KINETICS OF ORGANIC TRANSFORMATIONS UNDER MILD AQUEOUS CONDITIONS: IMPLICATIONS FOR THE ORIGIN OF LIFE AND ITS METABOLISM

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Abstract. The rates of thermal transformation of organic molecules containing carbon, hydrogen, and oxygen were systematically examined in order to identify the kinetic constraints that governed origin-of-life organic chemistry under mild aqueous conditions. Arrhenius plots of the kinetic data were used to estimate the reaction of half-lifes at 50 °C. This survey showed that hydrocarbons and organic substances containing a single oxygenated group were kinetically the most stable; whereas organic substances containing two oxygenated groups in which one group was an α- or β-positioned carbonyl group were the most reactive. Compounds with an α- or β-positioned carbonyl group (aldehyde or ketone) had rates of reaction that were up to 10^{24}-times faster than rates of similar molecules lacking the carbonyl group. This survey of organic reactivity, together with estimates of the molecular containment properties of lipid vesicles and liquid spherules, indicates that an origins process in a small domain that used C,H,O-intermediates had to be catalytic and use the most reactive organic molecules to prevent escape of its reaction intermediates.

Keywords: kinetics, reactivity, carbonyl group, metabolism, biosynthesis, sugar chemistry, diffusion, prebiotic synthesis, molecular evolution

1. Introduction

Previously we examined the free energy of carbon group transformations to identify the thermodynamic constraints governing aqueous organic transformations involved in the origin of life and metabolism under mild aqueous conditions (Weber, 2002). As a first step in understanding the kinetic constraints that would have governed the organic chemistry of an origin-of-life process under mild aqueous conditions, we here examine the rates of transformation of organic molecules containing only carbon, hydrogen, and oxygen. This comparative examination of the reactivity of organic molecules reveals how specific functional groups and their positioning effect organic transformation rates. Estimation of reaction rates at 50 °C was accomplished by extrapolation using Arrhenius plots of rate constants obtained from the chemical literature (references listed in Table I). The types of reactions examined include: decarboxylation, dehydration, decarbonylation, reduction-oxidation, aldolization, hydrolytic deacylation, isomerization, and dehydrogenation. Knowledge of the kinetics of organic transformations contributes

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to understanding the chemistry of (1) the first stage in the origin-of-life process that was determined by the energy and rates of uncatalyzed prebiotic reactions, and (2) the earliest autocatalytic stage in the origin-of-life process where self-synthesis had to be faster than escape of reaction intermediates from the catalytic domain. Knowledge of the rates of organic transformations also provides a framework for evaluating the plausibility of models of biogenesis based on the chemistry of core metabolic processes that use C,H,O-intermediates (Austin and Waddell, 1999; Buvet, 1977; Eakin, 1963; Hartman, 1975; Morowitz *et al.*, 2000; Morowitz *et al.*, 1995; Wachtershauser, 1992; Weber, 1987b, 1991, 1998, 2001a, b, 2002). In related studies Melendez-Hevia *et al.* (1996, 1997) examined the crucial role of organic reactivity in the design of metabolic pathways during evolution.

2. Methods

2.1. Estimation of reaction half-lifes and rate constants

The first-order rate constants (k_1) of unimolecular reactions that reported the yield of a product at a given time were estimated from the equation of a semi-log plot of the fraction of reactant remaining versus time using the computer application, KaleidaGraph 3.5 (Synergy Software). First-order rate constants and their half-lifes were interconverted using the expression: $k_1 = \ln 2/t_{1/2}$ (Moore, 1983a). Rate constant upper limits (half-life lower limits) of reactions showing no measurable substrate transformation were calculated by assuming a maximum product yield equal to the estimated detection limit of the analytical method (1% for GC/MS, and 5% for other methods).

The second-order rate constants (k_2) of bimolecular reactions (self-reactions) were estimated using the expression: $k_2 = x/at(a\text{-}x)$, where a is the initial concentration of the reactant, and x is the concentration of reactant converted to product at time t. The half-lifes were adjusted to 0.01 M initial reactant concentration using the rate constant (k_2) and the relationship: $t_{1/2} = 1/k_2a$ (Moore, 1983a).

Rate constants at 50 °C were estimated from the equation of an Arrhenius semi-log plot of the rate constant versus 1000/absolute temperature using the computer application, KaleidaGraph 3.5 (Synergy Software). Measurements at two or more temperatures were required to estimate the reaction rate at 50 °C.

Since the equilibrium constant is equal to the ratio of the rate constants of the forward (k_1) and backward (k_{-1}) reactions: $K_{eq} = k_1/k_{-1}$ (Moore, 1983a), the reverse rate of reactions described here can be estimated from their forward reaction rate and the equilibrium constant derived from their free energy (Weber, 2002).

