates are stable for several hours. From this experiment, the *apparent* sequence of intermediates in reactions at pH 12.7 is nitrile → 1,4-lactone → amide → aldonate.

The early appearance of 1,4-lactone in the quenched reaction mixture reflects the presence of imidolactone in the unquenched reaction mixture. The rate of imidolactone hydrolysis and the products formed (amide and/or lactone) are pH dependent.[31] Both the rate of imidolactone hydrolysis and the percentage of lactone produced increase as the pH is lowered. It appears that imidolactones present at pH 12.7 are rapidly hydrolyzed to lactones when the mixture is quenched to pH 4. The reaction sequence at pH 12.7, therefore, is nitrile → imido-1,4-lactone → amide → aldonate.

Aldononitrile hydrolysis at pH 10.5 (Figures 5A,B and 6) differs from hydrolysis at pH 12.7 in several respects. Neither starting aldose nor aldononitriles are detected by ^{13}C NMR or GLC. Instead, imidolactones predominate initially and hydrolyze rapidly to produce amides. The latter hydrolyze slowly to aldonates. Dimer **7** is present (U1, U2).

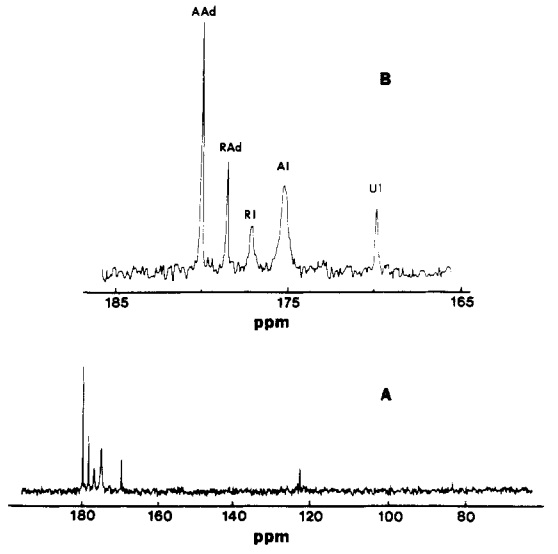


Figure 5. ^{1}H-decoupled, 15.08-MHz ^{13}C NMR spectra of 1-^{13}C intermediates in the reaction of 0.3 M K^{13}CN and 0.3 M D-erythrose after 11 min at pH 10.5 and 18 ± 1 °C, showing imido-1,4-lactone formation: A, the ^{13}C NMR spectrum (128 scans) showing the absence of aldononitriles; B, the expanded 170–180-ppm region of A showing the C-1 resonances of the epimeric imido-1,4-lactones, the epimeric aldonamides, and U1. The resonance of U2 is observed in A at 122.9 ppm. AAd, D-[1-^{13}C]arabinonamide; RAd, D-[1-^{13}C]ribonamide; RI, D-[1-^{13}C]ribonoimido-1,4-lactone; AI, D-[1-^{13}C]arabinonoimido-1,4-lactone.

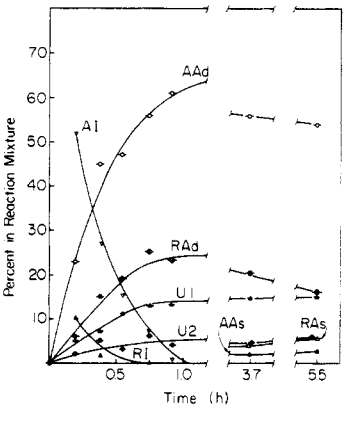


Figure 6. Profile of the reaction of D-erythrose with K^{13}CN at pH 10.5. Reaction conditions are as in Figure 5. AI, D-[1-^{13}C]-arabinonoimido-1,4-lactone; RI, D-[1-^{13}C]ribonoimido-1,4-lactone; AAd, D-[1-^{13}C]arabinonamide; RAd, D-[1-^{13}C]ribonamide; U1 and U2, dimer **7**; RAs, D-[1-^{13}C]ribonate; AAs, D-[1-^{13}C]arabinonate.

NMR analysis of samples from reaction mixtures at pH 10.5 taken during the first hour and quenched to pH 4 demonstrated that imidolactones present at pH 10.5 are quantitatively converted to aldono-1,4-lactones by this treatment. Assignment of the broad C-1 resonance at 175.3 ppm (Table III and Figure 5B) to D-[1-^{13}C]arabinonoimido-1,4-lactone is partly based on the observation that [1-^{13}C]arabinono-1,4-lactone is the predominant lactone produced in this experiment. At pH 10.5, the reaction sequence is nitrile → imido-1,4-lactone → amide → aldonate.

Aldononitrile hydrolysis at pH 8.5 is slow. During the first 30 min, aldononitriles comprise 95% of the reaction mixture (Figure 7). Imido-1,4-lactone (arabino), observed next, reaches its maximum concentration (5%) after 40 min. At this pH value, imidolactone hydrolysis produces both amide and lactone.[31a] Amides form slowly and are stable. Dimer **7** is produced concomitantly with amide. 1,4-Lactones produced from imido-1,4-lactones decompose to aldonates. The latter are not formed from amide hy-

