CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Anchimeric-assisted Spontaneous Hydrolysis of Cyanohydrins Under Ambient Conditions: Implications for Cyanide Initiated Selective Transformations.

Authors: Jayasudhan Reddy Yerabolu, Charles L Liotta, and Ramanarayanan Krishnamurthy

To be cited as: *Chem. Eur. J.* 10.1002/chem.201701497

Link to VoR: http://dx.doi.org/10.1002/chem.201701497

Supported by
ACES

WILEY-VCH

10.1002/chem.201701497

WILEY-VCH

Anchimeric-assisted Spontaneous Hydrolysis of Cyanohydrins Under Ambient Conditions: Implications for Cyanide Initiated Selective Transformations.

Jayasudhan Reddy Yerabolu[a,c], Charles L Liotta[b,c]*, Ramanarayanan Krishnamurthy[a,c]*

Dedication: To Professor Albert Eschenmoser on the occasion of his 92nd Birthday

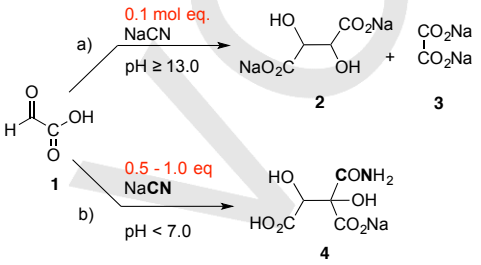
Abstract: Nitrile/cyanide hydrolysis is of importance from the perspective of organic chemistry, especially, prebiotic chemistry. Herein we report that cyanohydrins, generated by the reaction of cyanide with β-keto acids and γ-keto-alcohols, spontaneously hydrolyze under ambient conditions (aqueous medium, r.t. and a range of pH). The spontaneous hydrolysis is effected by an intramolecular-proton transfer and an intramolecular 5-*exo*-dig attack, but with a twist. In the case of β-keto acids, the hydrolysis is mediated by the neighboring carboxylic acid group only at pH values less than 7, while in the case of γ-keto-alcohols the hydrolysis is mediated by the neighboring hydroxyl group only at pH values greater than 7. The results, in combination with previous works, have implications for selective transformations of cyanide-initiated prebiotic systems chemistry.

Introduction

Introduction: The reaction of cyanide to form nitriles and the subsequent hydrolysis of nitriles to yield amides or carboxylic acids are classical reactions both in organic synthesis,[1-4] and in many prebiotic chemistry scenarios[5-8]. Examples include the Strecker synthesis of amino acids[9,10] and the homologation of monosaccharides via the Fischer-Kiliani synthesis[11,12]. In addition, as of late, the reactions of cyanide have also been considered in a prebiotic-systems-chemistry perspective.[13-15]

Recently, we reported that reaction of glyoxylate **1** with catalytic cyanide at pH 13 led to the production tartrate **2** and oxalate **3** in high yields via a novel deoxalation reaction (Scheme 1a).[16,17] Within a prebiotic context, however, such a high pH could be considered problematic. Therefore, in this study, we began an investigation of a similar set of reactions of glyoxylate on the acidic side of the pH scale. Surprisingly, the reaction of glyoxylic acid with 0.5-1.0 equivalent of hydrogen cyanide at pH ≤ 7, produced the 2-carbamoyl-2,3-dihydroxysuccinic acid **4** (Scheme 1b) presumably via the

[a] Dr. Jayasudhan R. Yerabolu, Prof. Dr. Ramanarayanan Krishnamurthy
Department of Chemistry, The Scripps Research Institute
10550 North Torrey Pines Rd, La Jolla, CA 92037, USA
E-mail: rkrishna@scripps.edu
[b] Prof. Dr. Charles Liotta
[2]School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332, USA, E-mail: charles.liotta@carnegie.gatech.edu
[c] NSF-NASA Center for Chemical Evolution, Atlanta, GA 30332 (USA)
Supporting information for this article is given via a link at the end of the document.



Scheme 1. The divergent reactions of glyoxylate with cyanide depending on the pH of the medium.

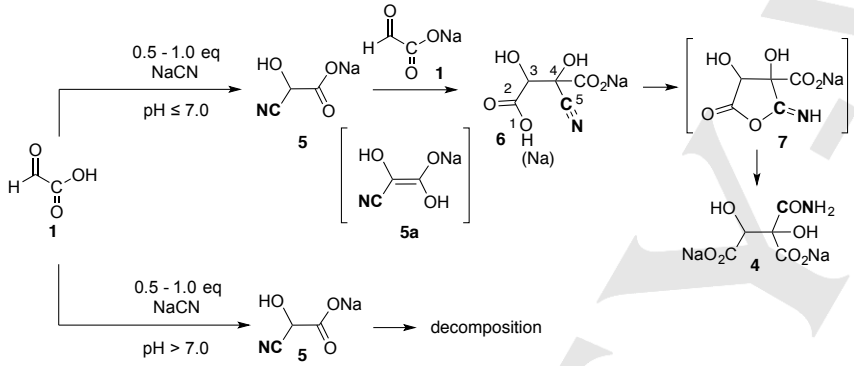
cyanohydrin of glyoxylic acid, which subsequently underwent a condensation reaction with unreacted glyoxylic acid. The fact that the cyano-group (as the cyanohydrin) did not survive, but was hydrolyzed spontaneously under the mild conditions (near neutral pH and room temperature) prompted an extended investigation of this reaction, and of NaCN with a variety of keto-acids and keto alcohols in water on both the acidic and basic side of the pH scale. Herein we report on the spontaneous anchimeric-assisted hydrolysis of cyanohydrins to α-hydroxy amides under room temperature conditions. In general, we observe that the ease of cyanide hydrolysis depended on the specific structure of the cyanohydrin intermediate. Specifically, the intermediate cyanohydrins were spontaneously hydrolyzed at room temperature only when (a) the pH of the aqueous medium was below 7 and a carboxylic acid substituent was located β to the cyano group or (b) the pH was above 7 and a hydroxyl substituent was located γ to the cyano group. We present evidence, primarily based on ^{13}C-NMR and mass spectral data, that establishes the anchimeric assistance provided is via an internal proton transfer leading to a 5-*exo*-dig attack of the internal nucleophile on the cyano-group. The results from these studies, combined with those from previous works, are of interest not only from the perspectives of organic chemistry[18-20], but also have implications for the selective transformations/manipulations in the context of prebiotic systems chemistry[13-15] (such as proto metabolic pathways and cycles[5,21]).

Results and Discussion

Reaction of cyanide with glyoxylate: The reaction 0.5 eq of NaCN with glyoxylic acid (**1**, ≈ 0.5M) at r.t. began with an initial unadjusted pH of 2 (Scheme 2). Monitoring by ^{13}C-NMR (Figure

1, bottom spectrum) showed the (fast) formation of glyoxylate-cyanohydrin **5** adduct along with unreacted glyoxylate as the major species with the pH slowly rising to 3 over days (Figure S1-S2). Over time, signals corresponding to both these species slowly diminished and with concomitant rise in signals attributed to the (diastereomeric) product **4** (Figure 1, middle spectrum). The intensity of signals for intermediate **6** was weak (Figure S2), suggesting that the cyanide moiety in the adduct **6** was continuously hydrolyzed at r.t. to the amide product (**4**), thus, keeping the concentration of **6** low. The reaction proceeds slowly over days-weeks at r.t. with the pH of the reaction medium rising to 4.5 and settling around 5 (Figure S3-S5, S8); complete consumption of starting materials and intermediates with the clean formation of two diastereomers of the mono-amide derivative **4** was observed (Figure 1, top spectrum) which was corroborated by mass spectral analysis (Figure S6-S7).