TABLE I

Rates of decomposition of organic compounds

Group type (R = H or hydrocarbon) Example reactants	Type of reaction [a]	Conditions ($t_{1/2}$ at given temp.) [b, c]	$t_{1/2}$ at 50 °C [d]	References
HOOC–COOH				
1. oxalic acid	decarbox.	0.5 M aq. 132, 144, 152, 164, 174 °C (12.6 3.25, 1.45, 0.43, 0.17 h)	200 y	(Lutgert and Schroer, 1940)
2. oxalate^{-2}	decarbox	0.5 M aq 160 °C [2.28 d]		(Dinglinger and Schroer, 1937)
R–CO–COOH				
3. pyruvic acid	decarbox.	0.25 M aq. 210, 220, 230, 240 °C (257, 224, 187, 161 s)	0.2 d	(Belsky *et al.*, 1999)
4. pyruvate	decarbox.	0.25 M aq. 220, 230, 240 °C (1000, 856, 630 s)	6.3 d	(Belsky *et al.*, 1999)
5. glyoxylate	decarbox.	5 mM aq. 25 °C–buf. pH 8 [>123 d]		(Halliwell and Butt, 1972)
6. benzoylformic acid	decarbox., decarbon.	0.9 M aq. 200 °C [5.72 d]		(Katritzky *et al.*, 1990b)
>COH–COOH				
7. lactic acid	decarbox., dehydr., decarbon.	0.4 M aq. 320, 340, 360, 380, 400 °C [1940, 1020, 358, 134, 78 s]	10^6 y	(Lira and McCrackin, 1993)
8. lactic acid	decarbox., dehydr., decarbon.	0.1 M aq. 350, 365, 375, 385, 400 °C [168, 91, 66, 38, 24 s]	10^5 y	(Mok *et al.*, 1989)
9. lactate	decarbox., dehydr., decarbon.	0.1 M aq. 385 °C [263 s]		(Mok *et al.*, 1989)
10. 3-deoxy-mannonic acid	decarbox., other react.	0.05 M aq. 340 °C (100 s)		(Luijkx *et al.*, 1995)
11. mandelic acid	decarbox., decarbon.	0.9 M aq. 200, 250 °C [8.6, 1.7 d]	10^5 y	(Katritzky *et al.*, 1990b)
≥C–CR_2–COOH				
12. acetic acid	decarbox.	1.0 M aq. 400, 422, 440 °C (170, 40, 16 d)	10^{20} y	(Palmer and Drummond, 1986)
13. acetate	decarbox.	1.0 M aq. 340, 359, 389 °C (51, 16, 2.6 d)	10^{18} y	(Palmer and Drummond, 1986)
14. 1-decanoic acid	no reaction	0.8 M aq. 250 °C [13.5 d–lower limit]		(Siskin *et al.*, 1990a)
15. benzoic acid	decarbox.	1.2 M aq. 350 °C–6 h [174 d]		(Katritzky *et al.*, 1990c)
16. phenylacetic acid	decarbox.	1.0 M aq. 250 °C–5 d [4.74 y]		(Katritzky *et al.*, 1990a)
17. γ-hydroxybutyric acid	no reaction	0.1 M aq. 385 °C [30 s–lower limit]		(Mok *et al.*, 1989)
HOOC–CR_2–COOH				
18. malonic acid	decarbox.	aq. 120, 160, 190, 210 °C (1350, 31, 2.9, 1.0 s)	46 d	(Maiella and Brill, 1996)
19. malonate^{-1}	decarbox.	aq. 120, 160, 190, 210 °C (1380, 43, 5.4, 1.4 s)	71 d	(Maiella and Brill, 1996)
20. malonate^{-2}	no reaction	0.5 M aq. 125 °C [48 h–lower limit]		(Fairclough, 1938)
>COH–CR_2–COOH				
21. 2-deoxy-gluconic acid	decarbox., other react.	0.05 M aq. 340 °C (20 s)		(Luijkx *et al.*, 1995)
22. β-hydroxybutyric acid	dehydr.-decarbox.	0.1 M aq. 385 °C–32 s [13 s]		(Mok *et al.*, 1989)
23. malate^{-1}	dehydr.	2 mM aq. 175 °C–buf. pH 5 (8.0 d)		(Bender and Connors, 1962)
–CO–CO–				
24. glyoxal	intramol. redox	0.02–20 mM aq. 50 °C–pH 9, 10, 11 (5.8, 0.40, 0.036 h)	(37 d–pH 7)	(Fratzke, 1986)
25. pyruvaldehyde	intramol. redox	1 mM aq. 180, 200, 220, 240 °C (462, 231, 109, 41 s)	(21 d)	(Bonn *et al.*, 1985)
26. pyruvaldehyde	intramol. redox	0.03 M aq. 20 °C [3.5 d]		(Weber, 1982)
27. phenylglyoxal	intramol. redox	0.06 mM aq. 35 °C–pH 7 [3.0 y]		(Hine and Koser, 1971)
>COH–CO–				
28. glycolaldehyde (see Table II for sugars)	aldol.	0.03 M aq. 50 °C–pH 6 [285 d–0.01 M bimol]	285 d	(Weber, 2001a)
≥C–CO–				
29. 2-decanone	aldol.-dehydr.	0.9 M aq. 250 °C [175 y–0.01 M bimol]		(Siskin *et al.*, 1990a)
	no hydro. deacylation	0.9 M aq. 250 °C [1.0 yr unimol–lower limit]		
30. cyclohexyl-phenyl-ketone	no reaction	0.8 M aq. 250 °C [5.5 d–lower limit]		(Siskin *et al.*, 1990b)
31. acetophenone	aldol.-dehydr.	1.2 M aq. 250 °C [101 y–0.01 M bimol]		(Katritzky *et al.*, 1990d)