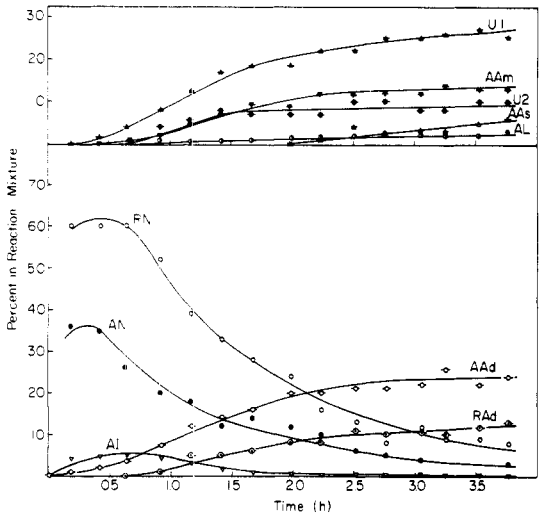
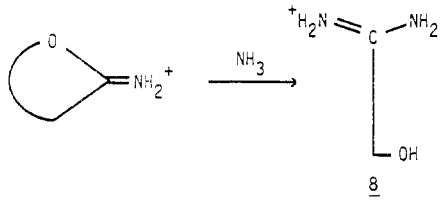


Figure 7. Profile of the reaction of D-erythrose with $K^{13}CN$ at pH 8.5. Reaction conditions are as in Figure 5. RN, D-[1-^{13}C]-ribononitrile; AN, D-[1-^{13}C]arabinononitrile; AI, D-[1-^{13}C]arabinonoimido-1,4-lactone; RAd, D-[1-^{13}C]ribonamide; AAd, D-[1-^{13}C]arabinonamide; AAm, D-[1-^{13}C]arabinonoamidine; AAs, D-[1-^{13}C]arabinonate; RAs, D-[1-^{13}C]ribonate; AL, D-[1-^{13}C]-arabinono-1,4-lactone; U1 and U2, dimer 7.

drolysis, which is very slow at this pH.

At pH 8.5, ammonia released from the hydrolysis of imidolactone reacts with the protonated imidolactones to produce amidines 8 (~15%). When stoichiometric



8

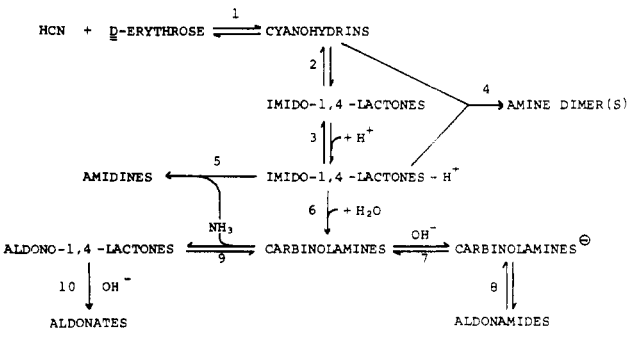
amounts of NH_4Cl, D-erythrose, and [^{13}C]cyanide are mixed at pH 8.5 or 9.5, amidine formation is enhanced. At pH 8.5, amidine formation is slow (55% in 50 min), whereas at pH 9.5, it is rapid and almost quantitative. These data are consistent with the observation[32] that the rate of aminolysis of ethyl benzimidate is pH dependent, with the maximum rate occurring at pH 8.9. Arabinonoamidine ($\delta_{C\text{-}1}$ 173.2) and ribonoamidine ($\delta_{C\text{-}1}$ 171.6) are produced in both cases in a 3:1 ratio. At pH 8.5, standard cyanohydrin reaction mixtures contain arabinonoamidine (13%) while the ribo isomer is barely observable (<2%).

Assignment of the arabino configuration to the amidine with a C-1 resonance at 173.2 ppm is based on the chemical shift of the principal product from the reaction of ammonia with authentic D-[1-^{13}C]arabinononitrile at pH 9.5. Under these conditions, 10% D-[1-^{13}C]ribononitrile is also formed by reversal of the condensation reaction.

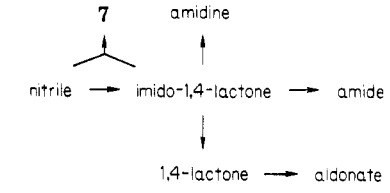
Dimer 7 comprises 35% of the reaction mixture after 4 h at pH 8.5, and, as observed at pH 10.5, appears to arise from imidolactone. When solutions containing large amounts of imidolactone (Figures 5B and 6) are adjusted to pH 8.5–9.0 and quickly examined, they are found to contain 7 in almost the same proportion as it is found after 4 h at pH 8.5 (Figure 7). At pH 8.5, the apparent sequence of the reaction is given in Scheme III.

The condensation of HCN with D-erythrose at pH 7 (Figure 3) produces aldononitriles in a ribo/arabino ratio of 3:2, and their hydrolysis is slow. After 11 h, nitriles comprise 38% of the reaction mixture. Hydrolysis products at this time include aldonates, amides, 1,4-lactones, amidines, and dimer 7. Imido-1,4-lactones are barely detectable (<2%), since their hydrolysis to lactones is stimulated at this pH. The arabino epimers predominate in all of the intermediates except in the nitriles. Aldonates are formed from 1,4-lactones rather than from amides. The apparent sequence of the reaction is similar to that at pH 8.5, with differences occurring only in the relative amounts of intermediates observed.

Scheme II



Scheme III

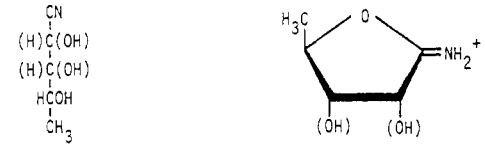


Imidolactone Formation. At all pH values, imidolactones appear to play an important role in the hydrolysis of aldononitriles that can form them. Varma and French[6] have proposed six-membered imidolactone intermediates in the reaction of cyanide with α-D-arabinose. The slower rate of hydrolysis of C_4 aldononitriles 2 relative to C_5 aldononitrile 4 (Figure 1) supports this proposal and suggests that the formation of five-membered-ring imidolactones is not favorable. There are, however, many examples[35] of ring-closure reactions that yield the more stable five-membered ring with an exocyclic double bond. For these reasons, the ring forms of imidolactone and lactone intermediates were investigated.