When one equivalent of NaCN was employed at r.t. (range of pH ≤ 7) the reaction proceeded as above, but relatively faster, to give the mono-amide **4** along with the cyanohydrin adduct of glyoxylate **5** (Figure S9). Reactions using doubly labeled glyoxylate with unlabeled cyanide confirmed the condensation of two glyoxylate molecules by the increase in the splitting of the signals in the ^{13}C-spectra (Figure S10) of the ^{13}C-labeled monoamide derivative **4**. Use of labeled Na^{13}CN with unlabeled glyoxylate showed cleanly the formation of the cyanohydrin-adduct **5** followed by its disappearance and the concomitant appearance of the amide signals of **4** in the ^{13}C-NMR spectra (Figure S11). Again, ^{13}CN-signals of the cyanohydrin group for the intermediate **6** could not be clearly discerned, suggesting its continuous consumption in the reaction.



Scheme 2. "Glyoxoin reaction" of glyoxylate mediate by cyanide at pH ≤ 7 at room temperature leading to the formation of a carboxamide derivative 4. At pH > 7, the adduct **5** persists and slowly decomposes by side reactions.

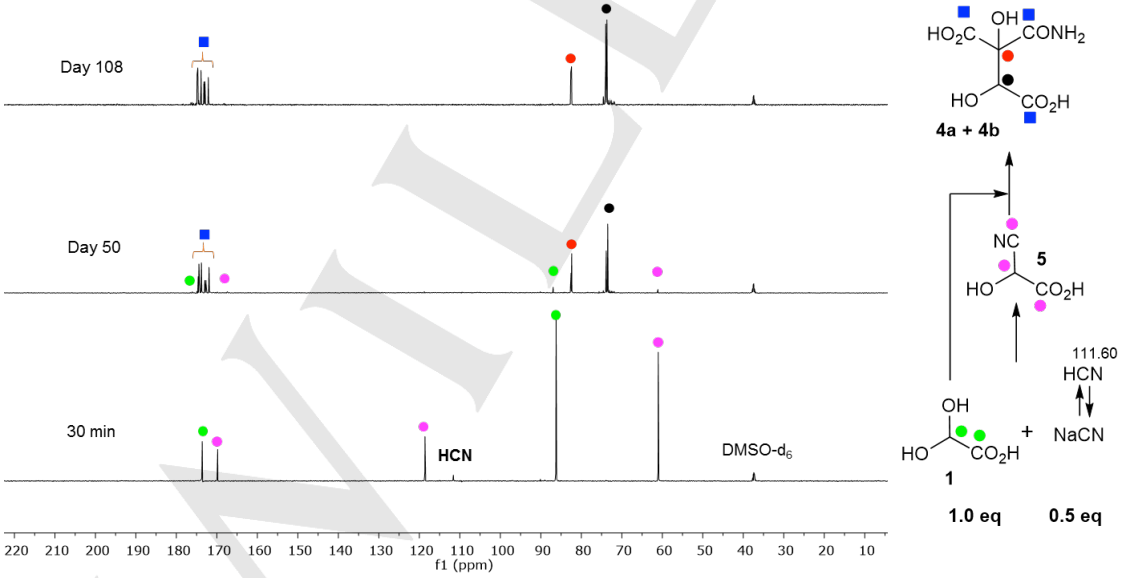
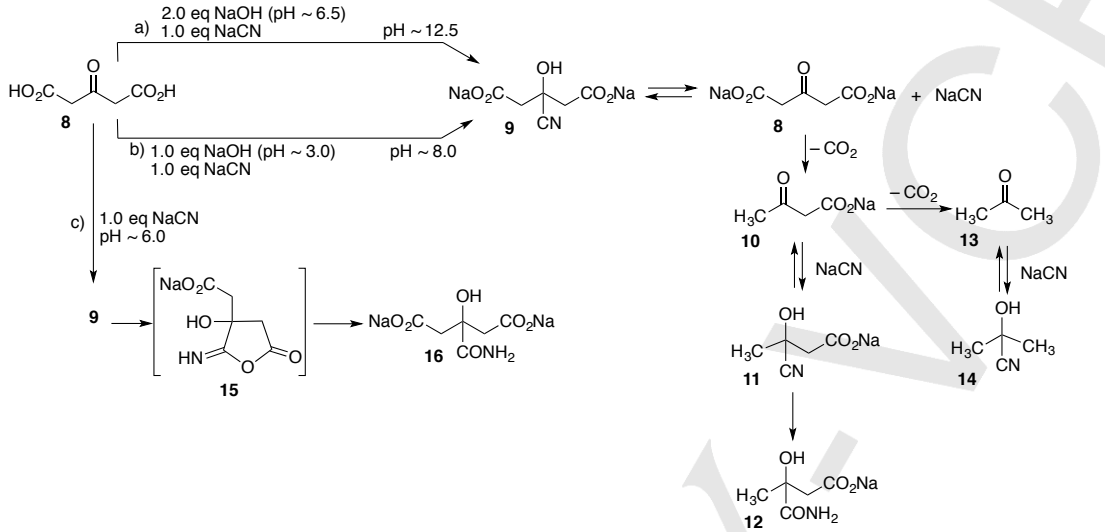


Figure 1. ^{13}C-NMR (H_2O with DMSO-d_6) monitoring of the reaction of 0.5 equiv. of NaCN with 1 equiv. of glyoxylate at pH < 7 documenting the clean conversion to the final diastereomeric mixture of amide **4**.

In all these reactions, the pH of the reaction medium was less than or equal to 7. When the pH of the reaction medium was maintained higher than 7, the clean formation and/or hydrolysis of condensation product **6** was not observed. For example, when a solution of glyoxylic acid whose pH was adjusted to pH 7 was treated with 0.5 eq. of NaCN, the pH of the solution raised to pH 12.5 and the cyanohydrin adduct **5** was formed, but was accompanied by side reactions and a messy ^{13}C-NMR spectrum (Figure S12) indicative of interference from Cannizzaro[22] type reactions or deoxalation[16] reactions.



Scheme 3. Reaction of 1,3-acetone dicarboxylic acid (8, 0.68 M) with 1.0 equivalent of sodium cyanide (a), (b) at pH greater than 7, and (c) at pH ≤ 7; all at room temperature.

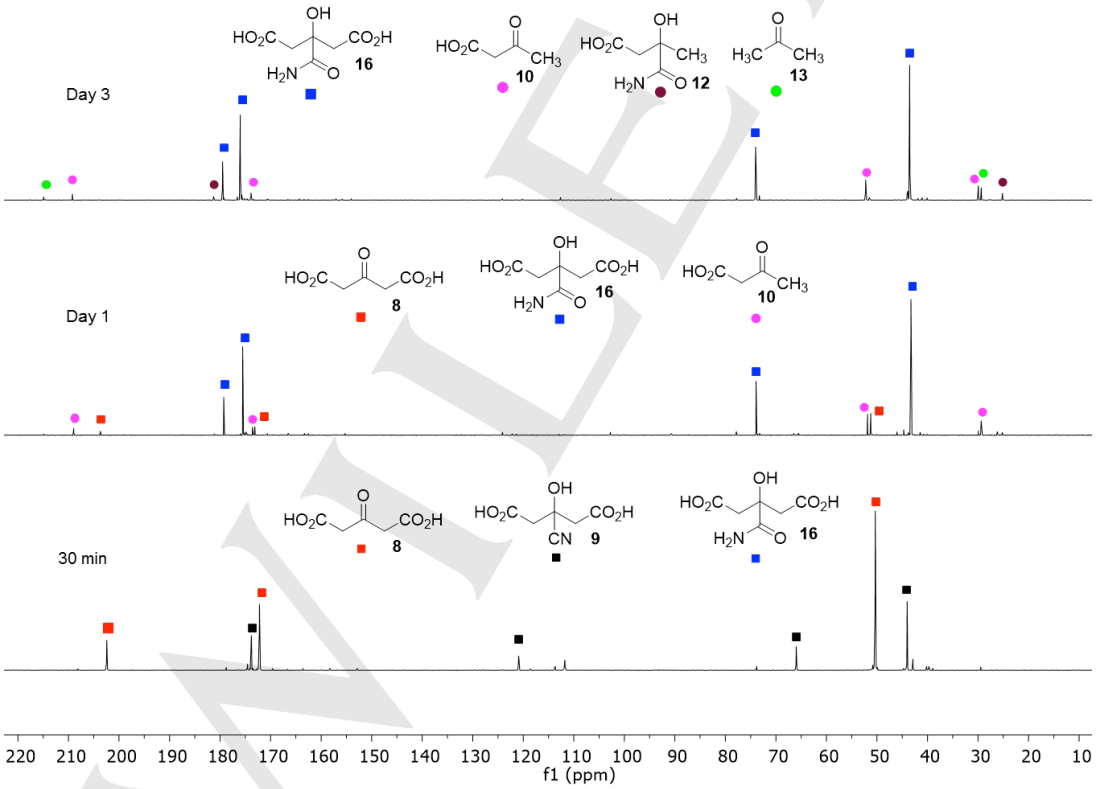
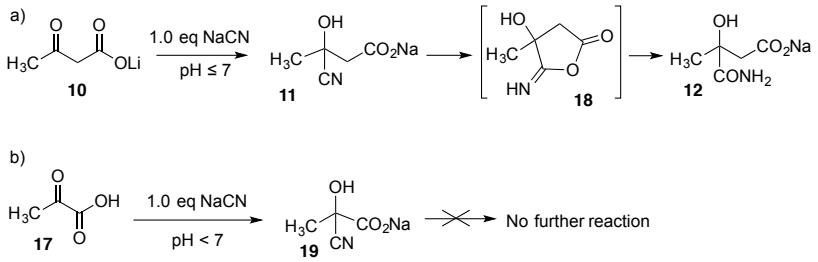