TABLE I
(Continued)

Group type (R = H or hydrocarbon) Example reactants	Type of reaction [a]	Conditions ($t_{1/2}$ at given temp.) [b, c]	$t_{1/2}$ at 50 °C [d]	References
32. acetaldehyde	aldol.-dehydr., decarbon. (2.5/1)	0.5 M aq. 385 °C [1.9 h–0.01 M bimol] and [262 s–unimol]		(Ramayya *et al.*, 1987)
33. 1-decanal	aldol.-dehydr., intermol. redox, decarbon. (45/1)	0.9 M aq. 250 °C [15 d–0.01 M bimol]		(Siskin *et al.*, 1990a)
34. phenylacetaldehyde	aldol.-dehydr.	1.2 M aq. 100 °C [248 d–0.01 M bimol]		(Katritzky *et al.*, 1990a)
35. benzaldehyde	intermol. redox	1.3 M aq. 250 °C [151 d–0.01 M bimol]		(Katritzky *et al.*, 1990c)
>COH-COH<				
36. ethylene glycol	radical fragm.	0.5 M aq. 385 °C [419 s]		(Ramayya *et al.*, 1987)
37. glycerol	dehydr., radical fragm.	aq. 500 °C [162 s]		(Antal *et al.*, 1985)
38. phenylethane-1,2-diol	dehydr.-aldol.	1.0 M aq. 200 °C [1.8 h]		(Katritzky *et al.*, 1990b)
≥C–COH<				
39. ethanol	dehydr., dehydrog., radical fragm.	1.0 M aq. 500 °C [2260 s]		(Ramayya *et al.*, 1987)
40. n-propanol	dehydr., radical fragm.	1.0 M aq. 500 °C [345 s]		(Ramayya *et al.*, 1987)
41. 1-decanol	intermol. redox-decarbon., dehydr. (7/1)	0.9 M aq. 250 °C [498 y–0.01 M bimol] and [3.1 y–unimol]		(Siskin *et al.*, 1990a)
42. t-butanol	dehydr.	0.05 M aq. 225, 250, 320 °C [142, 57, 3 s]	4.1 y	(Xu *et al.*, 1994, 1997)
43. cyclohexanol	dehydr.	0.05 M aq. 300 °C [6230 s]		(Kuhlmann *et al.*, 1994)
44. 2,2-dimethyl-propanol	no reaction	0.5 M aq. 300 °C [1 h–lower limit]		(Kuhlmann *et al.*, 1994)
45. pentaerythritol	no reaction	0.5 M aq. 300 °C [1 h–lower limit]		(Kuhlmann *et al.*, 1994)
46. 1,4-butanediol	no reaction	0.1 M aq. 250 °C [100 s–lower limit]		(Antal *et al.*, 1990)
47. benzyl alcohol	intermol. redox	1.2 M aq. 250 °C [13 d–0.01 M bimol]		(Katritzky *et al.*, 1990c)
48. 2-phenylethanol	dehydr.	1.3 M aq. 250 °C [313 d]		(Katritzky *et al.*, 1990a)
≥C–C≤				
49. cyclohexylbenzene	no reaction	0.9 M aq. 250 °C [5.5 d–lower limit]		(Siskin *et al.*, 1990b)
50. (cyclohexylmethyl)-benzene	no reaction	0.8 M aq. 250 °C [5.5 d–lower limit]		(Siskin *et al.*, 1990b)
51. benzene	no reaction	1.8 M aq. 250 °C [5 d–lower limit]		(Katritzky *et al.*, 1990c)
52. toluene	no reaction	1.6 M aq. 350 °C [14 d–lower limit]		(Katritzky *et al.*, 1990c)
53. ethylbenzene	radical fragm.	1.3 M aq. 250 °C [1316 d]		(Katritzky *et al.*, 1990d)
54. 1-decene	dimeriz., isomeriz. (1/1)	1.0 M aq. 250 °C [36 y–0.01 M bimol] and [93 d unimol]		(Siskin *et al.*, 1990a)
One carbon cmpd.				
55. formic acid	decarbox., dehydr.	1.0 M aq. 290, 300, 310, 320 °C (385, 248, 198, 177 s)	310 d	(Maiella and Brill, 1998)
56. formic acid	decarbox., dehydr.	2–15 mM aq. 320, 340, 360, 380, 420 °C (14, 7.1, 5.5, 4.2, 1.0 s)	325 d	(Yu and Savage, 1998)
57. formate	no reaction	1.0 M aq. 320 °C [35 sec–lower limit]		(Maiella and Brill, 1998)
58. formaldehyde	intermol. redox	4.5 M aq. 250 °C (1.2 h)		(Tsujino *et al.*, 1999)
59. formaldehyde	$CO + CO_2 + H_2$	0.25 M aq. 385 °C (8.8 s)		(Ramayya *et al.*, 1987)
60. formaldehyde	no reaction	0.1 M aq. 100 °C [16 h–lower limit]		(Schwartz and de Graaf, 1993)
61. methanol	no reaction	1.0 M aq. 500 °C [60 s–lower limit]		(Ramayya *et al.*, 1987)
62. methane	dehydrog.	gas at 800, 900, 1000 °C (108, 34, 4 h)	10^{19} y	(Sackett, 1995)