The C-1 chemical shifts of 1,4-lactones and 1,5-lactones differ (Table III). 1,5-Lactones do not revert to 1,4-lactones at pH <4, while imidolactones hydrolyze rapidly to lactones at this pH.[31] Therefore, the production of 1,4-lactones in quenched (pH 4) reactions reflects the presence of imido-1,4-lactones rather than imido-1,5-lactones.

Direct evidence for imido-1,4-lactone intermediates was obtained by preparing DL-[1,3-$^{13}C_2$]aldononitriles from DL-[2-^{13}C]erythrose and $K^{13}CN$ and by preparing DL-[1,4-$^{13}C_2$]aldononitriles from DL-[3-^{13}C]erythrose and $K^{13}CN$. With these compounds, the chemical shifts of C-3 and C-4 and the ^{13}C–^{13}C coupling constants between the enriched nuclei were easily and unequivocally determined (Table III). Following condensation at pH 8.5, the ^{13}C NMR spectra of the doubly enriched aldononitriles were obtained (Figures 8A and 9A). The reaction mixtures were then adjusted to pH 10.5 where rapid cyclization of aldononitrile to imidolactone occurs (Figure 5). Results are shown in Figures 8B,C and 9B. ^{13}C Chemical shifts and ^{13}C–^{13}C coupling constants of imidolactones obtained from these experiments are similar to those of 1,4-lactones prepared by standard methods (Table III). The large downfield shift of C-4 of the imidolactones establishes that OH-4, and not

(35) Brown, H. C.; Brewster, J. H.; Shechter, H. *J. Am. Chem. Soc.* **1954**, *76*, 467.



9 10

OH-5, is involved in imidolactone ring formation.

Further evidence supporting the formation of imido-1,4-lactone was obtained by preparing the four diastereomeric D-[2-^{13}C]aldononitriles (**9**) from *erythro,threo*-2,3-dihydroxy-D-[1-^{13}C]butanal and KCN. Aldononitriles **9** readily convert to imido-1,4-lactones **10** at pH 10.5. C-2 resonances of **10** were assigned on the basis of their close agreement with the C-2 resonances of the corresponding 5-hydroxy analogues (Table III) and on the basis of the similar ratio of epimeric imidolactones produced. Compounds **10** hydrolyze readily to the corresponding aldonamides at pH 10.5, as do the related 5-hydroxy compounds.

Brown et al.[35] have suggested that five-membered rings having exo double bonds form more readily than six-membered rings because the latter are more unstable and, therefore, more reactive. In the Kiliani reaction, the presence of imido-1,4-lactone in reaction mixtures does not prove that aldononitriles hydrolyze solely through this intermediate. An undetectable amount of imido-1,5-lactone may be present, which could hydrolyze very rapidly to yield 1,5-lactone and, from it, aldonate. The ^{13}C NMR data still would indicate that hydrolysis proceeded through the 1,4-ring, since only it is observed. The involvement of imido-1,5-lactone can be excluded, however, by examining the reaction at pH 7 (Figure 3) where aldononitriles cyclize very slowly and imidolactones decompose almost equally to amide and lactone. If imido-1,5-lactone was hydrolyzing, early reaction products would include 1,5-lactone or, since it is relatively unstable, its hydrolysis product (aldonate). However, 1,4-lactone accumulates 2–3 h before aldonate is detected, and 1,5-lactone is not observed. Thus, aldonate is formed from 1,4-lactone, and imido-1,4-lactone is the principal intermediate in nitrile hydrolysis at pH 7.

Discussion

The reactions that occur following the addition of cyanide to D-erythrose are summarized in Scheme II. In the following, we discuss the effect of pH and chemical structure on reactions 1–10 of Scheme II and the role of tetrahedral intermediates (carbinolamines) in the reaction sequence.

With stoichiometric amounts of reactants, aldononitrile formation (reaction 1) is essentially complete at pH values between 7 and 10.5,[36] while at pH >11, aldose is present during the first phase of the reaction. The rate of aldononitrile hydrolysis increases with increasing pH. After 6 h at pH 7, 67% of the reaction mixture is composed of aldononitriles (Table IV) compared with 9% after 4 h at pH 8.5 and none after 1.7 h at pH 12.7.

Imidolactone formation (reaction 2), while not essential, is the major route of hydrolysis of aldononitriles with hydroxyl groups situated to permit ring closure. It may also significantly affect the ratio of epimers produced from the reaction. For pentononitriles, imido-1,4-lactones are formed in preference to imido-1,5-lactones. At pH values below 9.5, imidolactone formation is slow, whereas at pH 10.5, it is rapid and essentially complete after 10 min (Figures 5 and 6). At low pH (<4), imidolactones hydrolyze rapidly to lactones via reactions 3, 6, and 9. As the pH is increased, hydrolysis of imidolactones to aldonamides is favored and occurs via reactions 3, 6, 7, and 8. At pH ≥10.5, amides are the major products of imidolactone hydrolysis (Figure 6).

(36) D-Erythrose exists mainly as furanoses and linear hydrates in dilute aqueous solutions[12] and, like the C_1–C_3 aldoses, reacts with cyanide under these conditions essentially quantitatively. The pentoses require a threefold excess of cyanide to promote completion of reaction 1 (Scheme II) at pH 8.0.