Figure 2. Progress of the reaction of NaCN with 1,3-acetone dicarboxylic acid **8** as documented by ^{13}C-NMR spectra (H_2O with drops of D_2O), giving rise to citric acid amide derivative **16**.



Scheme 4. (a) Reaction of acetoacetic acid (10, 0.23 M) with 1.0 equivalent of NaCN at pH ≈ 4.5; (b) Reaction of pyruvic acid (17, 0.45 M) with 1 equivalent of NaCN at pH 3.0; all at room temperature.

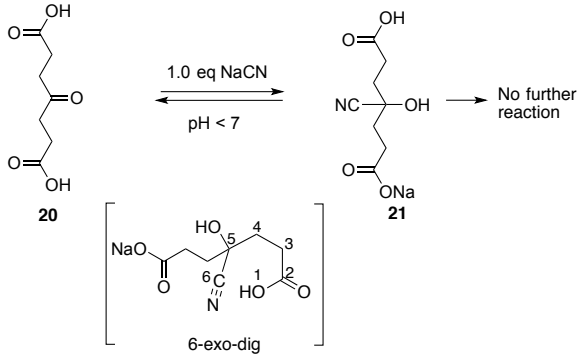
In another experiment, the glyoxylate-cyanohydrin adduct **5** was separately formed at pH 6.5, and the pH was adjusted to pH ≈ 10.5 (Figure S13). The consumption of **5** was observed through side reactions again with no clear indication of formation condensation product **6** or its hydrolysis product **4**.

This cyanide-mediated "glyoxoin"[16] (in analogy to the formoin) type condensation of glyoxylate at pH ≤ 7, resulting in the formation of a carboxamide derivative **4** was unexpected (based on literature precedence) for two reasons: (1) a high pH was thought to be necessary[16] for deprotonating the α-proton of the glyoxylate-cyanohydrin adduct **5** and (2) generally, highly acidic or basic pH[23] combined with elevated temperatures[24-26] is needed to hydrolyze the cyano-group (such as in **6**) to give the corresponding amide derivative **4**. The ease of the hydrolysis of cyano-group of **6** at room temperature led us to hypothesize that an internal anchimeric carboxylate/acid assistance[27] via a 5-membered ring intermediate **7** (Scheme 2) may have been responsible. Such an intramolecular hydrolysis is reminiscent of the borate-buffer mediated hydrolysis of cyanohydrins[28,29] and aldehyde mediated hydrolysis of α-aminonitriles[30,31] at high-pH (pH ≥ 10). However, our results indicate that the pH of the medium could also be on the lesser side of neutrality. To test this hypothesis, and the generality of this anchimeric assistance, we expanded the scope of the substrates to other keto-acids which are of relevance to the chemistries in the context of prebiotic chemistry[15,32] and proto-metabolic pathways[5,21].

Reaction of cyanide with 1,3-acetone-dicarboxylic acid (Scheme 3): 1,3-acetone-dicarboxylic acid **8** was chosen for two reasons: (1) the two-carboxylic acid groups have the same β-keto-relationship as in the intermediate **6** in Scheme 2 and (2) the hydrolysis product is expected to lead to citric acid, an important biological compound in the tricarboxylic acid (TCA) cycle[5]. Also, such a reaction may be relevant to the types of reaction products found in the meteorites[33] and proto-metabolic reactions[34,35].

Since **8**, a β-keto carboxylic acid, is prone to decarboxylation, we reasoned that as the dicarboxylate it may be more stable and available to react with NaCN. Therefore, two equiv. of aq. NaOH was added to make the disodium salt of **8** (pH ≈ 6.5) followed by one equiv. of NaCN. Within 10 min. the pH increased to 12.5 and ^{13}C-NMR indicated the formation of the cyanohydrin adduct **9**. The reaction however, over days, stalled at the cyanohydrin adduct with no anchimeric assisted hydrolysis of the cyanide (Figure S14). Rather, the unreacted portion of **8** began to decarboxylate to afford acetoacetic acid **10** and acetone **13**, and their respective cyanohydrin adducts **11** and **14** (Scheme 3a). When one equiv. of NaOH was used (pH ≈ 3) followed by addition of NaCN, the pH rose to 7.5–8 within days and with similar results as with 2 equiv. NaOH (Scheme 3b). However, ^{13}C-NMR indicated minor peaks that could be attributed to (trace amounts) of a citric acid-like derivative (Figure S15). This prompted addition of 1 equiv. of NaCN directly to **8** (pH unadjusted ≈ 2.5) even though it meant the risk of higher rates of decarboxylation of **8** at the acidic pH. Nevertheless, the formation of a citric acid derivative in ^{13}C-NMR was observed within hours with the pH rising to pH 5–6, with negligible side reactions due to competing decarboxylations (Figure S16-S17). Within 3 days, the peaks attributable to a citric acid derivative (surmised to be the amide derivative **16**, (Scheme 3c, Figure S18-S19) was dominant, along with small amounts of **10**, **12** and **13** as side products formed from decarboxylation of **8** (Figure 2). Spiking with citric acid, and mass-spectral data confirmed that it was indeed the amide derivative **16** (Figure S20-S22). The spontaneous hydrolysis of the cyanide moiety in cyanohydrin derivative **9** parallels the observation made in the glyoxylate reaction (Scheme 2); also, the hydrolysis to the corresponding α-hydroxy amide was observed only when the pH was less than or equal to 7 and not when above 7. The rate of cyanohydrin formation **9**, however, was much slower (days) when compared to the formation of cyanohydrin **5** (30 min.) attesting to the reactivity of the glyoxylate carbonyl group versus the keto-group of **8**.

Reaction of cyanide with acetoacetic acid and pyruvate: Based on the above results, acetoacetic acid **10**, also a β-keto carboxylic acid but with only one carboxylate moiety, was reacted with cyanide at pH 3, 7 and 13 (Scheme 4a). While the cyanide addition was found to occur (slower relative to pathways starting from **1** or **8**) at pH = 3-4.5 (Figure S 23) and 7-7.5 (Figure S25), no cyanohydrin-adduct **11** formation was observed at pH 13 by ^{13}C-NMR (S26). Paralleling the outcomes observed for 1,3-acetone-dicarboxylic acid (Scheme 3), spontaneous hydrolysis of cyanohydrin-adduct **11** occurred at pH 3-4.5 to form the corresponding succinamide derivative **12** (Figure S23-S24); however, the reaction at pH 7 (or higher) did not proceed beyond the cyanohydrin adduct **11**. Reaction with pyruvate **17** (at pH 3) resulted in the faster (within 30 min) and complete formation of the corresponding cyanohydrin adduct **19** (Scheme 4b), but with no further reaction (Figure S27).