[a] Abbreviations: decarboxylation (decarbox.), decarbonylation (decarbon.), dehydration (dehydr.), intramolecular reduction-oxidation (intramol. redox), aldolization (aldol.), intermolecular reduction-oxidation (intermol. redox), radical fragmentation (radical fragm.), dehydrogenation (dehydrog.), dimerization (dimeriz.), hydrolytic deacylation (hydro. deacylation). Reactions joined by a dash are sequential. The pathway relationships of reactions separated by a comma are unspecified. In a few cases the ratio of bimolecular to unimolecular reactions is given at the end of the reaction list.

[b] Half-lifes enclosed in parentheses were calculated from measured reaction rate constants (see Methods for all calculations).

[c] Half-lifes enclosed in brackets were estimated from product yields. Half-life lower limits ($t_{1/2}$-lower limit) were calculated for non-reactions where no product was detected. Bimolecular (biomol) half-lifes were calculated assuming a 0.01 M initial reactant concentration.

[d] Half-lifes at 50 °C were estimated by extrapolation using Arrhenius plots.

2.2. Estimation of the escape half-life at 50 °C of small organic molecules from a bilayer lipid vesicle

Equation (E1) below derived from the expression (J = PA[S], Deamer and Bramhall, 1986a) was used to estimate the first order rate constant of escape (efflux) of a small organic molecule (glycerol) from a bilayer lipid vesicle. Equation (E1) describes the rate of change of solute concentration within the vesicle as a first order process with rate constant ($k_{escape} = PA/V$). The escape rate constant (k_{escape}) at 25 °C of glycerol from a vesicle having a 0.005 cm radius was 3.24×10^{-3} sec^{-1} ($t_{1/2} = 214$ sec) estimated from glycerol's membrane permeation coefficient (5.4×10^{-6} cm sec^{-1}, Walter and Gutknecht, 1986). The escape half-life at 50 °C of glycerol was 19 seconds estimated from glycerol's average permeation activation energy (18.6 kcal/mol, Cohen, 1975; de Gier *et al.*, 1971; Deuticke, 1977). Organic acids are expected to have comparable escape half-lifes (Walter and Gutknecht, 1986).

$$J/V = PA/V[S], \tag{E1}$$

where J is the flux (moles sec^{-1}), V is the vesicle's volume (cm^3), P is the membrane permeability coefficient (cm sec^{-1}), A is the membrane's area (cm^2), and [S] is the solute concentration inside the vesicle (moles/cm^3). This relationship applies only when the rate of equilibration of the solute concentration in the vesicle is much faster than the rate of escape. Rapid equilibration is supported by the fact that a small molecule like glycerol travels an average distance equal to the vesicle's radius (0.005 cm) in only 0.25 seconds as estimated from the 3D-diffusion expression ($x^2 = 6Dt$, Kruk *et al.*, 1997), and the Stokes–Einstein equation ($D = RT/6\pi\eta r$, Swindells, 1985) using the aqueous diffusion coefficient of glycerol at 25 °C (D_{aq}-25 °C = 0.93×10^{-5} cm^2/sec, Hayduk and Laudie, 1974), and the viscosity of water at 25 °C and 50 °C (Swindells, 1985).