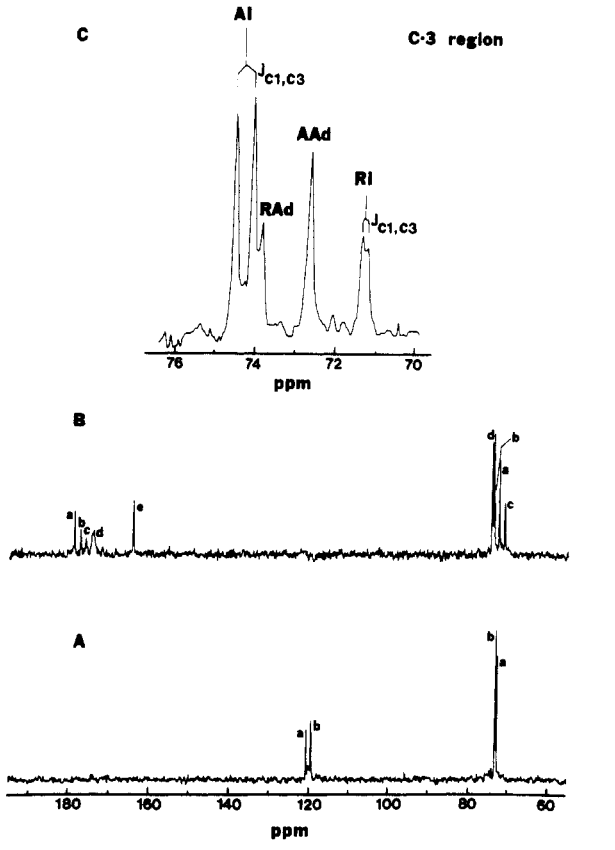


Figure 8. Addition of [^{13}C]cyanide to DL-[2-^{13}C]erythrose. (A) ^{13}C NMR spectrum (enriched carbons) of the reaction mixture after 13.5 min at pH 8.5, showing the formation of DL-[1,3-$^{13}C_2$]arabinononitrile (a) and DL-[1,3-$^{13}C_2$]ribononitrile (b). $^{2}J_{C\text{-}1,C\text{-}3}$ is <0.7 Hz for the aldononitriles. The broad peak at 120 ppm is H^{13}CN. (B) ^{13}C NMR spectrum of the reaction mixture from A after 11 min at pH 10.5: a, DL-[1,3-$^{13}C_2$]arabinonamide; b, DL-[1,3-$^{13}C_2$]ribonamide; c, DL-[1,3-$^{13}C_2$]ribonoimido-1,4-lactone; d, DL-[1,3-$^{13}C_2$]arabinonoimido-1,4-lactone; e, [^{13}C]cyanide. (C) ^{13}C NMR spectrum of the expanded C-3 region of B, showing $J_{c\text{-}1,c\text{-}3}$ for the imido-1,4-lactones. As in the linear aldononitriles in A, $^{2}J_{c\text{-}1,c\text{-}3}$ is <0.7 Hz for the aldonamides.

Table IV. Percentages of Intermediates and Products in the Cyanohydrin Reaction (D-Erythrose) at Various pH Values

	percent in reaction mixture[a] (±3%)			
compd	pH 7.0[b]	pH 8.5[c]	pH 10.5[d]	pH 12.7[e]
nitrile	67	9		
imido-1,4-lactone				
amide	8	36	84	
1,4-lactone	10	2		
aldonate	2	5		100
amidine	10	13		
U1, U2 (dimer 7)[f]	3	35	16	

[a] Determined by ^{13}C NMR. The absence of an entry indicates that <2% was observed. [b] After 6 h of reaction. [c] After 4 h of reaction. [d] After 55 min of reaction. [e] After 3.5 h of reaction. [f] Percentage of dimer 7 was determined by multiplying the fraction of the total spectral area under U1 and U2 × 100.