Scheme 5. (a) Reaction of 4-oxoheptanedioic acid (**20**, 0.28 M) with 1.0 equivalent NaCN at pH 4-5.5 at room temperature.

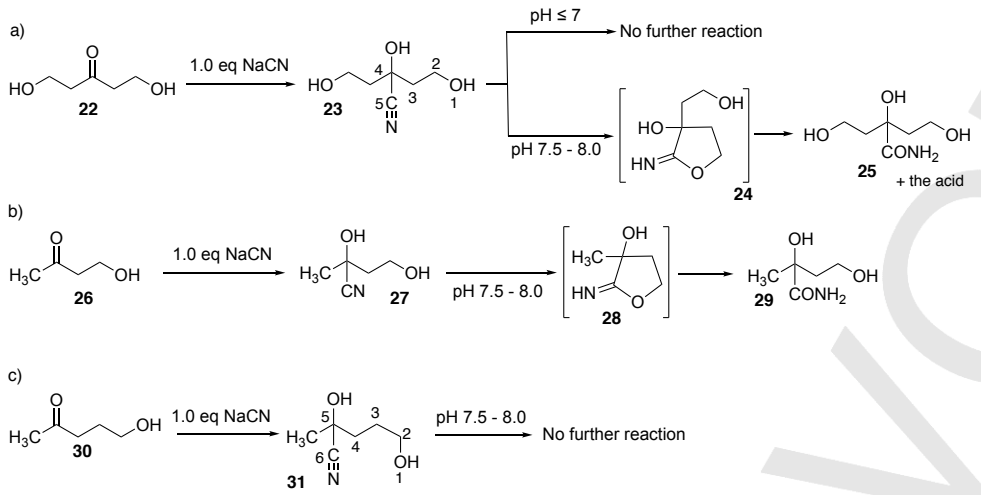
The resistance to hydrolysis of the pyruvate-cyanohydrin-adduct **19** indicates that neither the intramolecular attack of the carboxylic acid oxygen (via a four-membered ring intermediate), nor an *intermolecular* attack of a water molecule on the cyano-group of **19**, is taking place. The above set of reactions support a 5-*exo*-dig attack of the internal carboxylate nucleophile on the cyanide, via a five-membered ring intermediate. This would necessitate a 1,5-positional relationship between the cyano-group (of the cyanohydrin) and the attacking oxygen-moiety of the carboxylic acid. It immediately raises a question as to whether a 1,6-positional relationship leading to a six-membered ring intermediate (via a 6-*exo*-dig attack of the internal nucleophile) would be possible, since such 6-*exo*-dig additions on a cyano moiety are known.[36-38]

Reaction of cyanide with 4-oxoheptanedioic acid: To answer the question whether a 1,6-relationship between the carboxyl and the cyano-group would lead to hydrolysis, NaCN was reacted with 4-oxoheptanedioic acid **20**, a substrate in which the carboxylates are *gamma* in relation to the keto group (Scheme 5). This will result in a 1,6-relationship in **21**, necessitating a six-member(6-*exo*-dig) anchimeric-assisted intermediate. Though cyanohydrin adduct **21** formation was observed (pH ≈ 5), no hydrolysis of **21** was observed under the identical conditions where cyanohydrin adduct **15** of 1,3-acetone dicarboxylic acid **8** was spontaneously hydrolyzed. Further heating (50°C) did not change this result. This observation that the cyano-group of **21** is resistant to hydrolysis (under these conditions) demonstrates that a 6-*exo*-dig participation of the carboxylate group is not taking place (Figure S28). While 6-*exo*-dig cyclization on a cyanide moiety are not forbidden and are known,[27,36-39] there are also examples where there is a clear preference for the 5-*exo*-dig.[12] The stability of the resulting *exo*-double bond five-membered ring (5-*exo*-dig) versus the instability of the *exo*-double bond six-membered ring (6-*exo*-dig) has been proposed to play a role in this preference.[40] The results, while consistent with the latter observations and interpretations[12,40], imply that further activation of the cyanide is necessary[36-38] for the 6-*exo*-dig attack to take place and, unlike the 5-*exo*-dig, is not 'spontaneous'. This strengthens the supposition that a 1,5-positional relationship between the carboxylate and the nitrile (leading to a five-membered cyclic intermediate) indeed is necessary for the hydrolysis of the cyanohydrin adduct.

The observations with the carboxylic acids led to the question of whether a neighboring hydroxyl group (with similar 1,5-positional relationship to the cyano group) would also show the same behavior and be capable of spontaneous intramolecular transformation of the cyanohydrins to the corresponding α-hydroxy amides. This is akin to the Kiliani-reaction of cyanides with aldoses, where cyclic 5-membered ring participation of a hydroxyl-group is invoked for hydrolysis of the cyanohydrin to give the corresponding lactones under acid/base treatments.[12,41,42]

Reaction of cyanide with 1,5-dihydroxy pent-3-one: NaCN was reacted with 1,5-dihydroxy pent-3-one **22**. This substrate is analogous to acetone-1,3-dicarboxylic acid, where both the carboxylic acid moieties have been reduced to corresponding alcohols (Scheme 6a). When subjected to the identical acidic reaction conditions (pH < 7) as above, only the formation of the cyanohydrin adduct **23** was observed, with no further hydrolysis of **23** even after 5 days at rt (Figure S29). However, when the reaction was conducted starting at pH 7.5, we observed the hydrolysis of the cyanohydrin adduct giving rise to the corresponding amide **25** in 12 h at rt (pH changing to ≈ 8), which continued to proceed over a period of 5 days (pH ≈ 8.5, Figure S30). The formation of carboxamide **25** was also confirmed by mass spectral data (Figure S31). This result indicated that (a) there is indeed a difference in the pH requirements for the anchimeric assistance of carboxylic acid versus hydroxyl group in these acyclic systems – the former requiring a pH below 7 while the latter a pH above 7, and (b) there is no need to have a highly basic pH (like in the classic Kiliani-Fischer protocols) when there is anchimeric assistance from the hydroxyl group with a 1,5-relationship.[12,41,42]

To test whether the 1,5-positional relationship (5-*exo*-dig) also holds good for a nieghboring hydroxyl group, the reaction of 4-hydroxybutan-2-one **26** and 5-hydroxypentan-2-one **30** were investigated with NaCN (Scheme 6b and 6c). Under acidic pH, as observed for **22**, both compounds formed the cyanohydrin adducts **27** and **31** respectively, but no hydrolysis of these adducts were observed even after 3-5 days (Figure S32). On the other hand, when the reactions were repeated at pH 7.5-8.0, cyanohydrin adduct **27**, which has a 1,5-relationship, was not only found to hydrolyze to the corresponding α-hydroxy amide **29** (2 days, Figure 3) but further converted cleanly to the corresponding α-hydroxy acid (Figure S33-S35), which is consistent with anchimeric assisted hydrolysis of the amide as reported by Kirby.[43] However, cyanohydrin adduct **31**, which has a 1,6-relationship, was found to persist (Figure 4) over days with no further hydrolysis (Figure S36, S37); at pH 13, the formation of the cyanohydrin adduct itself was not observed (Figure S38). Observations from the above reactions confirm that (1) there is a pH divergence of the intramolecular reactivity of carboxylic acid (pH < 7) versus hydroxyl group (pH > 7) and (2) a 1,5-positional relationship of the attacking nucleophile to the cyano-group is required for both the carboxylic acid and hydroxyl groups; that is, a 5-*exo*-dig (as opposed to a 6-*exo*-dig) cyclic intermediate is preferred.



