



# Discovery of redox system enabling C–N–C bonds formation: Unprecedented Aza-Cannizzaro reaction



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## ABSTRACT

A novel reaction involving *in situ* redox conversion of glyoxylate esters to glycine is described. Simple starting materials and mild conditions for the synthesis of glycine derivatives probably indicate a pathway towards prebiotic chemistry. This proceeds analogous to Cannizzaro reaction involving ammonia therefore it can be termed as intramolecular Aza-Cannizzaro type reaction. This reaction is examined in detail with an aid of computational analysis to corroborate the proposed mechanism.

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## Introduction

The Miller-Urey experiment simulated probable conditions present on early earth and demonstrated the presence of basic building blocks of life.

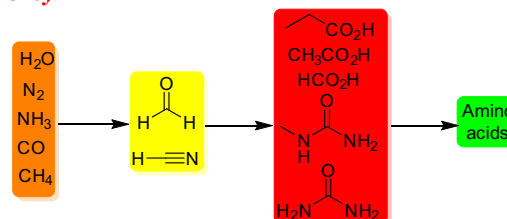
In essence, this experiment (Fig. 1) established emergence of amino acids and led credence to hypothesize that complex organic molecules can be derived from these simple building blocks.

Thus, it was proposed that the origin of life was not from anywhere else but from a chemical reaction that first afforded five amino acids.<sup>1</sup> Reanalysis of original reaction mixture of Miller-Urey's experiment which was performed in 2008 in fact revealed that there were twenty amino acids synthesized in one single experiment proves the origin of life hypothesis by chemical evolution.<sup>2</sup>

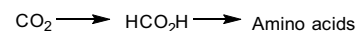
In this context there are several hypotheses leading to the synthesis of amino acid in the primordial atmospheric conditions prevailing on early earth. Reduction of CO<sub>2</sub> to formic acid in aqueous solution (Fig. 1) was demonstrated by Calvin et al. that indicates one carbon source reactive species towards amino acids.<sup>3</sup>

HCN was also investigated and found to be a source of amino acid due to basic hydrolysis (Fig. 1).<sup>4</sup> Few other hypotheses on the prebiotic origin of life have been postulated by various groups.<sup>5</sup>

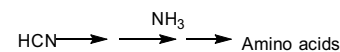
### Miller-Urey



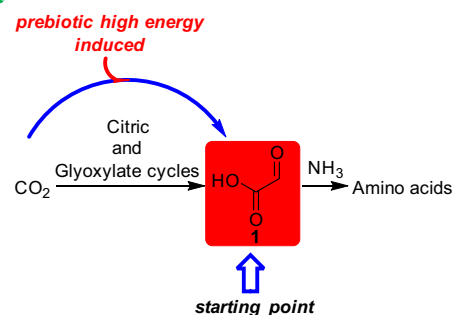
### Calvin



### Karat



### This work



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Fig. 1. Primordial conceived approaches for amino acids.

Here in, we report that glyoxylic acid **1** is an amino acid backbone which can be synthesized by nature starting from CO<sub>2</sub> via citric acid and glyoxylate cycles or under highly energetic conditions may be one of the sources of amino acids in prebiotic era (Fig. 1). We hypothesized that the amino acids can be accessed via redox event on glyoxylic acid **1** leading to glycine **2** and oxalic acid **3** as shown in Fig. 2.

In order to validate our hypothesis we turned our focus to understand the mechanistic aspect of Cannizzaro reaction, first discovered in 1853, is a base induced disproportionation of an aldehyde **4** leading to the formation of an oxidation product **6** and its reduced counterpart **5** (Fig. 2). Thus a salt of carboxylic acid and an alcohol are obtained as the products of this reaction. For this reaction to proceed successfully it is required that there should not be any hydrogen atom at alpha position to the aldehyde functionality, otherwise Aldol condensation product is preferably obtained.<sup>6</sup>

To the best of our knowledge, there are no reports outlining the imine taking part in these reactions instead of the carbonyl functionality. In this report we disclose a Cannizzaro type reaction for the first time in which the esters of glyoxylic acid undergo an *in situ* disproportionation in the presence of ammonium acetate leading to dimeric product bridged through imine functionality as shown in Scheme 1.