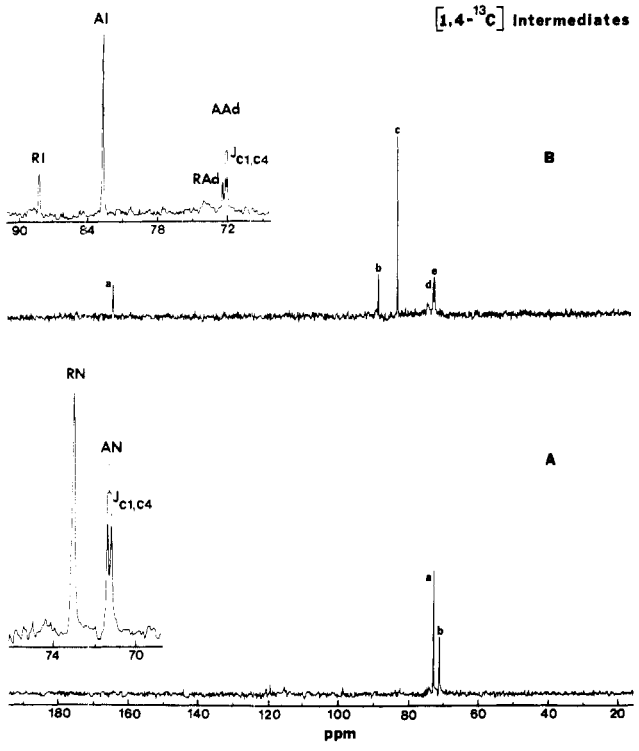


Figure 9. Addition of [^{13}C]cyanide to DL-[3-^{13}C]erythrose. ^{13}C NMR spectra show only the ^{13}C-enriched carbons at C-4, since the acquisition parameters [16-μs (90°) pulse with no delay time] did not permit detection of the unprotonated carbon at C-1. (A) ^{13}C NMR spectrum of the reaction mixture after 21.5 min at pH 8.0, showing the C-4 resonances of DL-[1,4-$^{13}C_2$]ribononitrile (a) and DL-[1,4-$^{13}C_2$]arabinononitrile (b). Inset shows $^3J_{C\text{-}1,C\text{-}4}$ for the arabino epimer (2.9 Hz). (B) ^{13}C NMR spectrum of the reaction mixture from A after 10 min at pH 10.5: a, [^{13}C]cyanide; b, DL-[1,4-$^{13}C_2$]ribonoimido-1,4-lactone; c, DL-[1,4-$^{13}C_2$]arabinonoimido-1,4-lactone; d, DL-[1,4-$^{13}C_2$]ribonamide; e, DL-[1,4-$^{13}C_2$]arabinonamide. The inset shows $^3J_{C\text{-}1,C\text{-}4}$ for D-[1,4-$^{13}C_2$]-arabinonamide (2.9 Hz) and a broadened C-4 resonance for DL-[1,4-$^{13}C_2$]ribonoimido-1,4-lactone.

Reaction 4 produces the proposed dimer **7**, yielding the greatest amount of product at pH 8.5 and lesser amounts at higher and lower pH values (Table IV), due to the effect of pH on the availability of nitrile and imidolactone. At pH 10.5, imidolactone formation is essentially complete, leaving less nitrile for reaction 4 than is present at pH 8.5. At pH 7, reaction 2 is slower and reaction 6 is probably faster,[31] resulting in lower concentrations of imidolactone than at pH 8.5. Aminolysis (reaction 5) also competes for the imidolactone and limits the production of **7**, and, at pH 7, imidolactone hydrolysis to lactone (reactions 3, 6, and 9) is rapid, yielding more ammonia to stimulate aminolysis.

Reaction 4 is bimolecular, so the amount of **7** formed should depend on the concentration of reactants. The condensation of cyanide with D-erythrose at pH 8.5 with 0.9 M reactant concentrations produces 50% more **7** after 4 h than the reaction with 0.3 M reactant concentrations.

Amidines are observed only at pH 7 and 8.5, and their formation depends on reaction 9 for ammonia. The occurrence of reaction 9 is signaled by the formation of lactone. At pH 8.5, imidolactones hydrolyze predominately to amides (5:1 amide/lactone + aldonate after 4 h;[37] Table IV), and amide hydrolysis proceeds slowly with the release of ammonia. In contrast, imidolactones hydrolyze to amides and lactones in a 2:3 ratio at pH 7 after 6 h, liberating ammonia for reaction 5 and leading to increased production of amidine (30% of the nonnitrile product after 6 h). Amidines hydrolyze to aldonates at pH >10.5 via amide intermediates.

Table V. Relative Amounts of Arabino Epimers Produced during the Cyanohydrin Reaction (D-Erythrose) at Various pH Values

	relative percent of arabino epimer[a] (±3%)			
compd	pH 7.0[b]	pH 8.5[c]	pH 10.5[d]	pH 12.7[e]
D-arabinononitrile	33	37[g]		~40
D-arabinonoimido-1,4-lactone		*f*	84[g]	86
D-arabinonoamidine	90	~95		
D-arabinono-1,4-lactone	~90	*b*		
D-arabinonamide	56	65	73	82

[a] Determined by ^{13}C NMR. Absence of an entry indicates <2% was observed. Relative percent = [*arabino* epimer/(*arabino* + *ribo* epimers)] × 100. [b] After 6 h of reaction. [c] After 4 h of reaction. [d] After 55 min of reaction. [e] Determined from pH-quench experiments. Amide percent is that observed after 45 min of reaction, while the imidolactone percent is that observed after 15 min of reaction and is estimated from the 1,4-lactone (acid hydrolysis) product. [f] Only the arabino epimer is observed at 40 min. [g] After 10 min of reaction.

Carbinolamines are implicated as key intermediates in Scheme II. Carbinolamines have been proposed[31] as intermediates in the hydrolysis of N-substituted imidolactones, and partitioning between lactone and N-substituted amide has been explained by the involvement of ionic forms of carbinolamine. Neutral carbinolamine (or its zwitterion) was proposed to yield lactone, while anionic carbinolamine yields amide (Scheme II). Although carbinolamine resonances are not observed in the ^{13}C NMR spectra, it is reasonable to propose reactions 6 and 7 on the basis of the observed behavior of imido-1,4-lactones in acidic and basic media and the results reported previously[31] on N-substituted imidolactone hydrolysis.

The hydrolysis of amides is facilitated when hydroxyl groups participate to produce cyclic carbinolamine intermediates.[38] Cunningham and Schmir[38c] studied the alkaline hydrolysis of 4-hydroxybutyranilide and concluded that reactions 7, 8, 9, and 10 or 8, 9, and 10 are involved. Aldonamides are stable over several hours at pH <10, while hydrolysis can be followed at pH >11. The alkaline hydrolysis of purified D-ribonamide or D-arabinonamide proceeds with retention of configuration at C-2, indicating that the overall reaction does not reverse to reaction 1, where the stereochemistry at C-2 can be altered.[39] In addition, only aldonates are observed by ^{13}C NMR during amide hydrolysis, demonstrating that reaction 6 is not appreciably reversible. If present (≥3%), imidolactone would be detected under these conditions. The irreversibility of reaction 6 in the hydrolysis of N-substituted imidolactones has been established.[31]

The rate of amide hydrolysis depends on the configuration of the aldityl residue. At pH 11, D-ribonate forms

(37) For consideration of the partitioning of imidolactone to lactone or amide at pH <10.5, the conversion of amide to aldonate can be neglected since amide hydrolysis by reactions 7–10 (Scheme II) is slow. Aldonates produced at pH <10.5 arise primarily from the sequence imidolactone → lactone → aldonate and are, therefore, added to the percentage of lactone when partitioning is discussed.