Scheme 6. Reaction of NaCN with γ-hydroxy ketones **22**, **26**, and δ-hydroxy ketone **30** illustrating the 1,5-positional relationship and the pH > 7 requirements for intramolecular hydrolysis.

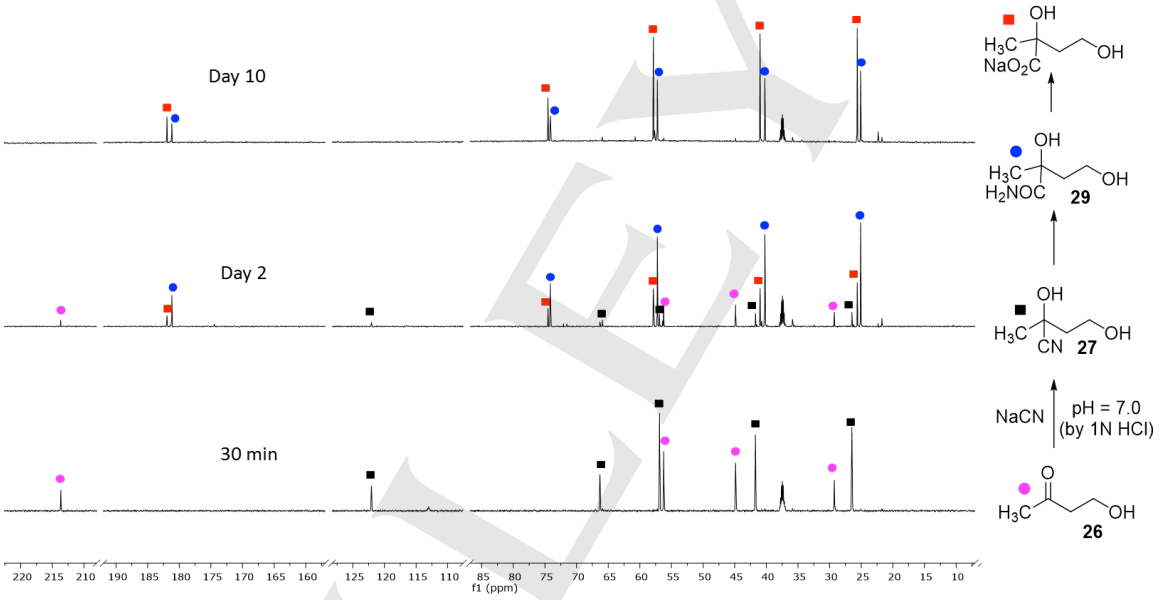


Figure 3. ^{13}C-NMR spectra (H_2O with DMSO-d_6) of the reaction of NaCN with 4-hydroxybutan-2-one **26** showing clean conversion to the hydrolyzed products amide and the corresponding acid.

With these conclusions in hand we probed the predictions from the reaction mechanism by expanding to other substrates within the context of prebiotic systems chemistry[14]. We designed three α-keto carboxylic acid substrates 2-hydroxy-4-ketoglutarate **32**[44], **35** and **38**[45] (Scheme 7) which contain both a hydroxyl (with a 1,4-relationship to the keto group, leading to a 5-*exo*-dig attack) and a carboxylate group (with a 1,5-relationship to the keto group, leading to a 6-*exo*-dig cyclization). These substrates were also chosen due to their potential role in the context of the glyoxylate scenario[21], and are generated by the reactions involving glyoxylic acid **1**.[32] If the above observations have predictive value, then the cyanohydrin adduct from these substrates (**33**, **36** and **39**, Scheme 7) are expected to hydrolyze only when pH is greater than 7 and not when pH is less than 7, since it is only the hydroxyl-group that has the correct 1,5-positional relation to the cyano-group.

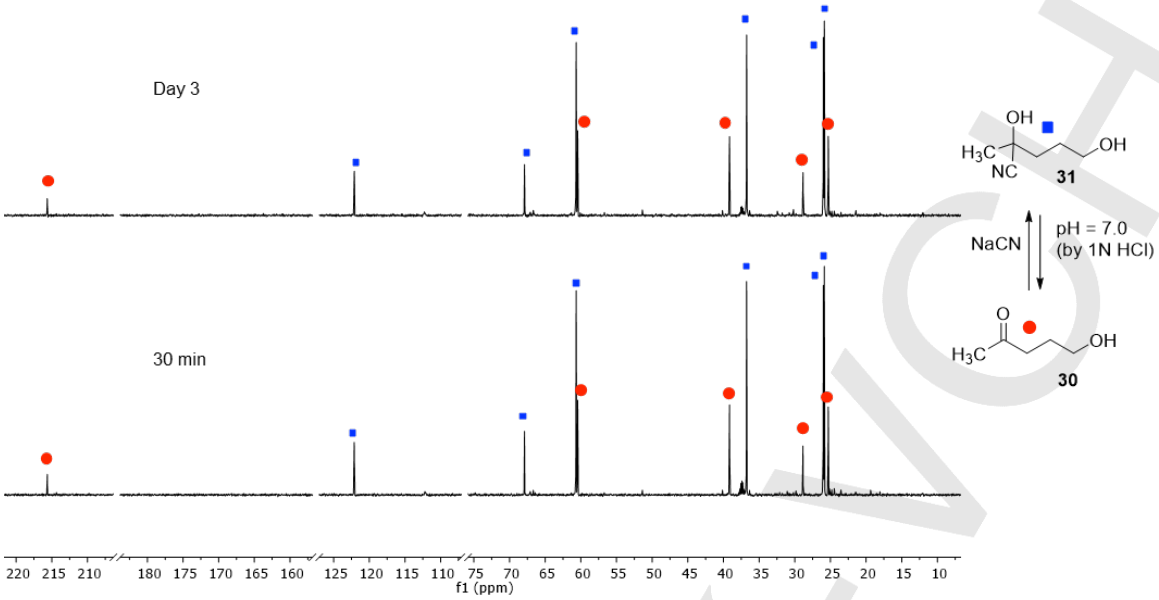
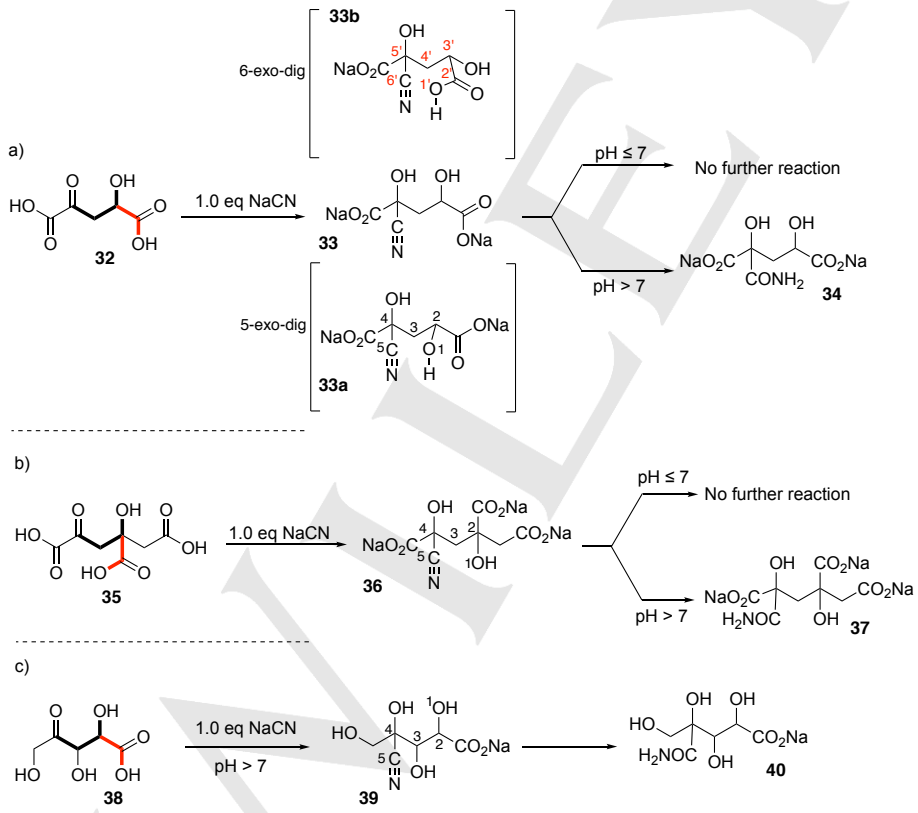


Figure 4. ^{13}C-NMR spectra (H_2O with DMSO-d_6) of the reaction of NaCN with 5-hydroxypentan-2-one **30** documenting the cyanohydrin formation with no further progress (hydrolysis to the corresponding amide).