2.3. Calculation of the escape half-lifes at 50 °C of small neutral molecules from a liquid spherule of high viscosity

The escape (efflux) half-life of glycerol (small molecule example) distributed uniformly in a liquid domain with a 0.005 cm radius was estimated using Equation (3.8) in Crank (1975) describing diffusion from a sphere [a typographical error in the equation was corrected by replacing the second $(a + r)$ term by $(a - r)$]. In the numerical solution the ratio of the diffusing solute inside and outside the domain was plotted as a function of Dt/a^2, where D is the diffusion coefficient, a is the radius of the domain, and t is the time of diffusion. For glycerol (D_{aq}-25 °C = 0.93×10^{-5} cm^2/sec) the estimated escape half-life from an aqueous domain with a 0.005 cm radius was 0.27 seconds at 25 °C. At 50 °C the escape half-life was 0.17 seconds as estimated using the Stokes–Einstein equation and the viscosity of water at 50 °C ($\eta_{50\,°C} = 0.5468$ cp) and 25 °C ($\eta_{25\,°C} = 0.8904$ cp) (Green, 1984; Weast,

1985). At 50 °C glycerol's escape half-life was estimated at 40,600 seconds in a medium with the viscosity of liquid glycerol at –20 °C ($\eta = 1.34 \times 10^5$ cp, Weast, 1985).

2.4. Estimation of the relative rates of diffusion-controlled and catalzyed reactions

At 25 °C the maximum rate constant of an aqueous diffusion-controlled encounter for two reacting molecules is 10^9–10^{11} M^{-1} sec^{-1} (Berg and von Hippel, 1985; Eigen and Hammes, 1963; Fersht, 1985), and for a molecule and an enzyme about 10^9 M^{-1} sec^{-1} (Abeles *et al.*, 1992a; Fersht, 1985; Moore, 1983c). By assuming a diffusion-controlled encounter constant of 10^9 M^{-1} sec^{-1}, and an orientation effect of 10^{-2} (a value of some enzymes, Abeles *et al.*, 1992a), we estimate that the diffusion-controlled rate constant ($k_{\text{diff. contrl}}$) of a prebiotic reaction is probably equal to or greater than 10^7 M^{-1} sec^{-1} at 25 °C (2×10^7 M^{-1} sec^{-1} at 50 °C). Using this value in rate Equation (E2) below we estimate that at 50 °C and 1 M catalyst an aqueous diffusion-controlled reaction is 2.5×10^8 times faster than a hypothetical primitive 10^4-fold catalyzed reaction with a half-life of 8.6 seconds (uncatalyzed half-life of one day). Furthermore, in a viscose spherule with a viscosity comparable to glycerol at –20 °C ($\eta = 1.34 \times 10^5$ centipoises, Weast, 1985) where the estimated diffusion-controlled rate constant is 134 M^{-1} sec^{-1} (Berg and von Hippel, 1985), the diffusion-controlled rate would still be 1680 times faster than the above primitive catalyzed reaction ($t_{1/2} = 8.6$ seconds).

$$v_{\text{diff. contrl.}} = k_{\text{diff. contrl.}}\,[\text{S}][\text{C}] \text{ or } 2 \times 10^7\ M^{-1}\ sec^{-1}\,[\text{S}][\text{C}] \text{ at } 50\,^{\circ}\text{C}, \qquad \text{(E2)}$$

where [S] and [C] are the substrate and catalyst concentrations, respectively.

3. Results

Tables I and II list the aqueous thermal transformation rates of a broad range of C,H,O-organic molecules. The molecules listed in Table II, but not Table I, contain a carbonyl group (aldehyde/ketone) in the β-position from the reacting group. In both tables the types of reactants are listed starting with those containing the most oxidized reactive group (–COOH) and progressing to reactive groups of higher reduction level. The tables list the reactants, type of reactions, reaction conditions, estimated half-life(s), and literature references. The half-lifes at 50 °C were estimated from Arrhenius plots for studies that measured the reaction rate at two or more temperatures.