(38) (a) Wolfrom, M. L.; Bennett, R. B.; Crum, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 944. (b) Bruice, T. C.; Marquardt, F. *Ibid.* **1962**, *84*, 365. (c) Cunningham, B. A.; Schmir, G. L. *Ibid.* **1967**, *89*, 917.

(39) It is assumed that reaction 1 established the C-2 configuration and that the predominant epimer is determined by reactions 1 and 2. Isomerization of imidolactone to enimine could provide another route for epimerization. This has been ruled out, however, since reactions at pH 8.5 and 12.7 in ^3H_2O produce products containing only 0.003 and 0.014% tritium, respectively.

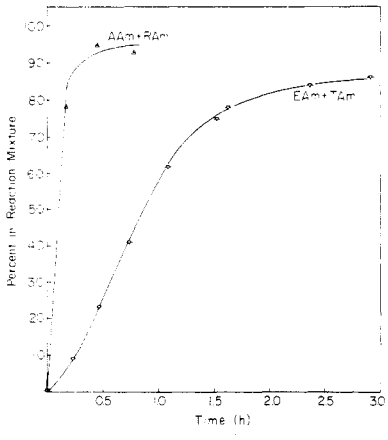


Figure 10. Rates of amidine formation from C_4 and C_5 aldononitriles. Data were obtained from ^{13}C NMR spectra of 1-^{13}C-enriched nitriles (100–200 scans). Reaction conditions: 0.3 M in aldose (D-glyceraldehyde or D-erythrose), [^{13}C]cyanide, and NH_4Cl; 18 ± 1 °C; pH 9.5 ± 0.2. AAm, D-[1-^{13}C]arabinonoamidine; RAm, D-[1-^{13}C]ribonoamidine; TAm, D-[1-^{13}C]threonoamidine; EAm, D-[1-^{13}C]erythronoamidine.

about 2.5 times faster than D-arabinonate from their respective amides, probably due to differences in the rates of cyclization (reaction 8) and/or the rates of carbinolamine breakdown (reactions 7 and 9). C-2 epimers should not significantly differ in the rate of direct OH^- attack on the carbonyl of linear amides, whereas reactions involving cyclic intermediates should show substantial rate differences.[40]

Reaction 10 occurs rapidly at pH >10.5, and lactones are not observed in reaction mixtures at these pH values. When lactone hydrolysis is slow (pH 8.5 and 7), lactones[41] are detected in reaction mixtures.

Differences in the proportions of the arabino and ribo epimers are apparent at various stages of the reaction, as shown in Table V. At all pH values examined, ribononitrile predominates (63–67%).[42] Nitrile cyclization (reaction 2) favors the arabino configuration, with arabinonoimido-1,4-lactone accounting for ~85% of the imidolactones under conditions where hydrolysis is slow. The predominance of arabinonoimido-1,4-lactone is reflected in acidic (1,4-lactone) and alkaline (amide) hydrolysis products and in aminolysis (amidine) products, with 70–90% having the arabino configuration (Table V).

Reaction 6 may be sensitive to configuration. The percentage of arabinonoimido-1,4-lactone (~85%) is greater than the epimeric percentage of arabinonate after total hydrolysis (68–79%) (Table I). Since aldonamides do not epimerize during hydrolysis, this difference cannot be attributed to differences in the rates of reactions 7–10.

C_4 aldononitriles **2** hydrolyze more slowly than the C_5 homologue **4** (Figure 1). This difference is not due to the involvement of different ring forms since hydrolysis of C_5 aldononitriles proceeds through imido-1,4-lactone intermediates. The relative ease of cyclization of **2** and **4** can be estimated by measuring the relative rates of amidine formation. Ammonia does not react with DL-glyceronitrile at pH 9.5 to form an amidine, in agreement with previous studies,[32] while amidine formation occurs readily from imidates. The rates of aminolysis of C_4 and C_5 imido-1,4-lactones should not differ significantly. Thus, a difference in the overall rates of conversion of **2** and **4** to amidines will reflect a difference in their rates of cyclization (cyclization is rate determining).

Rates of amidine formation are shown in Figure 10. Compound **4** reacts ~5 times faster than **2**. We conclude that imido-1,4-lactones form less readily when a primary OH is participating than when a secondary OH is involved. The presence of a CH_2OH or CH_3 substituent on C-4 may orient OH-4 for easier attack on the nitrile carbon and/or affect its nucleophilicity. The slower rate of disappearance of **2** (Figure 1) is primarily due to a slower rate of cyclization to imidolactone. The fact that **2** can cyclize to form an imido-1,4-lactone is apparent from its slow but eventual conversion to amidine.

Summary

In summary, we have presented evidence for the following.

(a) In the cyanohydrin reaction involving C_3 and higher carbon aldoses, an equilibrium exists between the parent aldose and cyanide and the 2-epimeric nitriles. The latter, in turn, are in equilibrium with imido-1,4-lactones. Imido-1,4-lactones hydrolyze, presumably via carbinolamines, to 1,4-lactones and/or aldonamides, and this reaction is not freely reversible. Carbinolamines are in equilibrium with side-product aldonamides which hydrolyze via carbinolamines and 1,4-lactones to aldonates.

(b) At pH 7–9, cyanide condenses stoichiometrically and quantitatively with C_1–C_4 aldoses to form aldononitriles. Aldoses that form pyranose rings require a threefold excess of cyanide under similar conditions to promote complete condensation.

(c) The extent of cyanide addition decreases with increasing pH.