Scheme 7. Reaction of NaCN with keto-substrates that contain both the hydroxyl group (with a 1,5-positional relationship) and the carboxylate group (with a 1,6-positional relationship) demonstrating the requirement of a 1,5-relationship for enabling the spontaneous hydrolysis of the cyano-group.

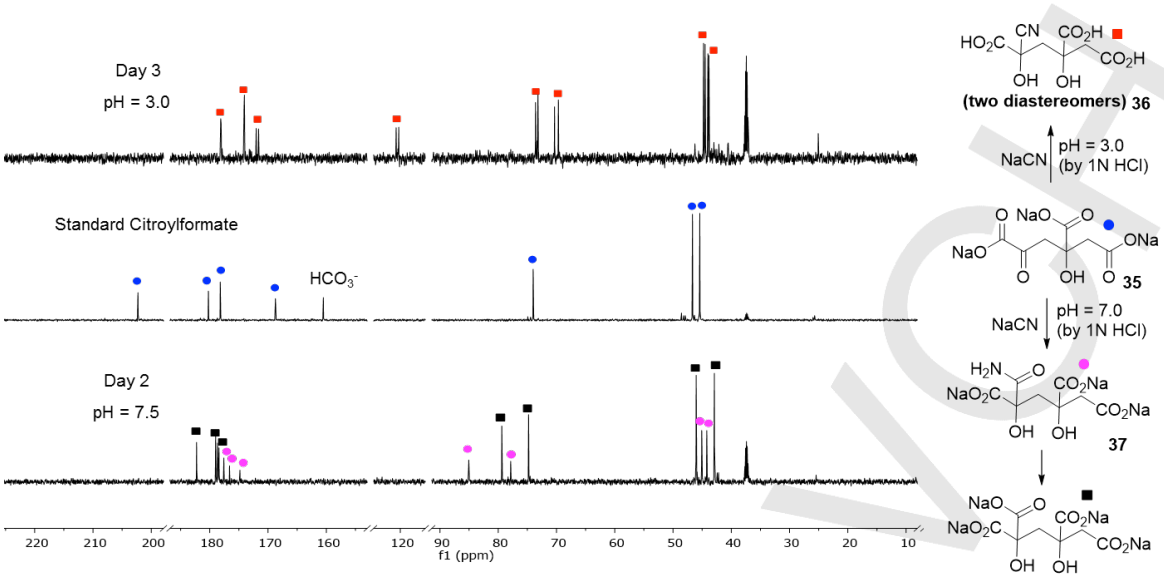
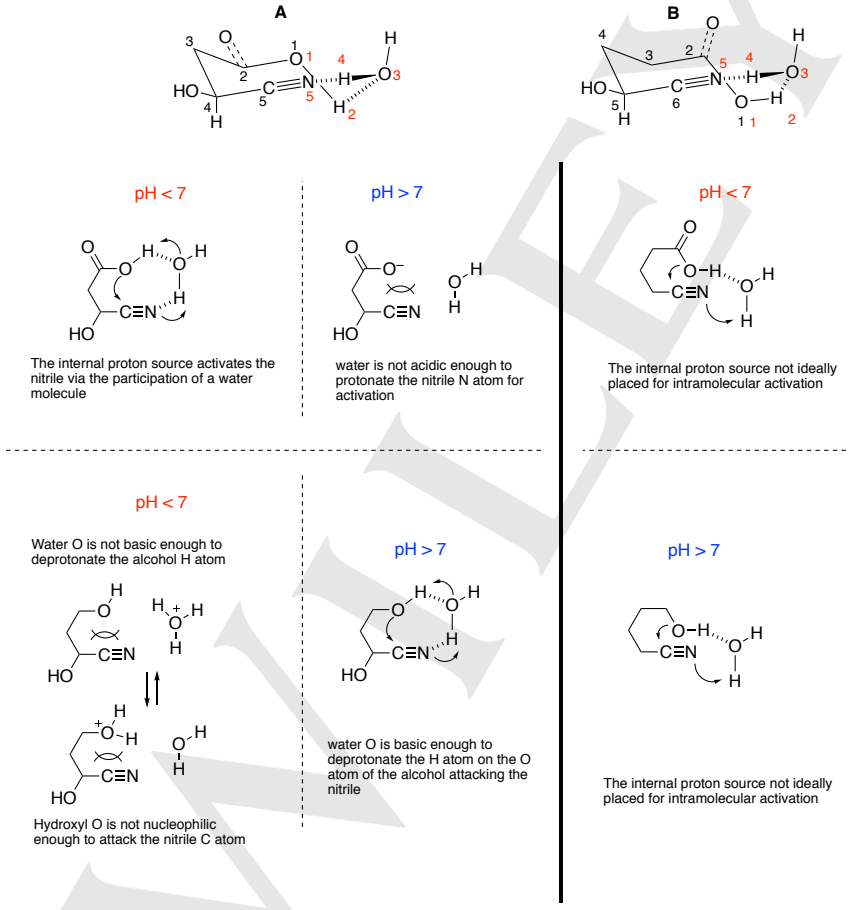
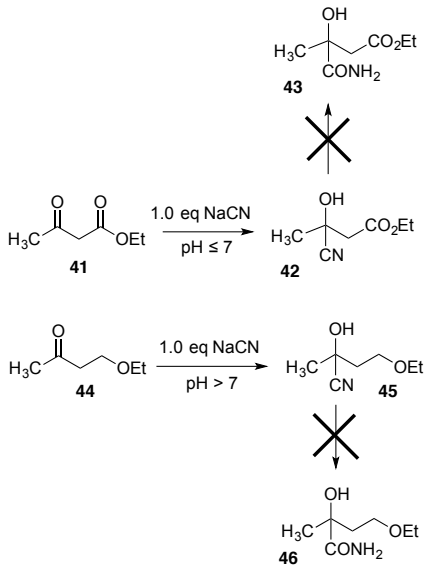


Figure 5. ^{13}C-NMR spectra (H_2O with DMSO-d_6) of the reaction of NaCN with (middle spectra) citroylformate **35**, documenting (top spectra) the cyanohydrin formation with no further progress at pH < 7 and (bottom spectra) the addition-followed-by-hydrolysis product at pH > 7.



Scheme 8. Rationalization of the pH dependence of the anchimeric assistance provided by the carboxylic acid group (pH < 7) and the alcoholic hydroxyl group (pH > 7), referring to (A) 5-exo-dig that does take place, and (B) 6-exo-dig attack that does not take place.



