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Exploring the Role and Reaction Constraints of Malonate within the Context of the “Glyoxylate Scenario”

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Introduction: Malonate has been demonstrated to be the common denominator in the abiotic degradation of numerous organic acids [1]. This inherent stability of malonate and the fact that it is used by current biology in processes like fatty acid biosynthesis [2] suggests an evolutionary persistence. We were interested in whether malonate could have played a role in the “glyoxylate scenario” [3][4], producing prebiotic metabolites for the synthesis of biogenic molecules [5].

Malonate combines cleanly with glyoxylate in an aldol addition reaction, one of the most important carbon-carbon bond forming reactions in current biology, at neutral pH (pH = 7) at 50 °C within approximately 24 hours. A key interest of ours, that will be presented, is understanding why clean aldol addition products are observed at neutral pH given malonate’s relatively low α -carbon acidity ($pK_a = 13-16$). Additionally, the reactivity of enolate nucleophiles is expected to increase with increasing pH of the solution, but our preliminary results indicate diminished reaction rates at elevated pH. One hypothesis that is being explored is the formation of a Meldrum’s acid-like cyclic acetal intermediate which would be anticipated to drastically reduce the pK_a of the α -carbon on malonate [6], and increase its nucleophilicity at neutral pH (Figure 1a). The potential of Lewis acids to influence the nucleophilicity of malonate in this aldol reaction (Figure 1b) is also being investigated. The presentation will highlight our findings toward better understanding roles and specific reaction constraints of the aldol addition between malonate and glyoxylate within a prebiotic environment.

[1] Rice, G.B.; Yerabolu, J.R.; Krishnamurthy, R. and Springsteen, G. (2016) *Synlett* 28:98–102. [2] Garret, R.H. and Grisham, C.M. *Biochemistry* 2nd ed.; Harcourt, Inc.: Orlando, 1995. [3] Koch, K.; Schweizer, W.B. and Eschenmoser, A. 2007. *Chemistry & Biodiversity* 4: 541–553. [4] Eshenmoser, A. 2007. *Tetrahedron* 63: 12821–12844. [5] Sagi, V.N. et al. 2012. *Journal of the American Chemical Society* 134: 3577–3589. [6] Wang, X. and Houk, K.N. 1988. *Journal of the American Chemical Society* 110: 1870–1872.

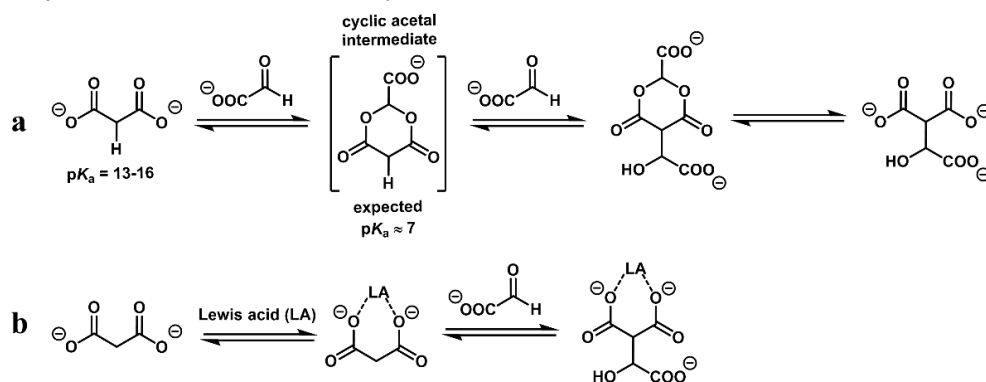


Figure 1 – Possible prebiotically relevant methods that the aldol addition of malonate and glyoxylate might be influenced by (a) formation of a cyclic acetal intermediate or (b) through coordination to a Lewis acid.