(d) The rate of aldononitrile disappearance decreases as pH decreases and is affected by aldononitrile structure. C_3 and C_4 aldononitriles disappear more slowly than C_5 nitriles at all pH values examined. The overall rate of disappearance is faster for aldononitriles derived from D-erythrose than for those derived from D-threose. Aldononitriles having the arabino configuration hydrolyze more readily than those having the ribo configuration. Aldononitriles having lyxo and xylo configurations hydrolyze at similar rates.

(e) Hydroxyl groups in the proper position(s) facilitate aldononitrile hydrolysis through the formation of imidolactones. Cyclization of C_5 aldononitriles to imido-1,4-lactones occurs almost quantitatively at pH 10.5. Aldononitriles having the arabino configuration cyclize faster to form five-membered rings than do those having the ribo configuration.

(f) C_4 aldononitriles (erythro, threo) cyclize more slowly and, therefore, hydrolyze more slowly than C_5 aldononitriles (ribo, arabino), although five-membered imido-1,4-lactones are involved in both cases.

(g) Imido-1,4-lactones hydrolyze in alkaline (pH >10.5) and acidic (pH <4) solutions to yield aldonamides and aldono-1,4-lactones, respectively, in agreement with the behavior of N-substituted imido-1,4-lactones.[31]

(h) At pH 11, D-ribonamide hydrolyzes ~2.5 times faster than D-arabinonamide.

(i) Amidines are formed at pH 9.5 in 85–95% yield from intermediate C_4 and C_5 imidolactones when 1 equiv of ammonia is added during cyanide addition to aldose.

(j) Linear compounds having arabino and ribo configurations can be distinguished by their $^3J_{C\text{-}1,C\text{-}4}$ values. Furanoid forms (with an sp^2-hybridized C-1 carbon) having arabino and ribo configurations can be distinguished by $J_{C\text{-}1,C\text{-}3}$ and $J_{C\text{-}1,C\text{-}4}$ values and by ^{13}C chemical shifts. The

(40) Hudson, B. G.; Barker, R. *J. Org. Chem.* **1967**, *32*, 3650.

(41) Lactones in reaction mixtures at these pH values are produced from the direct hydrolysis of imidolactone and not from amide hydrolysis.

(42) In comparison, D-erythrose 4-phosphate, which cannot cyclize and exists predominantly as a hydrate in aqueous solution, reacts with cyanide at pH 8.0 to yield 58% ribononitrile 5-phosphate.[16]

^{13}C NMR parameters of 1,4-lactones and imido-1,4-lactones are similar.

(k) The following 2-epimeric intermediates and products are observed by ^{13}C NMR using $K^{13}CN$ in reaction with D-erythrose: nitriles, imido-1,4-lactones, amidines, amides, aldono-1,4-lactones, and aldonates. A dimer(s) formed by reaction between imido-1,4-lactone and nitrile is proposed.