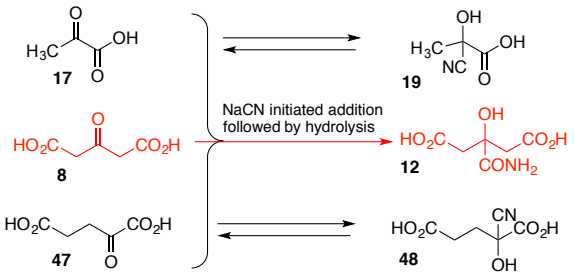
Scheme 9. Reaction of the ethyl acetotacetate **41** and 4-ethoxybutan-2-one **44** with NaCN forms only the corresponding cyanohydrin adduct with no further hydrolysis to the respective amides

Accordingly, two sets of reactions of **32** and **35** with NaCN, one at pH 3-4 and one at pH 7-8 and another at pH 13.0 were carried out (Scheme 7). With **38**, reactions only at pH > 7 were carried out, since at pH < 7 (pH ≈ 3) **38** was found to be unstable. In these cases, as predicted, hydrolysis of the cyanohydrin-adduct to the corresponding amides **34**, **37** and **40** was observed only when the pH was greater than 7 (Figure S39-S57). For example, in the case of hydroxy-acid **35**, the cyanohydrin-adduct **37** was formed under both the acidic and basic conditions, but hydrolysis to the amide was observed only when pH was greater than 7 (Figure 5); and, furthermore, even the corresponding acids were also observed (Figure S48-S50). This indicated that only the hydroxyl group which has a 1,5-positional relationship to the cyano-moiety of **33**, **36** and **39** participated in the intramolecular 5-*exo*-dig mediated hydrolysis leading to the corresponding amides (and even to the acids in certain cases). The carboxylate moiety, which has a 1,6-relationship, did not participate in this reaction. We wanted to check the 'reverse'-substrates with both a hydroxyl (with a 1,5-relationship to the keto group, leading to a 6-*exo*-dig attack) and a carboxylate group (with a 1,4-relationship to the keto group, leading to a 5-*exo*-dig cyclization). Here, the hydrolysis of the cyanide would be expected to occur only at pH ≤ 7 mediated by the carboxylic acid group, with the hydroxyl group not participating. Unfortunately, the substrates we considered proved unstable, and, therefore, we were unable to check the reverse-possibility.

Mechanism: The consistent effect of pH on determining which group provides the intramolecular anchimeric assistance – the carboxylic acid group aiding the hydrolysis of the cyano-group only at pH lower than 7 and not above, while the alcoholic-hydroxyl group hydrolyzing the cyano-group only at a pH greater than 7 and not below – suggests that there are two factors critical for the spontaneous hydrolysis of the cyanohydrin: (1) the proper positioning of the nucleophile for a 5-*exo*-dig attack, (2) and, more importantly, an *intramolecular proton mediated activation* of the nitrile from the *internal* carboxylic acid or the alcoholic-hydroxyl group, perhaps through the participation of a water molecule (Scheme 8A). This implies that just as the intramolecular nucleophilic attack is important, so is the activation of the cyano-group mediated by intramolecular (water-hydrogen bond mediated) proton transfer[46]. Involving a water molecule to mediate the internal-proton-transfer-activation results in a 5-membered transition state which may be more energetically favorable than a direct internal-proton-transfer-activation (a 4-membered transition state). This would involve two 5-membered rings (one for the nucleophilic attack and one for the proton transfer) as depicted in Scheme 8A. This postulate also suggests another plausible reason for the failure of cyanohydrins such as **21** (Scheme 5) and **31** (Scheme 6c) to react further. Apart from the previously pointed out 6-*exo*-dig requirement leading to an unfavorable *exo*-double bond on a developing six-membered ring transition state[40], the geometrical requirement for an internal proton activation may also not be that favorable; here, a 6-membered ring (6-*exo*-dig) required for the nucleophilic attack may distort the 5-membered ring geometry required for the internal proton transfer (Scheme 8B). And, without the internal-proton-transfer-activation of the cyano-group in **21** and **31**, the hydrolysis mediated by intramolecular attack of the oxygen nucleophile is not expected to happen. This line of argument seems to be in consonance with the literature data showing the necessity of metals[36-38] for activating the cyano-group to enable intramolecular 6-*exo*-dig nucleophilic attacks. We are currently pursuing computational studies (ab initio calculations) that would be able to shed more details of the proposed mechanism in Scheme 8.

That an internal proton source[46] is necessary to enable the spontaneous hydrolysis of cyano-group was tested with two substrates, ethyl acetoacetate **41**, and ethyl ether of butan-2-one **44**, where the protons have been replaced by ethyl groups, thus eliminating the internal proton source (Scheme 9). These two substrates should add the cyanide to form the corresponding cyanohydrin derivatives **42** and **45** respectively; but then there should be no further conversion (no spontaneous hydrolysis) even under the most favorable conditions (pH < 7 for **42** and pH > 7 for **45**)) to the corresponding amides **43** and **46**, if the internal proton source is necessary. And this is indeed what is observed by ^{13}C-NMR spectroscopy (Figures S58 and S59). Under the conditions where the cyanohydrin adducts **11** and **27** (which have the internal proton source) are found to hydrolyze spontaneously to afford the corresponding amides **12** and **29** in 5 days at room temperature, cyanohydrins **42** and **45** (which do not have the internal proton source) are stable as such (even after 15 days at r.t.), and do not form the corresponding amides **43** and **46** (Figure S58-S59). This observation supports the idea that the internal proton is *necessary* for the activation of the cyano-group, enabling the subsequent intramolecular oxygen nucleophilic attack for its conversion to the corresponding amide (and acid).

Implications in the context of prebiotic systems chemistry: Prebiotic systems chemistry has come to the forefront in recent years [14,47] and cyanide initiated reactions play a major role as exemplified by the work of Sutherland[13,15] and Powner[49]. In that context, the results presented here provide for selective transformations which would be important in prebiotic chemistry where generally mixtures of reactants and products co-exist.[33]



Scheme 10. Potential selective transformation of only the 1,3-acetone dicarboxylic acid **8** in the presence of pyruvic acid and α-ketoglutaric acid (a structural isomer of **8**).

The above results show that there is a difference and a preference in the cyanide initiated transformations – via addition to a carbonyl group to form cyanohydrin and the subsequent hydrolysis of the cyano-group – based on the structure and constitution of the starting compounds. For example, in a prebiotic mixture containing the acetone-1,3-dicarboxylic acid **8**, pyruvic acid **17**, and α-keto glutaric acid **47** (isomer of **8**), based on the above results one would expect that while **8**, in the presence of cyanide, would be transformed to the citric acid amide **12**, pyruvic acid **17** and α-ketoglutarate would remain as the respective cyanohydrin adducts **19** and **48** with no further transformation and could revert, back to the respective starting materials (Scheme 10). Thus, there is a distinct possibility that cyanide would be able to mediate selective transformations of substrates with appropriate anchimeric-assistance-capable-functional-groups within a given, prebiotically relevant [5,33,49], mixture of compounds – a direction of research that is under active investigation in our laboratory. The cleanliness of the conversions to α-hydroxy amides under very mild conditions can lend itself to applications in organic chemistry.[18-20]

Conclusions

The cyanide initiated addition to keto-acids and keto-alcohols is followed by a spontaneous intramolecular hydrolysis which exhibits interesting selectivity based on pH divergence and structural features. There is a strict preference for a 5-exo-dig (over a 6-exo-dig) mode of attack. Moreover, reactions with the keto-acids proceeds only under pH ≤ 7 while the reaction with keto-alcohols require a pH > 7. Such a bias enables a differentiation between a mixture of substrates, and is pertinent for facilitating selective transformations in cyanide initiated reactions in prebiotic systems chemistry.[14]

Experimental Section

Description of materials and experimental methods, NMR spectra, mass spectrometry data of isolated compounds, experimental comparison NMR spectra, quantitative NMR information, calculated yields, and chemical shift information are provided in the supporting information.

Acknowledgements

This work was jointly supported by NSF and the NASA Astrobiology Program under the NSF Center for Chemical Evolution, CHE-1504217. We thank Professor Ryan Shenvi for comments and feedback on the manuscript.