The rate data in Tables I and II are graphed in Figures 1–3 as Arrhenius plots in which the logarithms of the rate constants are plotted as a function of the reciprocal of the absolute temperature multiplied by 1000. The plotted rate constant of each reaction is marked by the number given that reaction in Tables I and II. Reactions

TABLE II

Rates of decomposition of organic compounds containing a β-carbonyl group

Group type (R = H or hydrocarbon) Examples		Type of reaction [a]	Conditions ($t_{1/2}$ at given temp.) [b, c]	$t_{1/2}$ at 50 °C [d]	References
–CO–CR_2–COOH					
A.	acetoacetic acid	decarbox.	aq. 30 °C (0.28 d)		(Guthrie and Jordan, 1972)
B.	acetoacetate	decarbox.	aq. 30 °C (17.6 d)		
C.	acetoacetic acid	decarbox.	0.01 M aq. 37, 35, 18 °C (0.231, 1.12, 2.99 d)	0.05 d	(Pedersen, 1929)
D.	acetoacetate	decarbox.	0.01 M aq. 37, 25, 18 °C (12.5, 54, 134 d)	2.9 d	
E.	2,2′-dimethyl-acetoacetic acid	decarbox.	0.01 M 18 °C (0.67 d)		(Pedersen, 1929)
F.	2,2′-dimethyl-acetoacetate	decarbox.	0.01 M 18 °C (∼120 d)		
G.	oxaloacetic acid	decarbox.	aq. 25, 30, 37 °C (7.50, 3.60, 1.39 d)	0.26 d	(Gelles, 1956)
H.	oxaloacetate (–1)	decarbox.	aq. 25, 30, 37 °C (0.141, 0.072, 0.031 d)	0.007 d	
I.	oxaloacetate (–2)	decarbox.	aq. 25, 30, 37 °C (0.480, 0.241, 0.115 d)	0.027 d	
J.	tartronic semiald.	decarbox.	0.01 M aq. 30 °C–buf. pH 5 (5.8 h)		(Fukunaga, 1960)
–CO–CR_2–CO–					
K.	acetylacetone	hydro. deacylation	aq. 45 °C–pH 7.3 (12 d)	8.9 d [c]	(Calmon and Maroni, 1968)
L.	5-Me-2,4-hexanedione	hydro. deacylation	aq. 45 °C–pH 7.3 (69 d)	51 d [c]	(Calmon and Maroni, 1968)
–CO–CR_2–COH<					
M.	glyceraldehyde (GA)	dehydr., isomer	1 mM aq. 180, 200, 220, 240 °C (207, 83, 39, 21 s)	6.0 d	(Bonn *et al.*, 1985)
N.	glyceraldehyde	dehydr., isomer.	0.06 M aq. 37 °C–buf. pH 7.7 (2.9 d)		(Bonsignore *et al.*, 1972)
O.	dihydroxyacetone (DHA)	dehydr., isomer.	1 mM aq. 180, 200, 220, 240 °C (613, 241, 108, 33 s)	141 d	(Bonn *et al.*, 1985)
P.	triose (GA + DHA)	dehydr., isomer.	0.01 M aq. 40 °C–buf. pH 5.5 [37.6 d]		(Weber, 2001b)
Q.	triose (GA + DHA)	dehydr., isomer.	0.01 M aq. 50 °C–buf. pH 7.3 (1.1 d)	1.1 d	(Federonko *et al.*, 1969)
R.	ribose	C-1 transform.	aq. 118, 100, 80, 60 °C–buf. pH 7 (0.21, 1.5, 10, 64 h)	10.2 d	(Larralde *et al.*, 1995)
S.	2-deoxyribose	C-1 transform.	aq. 100 °C–buf. pH 7 (3.8 h)		(Larralde *et al.*, 1995)
T.	arabinose	C-1 transform.	aq. 100 °C–buf. pH 7 (7.7 h)		(Larralde *et al.*, 1995)
–CO–CR_2–COH<					
U.	idose	C-1 transform.	aq. 100 °C–buf. pH 7 (0.36 h)		(Larralde *et al.*, 1995)
V.	glucose	C-1 transform	aq. 100 °C–buf. pH 7 (35 h)		(Larralde *et al.*, 1995)
W.	glucose	C-1 transform.	0.2 M aq. 240, 273, 298, 322 °C (102, 21, 7.6, 5.6 s)	352 d	(Adschiri *et al.*, 1993)
X.	fructose	dehydr., isomer., fragm., intramol. redox	0.05 M aq. 250 °C–pH 6 [23 s]		(Antal *et al.*, 1990)
Y.	fructose	dehydr., isomer., intramol. redox	0.25 M aq. 175 °C–buf. pH 5–6 (208 s)		(Kuster and Temmink, 1977)
Z.	fructose	dehydr.	0.25 M aq. 175 °C–unbuf. pH 7 drops to pH 3 (2310 s)		(Kuster and Temmink, 1977)
AA.	3-hydroxypropanal	dehydr.	0.03 M aq. 20, 30, 100 °C [43, 24, 0.29 d]	5.2 d	(Pressman and Lucas, 1942)
BB.	3-hydroxybutanal	dehydr.	0.001 mM aq. 25 °C–pH 10 (2.3 d)		(Guthrie, 1974)
BB′.	3-hydroxybutanal	dealdol.	0.001 mM aq. 25 °C–pH 10 (29 d)		
CC.	3-OH-3-Me-butanal	dehydr.	0.01 mM aq. 25 °C–pH 10 (9.6 d)		(Guthrie and Dawson, 1983)
CC′.	3-OH-3-Me-butanal	dealdol.	0.01 mM aq. 25 °C–pH 10 (1.4 d)		