Registry No. 7, 73713-14-1; D-glyceraldehyde, 453-17-8; D-threose, 95-43-2; D-erythrose, 583-50-6; D-arabinose, 10323-20-3; D-lyxose, 1114-34-7; D-ribose, 50-69-1; D-xylose, 58-86-6; [*R*-(*R**,*S**)]-2,3,4-trihydroxybutanoic acid, 7306-96-9; D-lyxonic acid, 526-92-1; D-arabinonic acid, 488-30-2; D-gluonic acid, 526-95-4; D-mannonic acid, 642-99-9; D-galactonic acid, 576-36-3; D-allonic acid, 21675-42-3; D-gulonic acid, 20246-33-7; D-gluconate pertrimethylsilylated, 38165-89-8; glycolaldehyde trimethylsilylated, 18147-36-9; D-glyceraldehyde pertrimethylsilylated, 73712-76-2; 2,4-*O*-ethylidene-D-erythrose trimethylsilylated, 73712-77-3; D-erythrose pertrimethylsilylated, 73745-84-3; D-threose pertrimethylsilylated, 73788-50-8; D-arabinose pertrimethylsilylated, 18622-97-4; D-lyxose pertrimethylsilylated, 73745-85-4; D-ribose pertrimethylsilylated, 33648-69-0; D-xylose pertrimethylsilylated, 18623-22-8; D-glycerate pertrimethylsilylated, 73712-78-4; D-erythronate pertrimethylsilylated, 73745-86-5; D-threonate pertrimethylsilylated, 73745-87-6; D-arabinonate pertrimethylsilylated, 73745-88-7; D-ribonate pertrimethylsilylated, 65167-67-1; D-lyxonate pertrimethylsilylated, 73745-89-8; D-xylonate pertrimethylsilylated, 73745-90-1; D-allonate pertrimethylsilylated, 73745-91-2; D-altronate pertrimethylsilylated, 73745-92-3; D-gulonate pertrimethylsilylated, 73745-93-4; D-idonate pertrimethylsilylated, 73745-94-5; D-mannonate pertrimethylsilylated, 73745-95-6; D-galactonate pertrimethylsilylated, 73745-96-7; D-talonate pertrimethylsilylated, 73745-97-8; D-glyceronitrile pertrimethylsilylated, 73712-79-5; D-erythrononitrile pertrimethylsilylated, 73712-80-8; D-threononitrile pertrimethylsilylated, 73712-81-9; 3,5-*O*-ethylidene-D-arabinonitrile pertrimethylsilylated, 73712-82-0; 3,5-*O*-ethylidene-D-ribononitrile pertrimethylsilylated, 73712-83-1; D-arabinononitrile pertrimethylsilylated, 73712-84-2; D-ribononitrile pertrimethylsilylated, 73712-85-3; D-lyxononitrile pertrimethylsilylated, 73712-86-4; D-xylononitrile pertrimethylsilylated, 73712-87-5; D-gluconontrile pertrimethylsilylated, 73712-88-6; D-mannononitrile pertrimethylsilylated, 73712-89-7; D-galactononitrile pertrimethylsilylated, 73712-90-0; D-allononitrile pertrimethylsilylated, 73712-91-1; D-gulononitrile pertrimethylsilylated, 73712-92-2; D-idononitrile pertrimethylsilylated, 73712-93-3; D-arabinono-1,4-lactone pertrimethylsilylated, 32384-55-7; D-ribono-1,4-lactone pertrimethylsilylated, 10589-34-1; D-arabinonamide pertrimethylsilylated, 73712-94-4; D-ribonamide pertrimethylsilylated, 73712-95-5; D-lactaldehyde hydrate, 73712-96-6; D-*threo*-2,3-dihydroxybutanal hydrate, 73712-97-7; D-*erythro*-2,3-dihydroxybutanal hydrate, 73728-17-3; DL-glyceronitrile, 70849-07-9; DL-2-hydroxybutyronitrile, 73683-30-4; D-*threo*-2,3-dihydroxybutyronitrile, 73712-98-8; D-*erythro*-2,3-dihydroxybutyronitrile, 73712-99-9; D-threononitrile, 70849-39-7; D-erythrononitrile, 73713-00-5; D-lyxononitrile, 70878-63-6; D-xylononitrile, 52387-25-4; DL-2-hydroxybutyrate, 600-15-7; D-lyxono-1,4-lactone, 15384-34-6; D-xylono-1,4-lactone, 15384-37-9; D-threonoamidine, 73713-01-6; D-erythronoamidine, 73713-02-7; D-arabinonitrile, 70878-64-7; D-arabinoimido-1,4-lactone, 73713-03-8; D-arabinonamide, 15909-88-3; D-arabinono-1,4-lactone, 2782-09-4; D-arabinono-1,5-lactone, 73745-98-9; D-arabinonoamidine, 73713-04-9; D-ribononitrile, 52387-24-3; D-ribonoimido-1,4-lactone, 73713-05-0; D-ribonamide, 73713-06-1; D-ribono-1,4-lactone, 5336-08-3; D-ribono-1,5-lactone, 6866-49-5; D-ribonic acid, 642-98-8; D-ribonoamidine, 73713-07-2; D-5-deoxyarabinonoimido-1,4-lactone, 73713-08-3; D-5-deoxyribonoimido-1,4-lactone, 73713-09-4; D-5-deoxylyxonoimido-1,4-lactone, 73713-10-7; D-5-deoxyxylonoimido-1,4-lactone, 73713-11-8; D-5-deoxyarabinonamide, 73745-99-0; D-5-deoxyribonamide, 73746-00-6; D-erythronoimido-1,4-lactone, 73713-12-9; D-erythroamide, 73713-13-0; D-erythro-1,4-lactone, 23732-41-4; D-talononitrile, 70849-36-4; D-altrononitrile, 70849-34-2.

Notes

Conversion of Alcohols to Methylene Acetals by Reaction with Dimethyl Sulfoxide-Bromine

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Dimethyl sulfoxide (Me_2SO) oxidizes alcohols to carbonyl compounds in the presence of electrophilic reagents[1] such as chlorine,[2] dicyclohexylcarbodiimide,[3] acetic anhydride,[4] and trifluoroacetic anhydride[5] at low temperatures. These oxidations are, however, found to be inefficient above room temperature due to competing Pummerer rearrangements which give rise to dimethylthio ethers. In the presence of *N*-bromosuccinimide (NBS) at 50 °C, Me_2SO transforms alcohols to the corresponding methylene acetals.[6] Acetal formation has been suggested to arise from the Pummerer rearrangement of an initially formed bromosulfoxonium ion to give an α-alkoxy sulfoxide intermediate.

In this paper, we wish to report that alcohols also react with Me_2SO in the presence of bromine above room temperature to give the corresponding dialkyl methylene acetals (1) in the yields indicated in Table I. We also

$$Me_2SO + Br_2 \xrightarrow[CCl_4]{ROH} \underset{1}{ROCH_2OR} \qquad (1)$$

suggest that the methylene group originates from a "dimethyl sulfide–bromine" adduct (Me_2S–Br_2) and not from the expected Me_2SO–Br_2 adduct.[7]

The sequence of mixing the reagents has a profound effect on the course of the reaction and the yields of the acetals. Thus, addition of 1-butanol to a preformed Me_2SO–Br_2 mixture (procedure A) gave 78% of di-*n*-butyl methylene acetal; while this product was isolated in only 45% yield when a solution of bromine in CCl_4 was added to a mixture of 1-butanol and Me_2SO in CCl_4 (procedure B).

In the case of secondary alcohols, procedure B also leads to oxidation products. Thus, for example, 3-pentanol gives 2-bromo-3-pentanone (2) and 2,4-dibromo-3-pentanone (3),

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(2) E. J. Corey and C. U. Kim, *Tetrahedron Lett.*, 919 (1973).
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(6) S. Hanessian, G. Yang-Chung, P. Lavalee, and A. G. Pernet, *J. Am. Chem. Soc.*, **94**, 8929 (1972); S. Hanessian and A. G. Pernet, *Carbohydr. Res.*, **26**, 258 (1973).

(7) A Me_2SO–Br_2 adduct has been postulated as the brominating species in the conversion of aniline hydrobromide to *p*-bromoaniline in Me_2SO: P. A. Zoretic, *J. Org. Chem.*, **40**, 1867 (1975). Its structure would be expected to be similar to that of the Me_2SO–Cl_2 adduct suggested by Corey:[2] $(Me_2S^+(Cl)=O)Cl^-$.

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