Reaction proceeds through imine intermediate **7** which further reacted with another equiv. of ethyl glyoxylate to yield atom efficient derivative **8**. There is fascinating aspect of atom convergency in the redox event leading to the intermediate **9**. In general, imine reduction requires hydride/metal-hydrogen source however in this case intermediate **8** undergoes oxidation of secondary hydroxyl to ketone and the liberated hydrogen gets accommodated in reduction of imine without any external assistance of metal. Eventually,

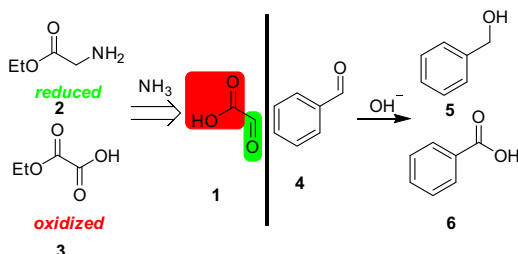
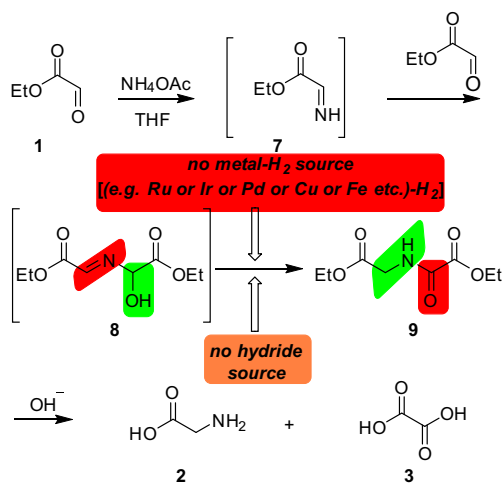


Fig. 2. Redox chemistry on ethyl glyoxylate and Cannizzaro reaction.



Scheme 1. Synthesis of glycine **2**.

it was possible to access amino acid backbone containing intermediate **9** which has further been converted to glycine **2** and oxalic acid **3** as evocative of Cannizzaro reaction. Although we conceived that this novel transformation was similar to Cannizzaro reaction, we were not assured of operating mechanism. It is being first of its kind we attempted to probe it with an aid of computational analysis aiming to find out which one of the two reaction pathways is favoured from energy standpoint as shown in Fig. 3.

Energy barriers were ascertained by the DFT calculations performed with the Dmol3 module of Accelrys MS using a local density approximation, the exchange-correlation local functional PWC.<sup>7</sup> Dmol<sup>3</sup> uses numerical orbitals for the basic functions, each function corresponding to an atomic orbital (AO). Double numerical plus d-functions (DND), it is like DN with a polarization d-function on all non-hydrogen atoms (Fig. 4).

This is the default basic set, providing reasonable accuracy for modest computational cost. The final energies were extrapolated to zero smearing. Transition states (TS) of Aza Cannizzaro reaction were located with the nudged elastic band method.<sup>8</sup> We calculated reaction and activation energies in gas phase. Each of the TS structures presented was probed by a normal-mode analysis to ensure that it indeed exhibited only one vibrational mode with an imaginary frequency. However, there might be an energy difference of ~20–30 kJ/mol if we change the methods used in calculations for TS.

In the computational analysis, we considered both the following reaction mechanism; paths **a** and **b** for this novel Aza-Cannizzaro reaction. Path **a** will be a concerted [1,3]-H shift reaction when compared to a stepwise reaction as elucidated in path **b**.

Calculations lead to a new intermediate stable state which is not shown in path **a**, wherein we observed the formation of water molecule, even before achieving the step 1 stable state as shown in path **a** of Fig. 3. Hydrogen atom (H1) located on carbon, first forms a water molecule with an energy barrier of 257 kJ/mol, with the adjacent OH group and then dissociates from water molecule again with approximately similar energy barrier and adds to other carbon atom leading to step 1 as shown in path **a**. Accordingly the double bond of nitrogen shifts satisfying the valency. Final product was formed starting from intermediate stable state (InS2) where the hydrogen of hydroxyl group attacks nitrogen with an energy barrier of 278 kJ/mol. However, the reaction is 142 kJ/mol exothermic and above reaction pathway carries three transition states with ~250 kJ/mol barriers (Fig. 5) that made us think and redesign path **a** leading to path **b**. Different transition states of it is elucidated in Fig. 6 and energy landscape in Fig. 7.

Based on reaction energy landscape shown in Fig. 6, path **b** is the desired reaction pathway with lower and lesser activation bar-

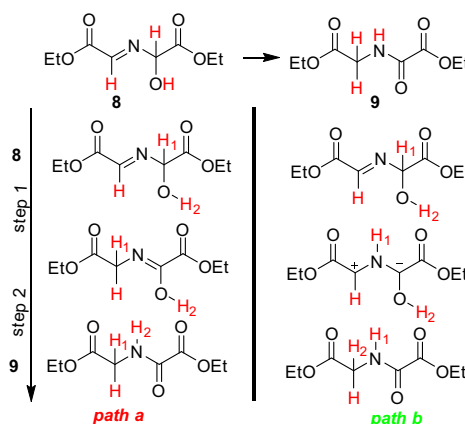


Fig. 3. Two different reaction pathways (**a** and **b**).

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