Keywords: Anchimeric Assistance • Spontaneous Hydrolysis of Cyanohydrins/Nitriles • α-Hydroxy Amides • Prebiotic Systems Chemistry

[1] V. Y. Kukushkin, A. J. L. Pombeiro, *Inorg. Chim. Acta* **2005**, *358*, 1-21.
[2] M.-X. Wang, *Acc. Chem. Res.* **2015**, *48*, 602-611.
[3] (a) P. M. Angus, W. G. Jackson, *Inorg. Chem.* **1994**, *33*, 1569-1571. (b) A. W. Parkins *Platinum Met. Rev.* **1996**, *40*, 169.
[4] N. K. Thallaj, J. Przybilla, R. Welter, D. Mandon, *J. Am. Chem. Soc.* **2008**, *130*, 2414-2415.
[5] Eschenmoser, A. *Chem. Biodiversity* **2007**, *4*, 554-573.
[6] J. P. Ferris, J. D. Wos, T. J. Ryan, A. P. Lobo, D. B. Donner, *Origins Life* **1974**, *5*, 153-157.
[7] J. Oro, *Nature* **1961**, *191*, 1193-1194.
[8] J. P. Ferris, W. J. Hagan Jr. *Tetrahedron* **1984**, *40*, 1093-1120.
[9] A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27-45.
[10] E. T. Parker, M. Zhou, A. S. Burton, D. P. Glavin, J. P. Dworkin, R. Krishnamurthy, F. M. Fernández, J. L. Bada, *Angew. Chem., Int. Ed.* **2014**, *53*, 8132-8136.
[11] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 2204-2205.
[12] A. S.; Serianni, H. A.; Nunez, R. Barker, *J. Org. Chem.* **1980**, *45*, 3329-3341.
[13] B. H. Patel, C. Percivalle, D. J. Ritson, C. D. Duffy, J. D. Sutherland, *Nat. Chem.* **2015**, *4,* 301-307.
[14] K. Ruiz-Mirazo, C. Briones, A. de la Escosura, *Chem. Rev.* **2014**, *114*, 285-366.
[15] J. D. Sutherland, *Angew. Chem., Int. Ed*. **2016**, *55*, 104-121.
[16] C. Butch, E. D. Cope, P. Pollet, L. Gelbaum, R. Krishnamurthy, C. L. Liotta, *J. Am. Chem. Soc.* **2013**, *135*, 13440-13445.
[17] C. J. Butch, J. Wang, J. Gu, R. Vindas, J. Crowe, P. Pollet, L. Gelbaum, J. Leszczynski, R. Krishnamurthy, C. L. Liotta, *J. Phys. Org. Chem.* **2016**, *29*, 352-360.
[18] N. C. Mamillapalli, G. Sekar, *Chem. Eur. J.* **2015**, *21*, 18584-18588.
[19] H. H. Wasserman, M. Xia, A. K. Petersen, M. R. Jorgensen, E. A. Curtis, *Tetrahedron Lett.* **1999**, *40*, 6163-6166.
[20] J. Stambasky, M. Hocek, P. Kocovsky, *Chem. Rev.* **2009**, *109*, 6729-6764.
[21] A. Eschenmoser, *Tetrahedron* **2007**, *63*, 12821-12844.
[22] S. C. Chang, Y. Ho, M. J. Weaver, *J. Am. Chem. Soc.* **1991**, *113*, 9506-9513.
[23] Z. Rappoport, *The Chemistry of the Cyano Group*; Interscience Publishers, 1970.
[24] J. L. Garcia Ruano, A. M. Martin Castro, J. H. Rodriguez, *J. Org. Chem* **1992**, *57*, 7235-7241.
[25] J. L. García Ruano, A. M. Martin Castro, J. H. Rodriguez Ramos, *Tetrahedron Lett.* **1996**, *37*, 4569-4572.

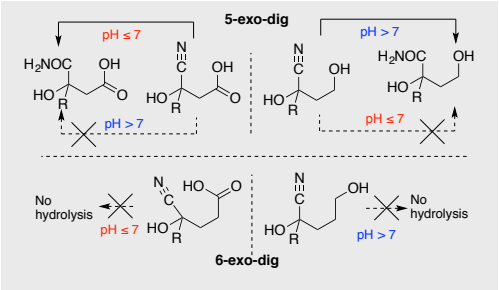
[26] T. J. Ahmed, B. R. Fox, S. M. M. Knapp, R. B. Yelle, J. J. Juliette, D. R. Tyler, *Inorg. Chem.* **2009**, *48*, 7828-7837.
[27] R. M. Smyth, A. *J.* Williams, *Chem. Soc., Perkin Trans. 2* **1993**, 2171-2174.
[28] J. Jammot, R. Pascal, A. Commeyras, *Tetrahedron Lett.* **1989**, *30*, 563-564.
[29] J. Jammot, R. Pascal, A. Commeyras, *J. Chem. Soc., Perkin Trans.2* **1990**, 157-162.
[30] R. Pascal, J. Taillades, A. Commeyras, *Tetrahedron* **1978**, *34*, 2275-2281.
[31] R. Pascal, J. Taillades, A. Commeyras, *Tetrahedron* **1980**, *36*, 2999-3008.
[32] V. N. Sagi, V. Punna, F. Hu, G. Meher, R. Krishnamurthy, *J. Am. Chem. Soc.* **2012**, *134*, 3577-3589.
[33] G. Cooper, C. Reed, D. Nguyen, M. Carter, Y. Wang, *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14015-14020.
[34] X. V. Zhang, S. T. Martin, *J. Am. Chem. Soc.* **2006**, *128*, 16032-16033.
[35] M. I. Guzman, S. T. Martin, *Chem. Commun.* **2010**, *46*, 2265-2267.
[36] A. Saito, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2014**, *55*, 3167-3171.
[37] B. Jiang, R. Fu, J.-K. Qiu, Y. Yu, S.-L. Wang, S.-J. Tu, *RSC Adv.* **2016**, *6*, 74372-74375.
[38] P. Prasanna, S. Perumal, J. C. Menendez, *Green Chem.* **2013**, *15*, 1292-1299.
[39] J. H. Peet, B. W. Rockett, *Chem. Commun. (London)* **1968**, 120a.
[40] H. C.; Brown, J. H. Brewster, H. Shechter, *J. Am. Chem. Soc.* **1954**, *76*, 467-474.
[41] D. L. Williams, T. W. Whaley, *J. Labelled Compd. Radiopharm.* **1982**, *19*, 669-679.
[42] H. S. Isbell, J. V. Karabinos, H. L. Frush, N. B. Holt, A. Schwebel, T. T. Galkowski, *J. Res. Natl. Bur. Stand. (U.S.)* **1952**, *48*, 163-171.
[43] M. F. Aldersly, A. J. Kirby, P. W. Lancaster, J. *Chem. Soc., Chem. Commun*. **1972**, 570-571.
[44] R. H. Wiley, K. S. Kim, *J. Org. Chem.* **1973**, *38*, 3582-3585.
[45] C. V. Ramana, A. Vasella, *Helv. Chim. Acta* **2000**, *83*, 1599-1610.
[46] S. A. Benner, *Tetrahedron Lett.* **1981**, *22*, 1855-1858.
[47] S. Chitale, J. S. Derasp, B. Hussain, K. Tanveer, A. M. Beauchemin, *Chem. Commun.* **2016**, *52*, 13147-13150
[48] H. J. Morowitz, J. D. Kostelnik, J. Yang, G. D. Cody, *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7704-7708.
[49] S. Islam, D.-K. Bučar, M. W. Powner, Nat. Chem. 2017, advance online publication. doi:10.1038/nchem.2703

10.1002/chem.201701497

WILEY-VCH

FULL PAPER

Selection by Hydrolysis. Cyanide initiated addition followed by hydrolysis could be useful tool to select among a set of substrates.



Jayasudhan Reddy Yerabolu[1,3], Charles L Liotta[2,3], Ramanarayanan Krishnamurthy[1,3]**

Page No. – Page No.

Anchimeric-assisted Spontaneous Hydrolysis of Cyanohydrins Under Ambient Conditions: Implications for Cyanide Initiated Selective Transformations.