[a] Abbreviations: decarboxylation (decarbox.), dehydration (dehydr.), isomerization (isomer.), unspecified C-1 transformation (C-1 transform.), fragmentation (fragm.), intramolecular reduction-oxidation (intramol. redox), dealdolization (dealdol.), hydrolytic deacylation (hydro. deacylation). The pathway relationships of reactions are unspecified.

[b] Half-lifes enclosed in parentheses were calculated from measured reaction rate constants (see Methods for all calculations).

[c] Half-lifes enclosed in brackets were estimated from product yields.

[d] Half-lifes at 50 °C were estimated by extrapolation using Arrhenius plots.

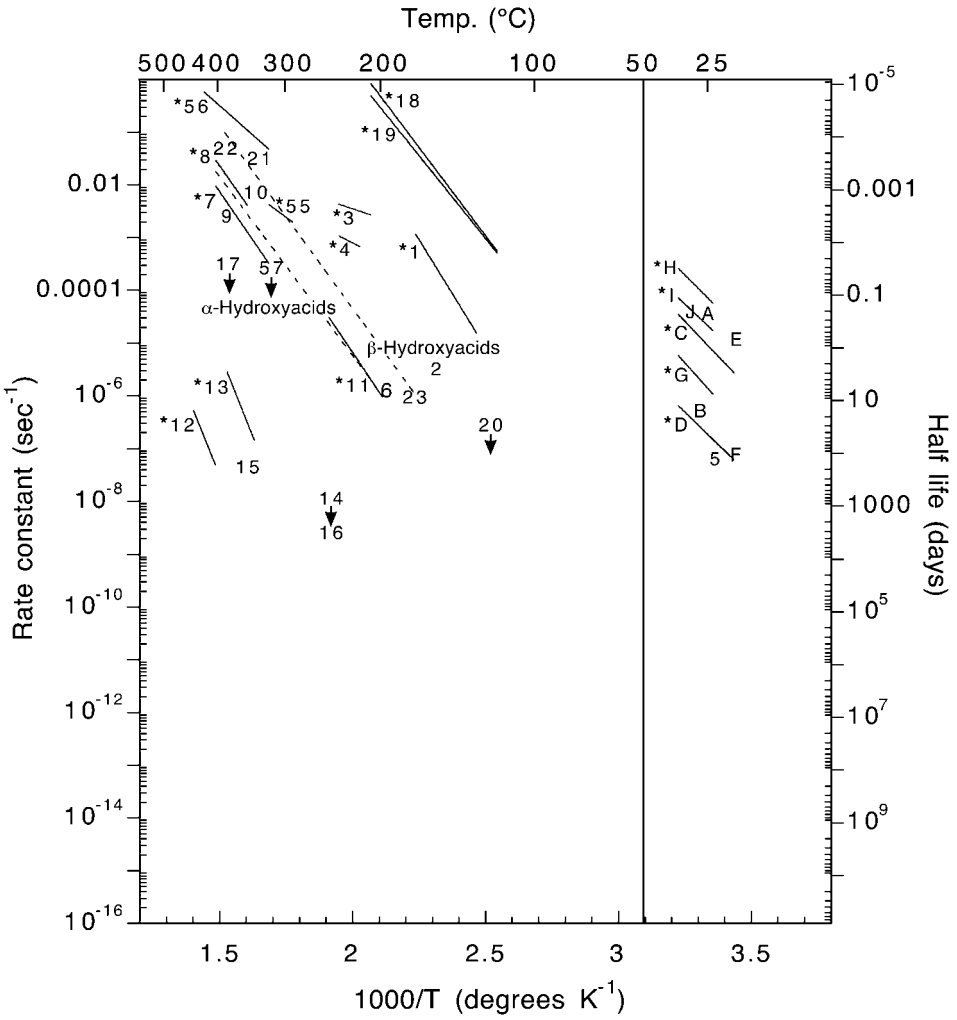

Figure 1. Arrhenius plots of the reactions of carboxylic acids in which the logarithms of the rate constants are plotted as a function of the reciprocal of the absolute temperature multiplied by 1000. The plotted rate constant of each reaction is marked by the number given that reaction in Tables I and II. Reactions carried out at several temperatures are plotted as solid lines identified by adjacent asterisked numbers. Bimolecular reactions are depicted as bracketed numbers. Rate constant upper limits of unreactive molecules have a downward arrow below their reaction numbers.

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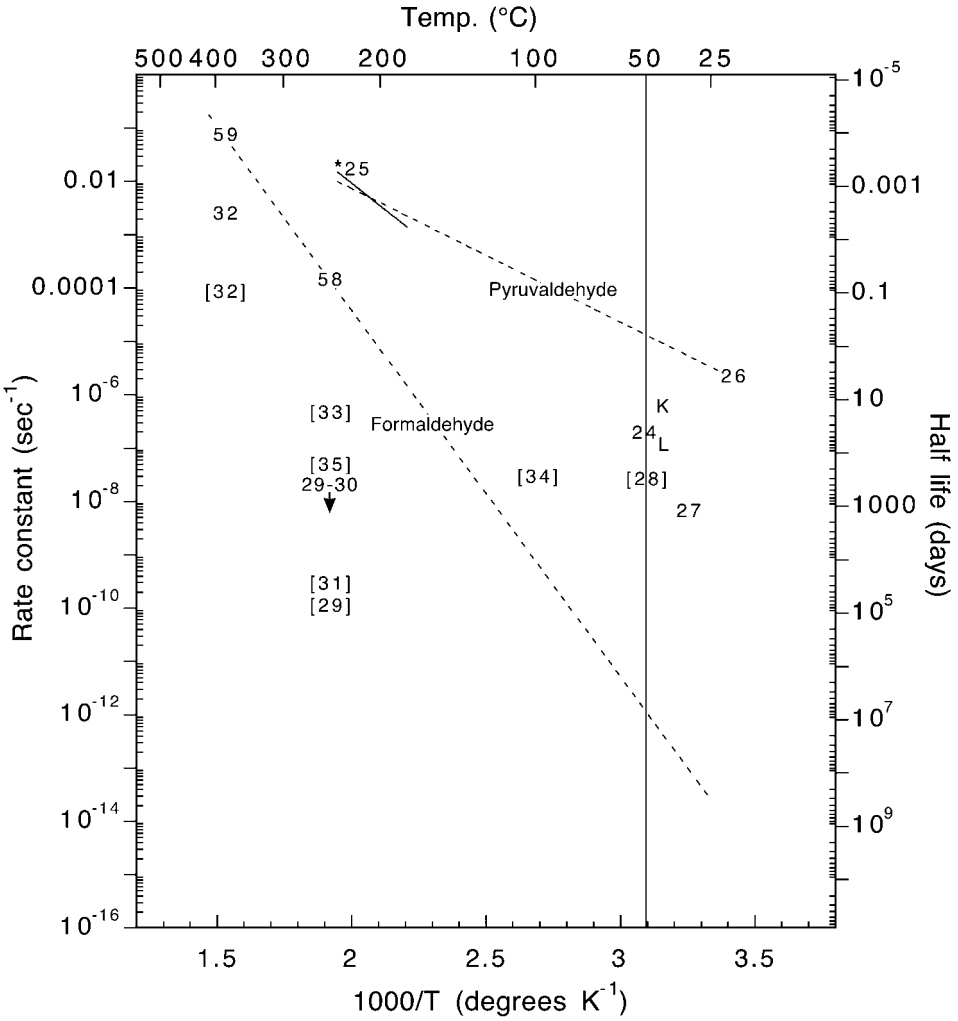

Figure 2. Arrhenius plots of the reactions of aldehydes and ketones in which the logarithms of the rate constants are plotted as a function of the reciprocal of the absolute temperature multiplied by 1000. The plotted rate constant of each reaction is marked by the number given that reaction in Tables I and II. Reactions carried out at several temperatures are plotted as solid lines identified by adjacent asterisked numbers. Bimolecular reactions are depicted as bracketed numbers. Rate constant upper limits of unreactive molecules have a downward arrow below their reaction numbers.

3.1. TRANSFORMATION RATES OF CARBOXYLIC ACIDS

Figure 1 shows Arrhenius plots of the thermal transformation of carboxylic acids and their salts. The figure shows that carboxylic acids (A-J) with a β-positioned carbonyl group (aldehyde or ketone) have the fastest decomposition rates. Their

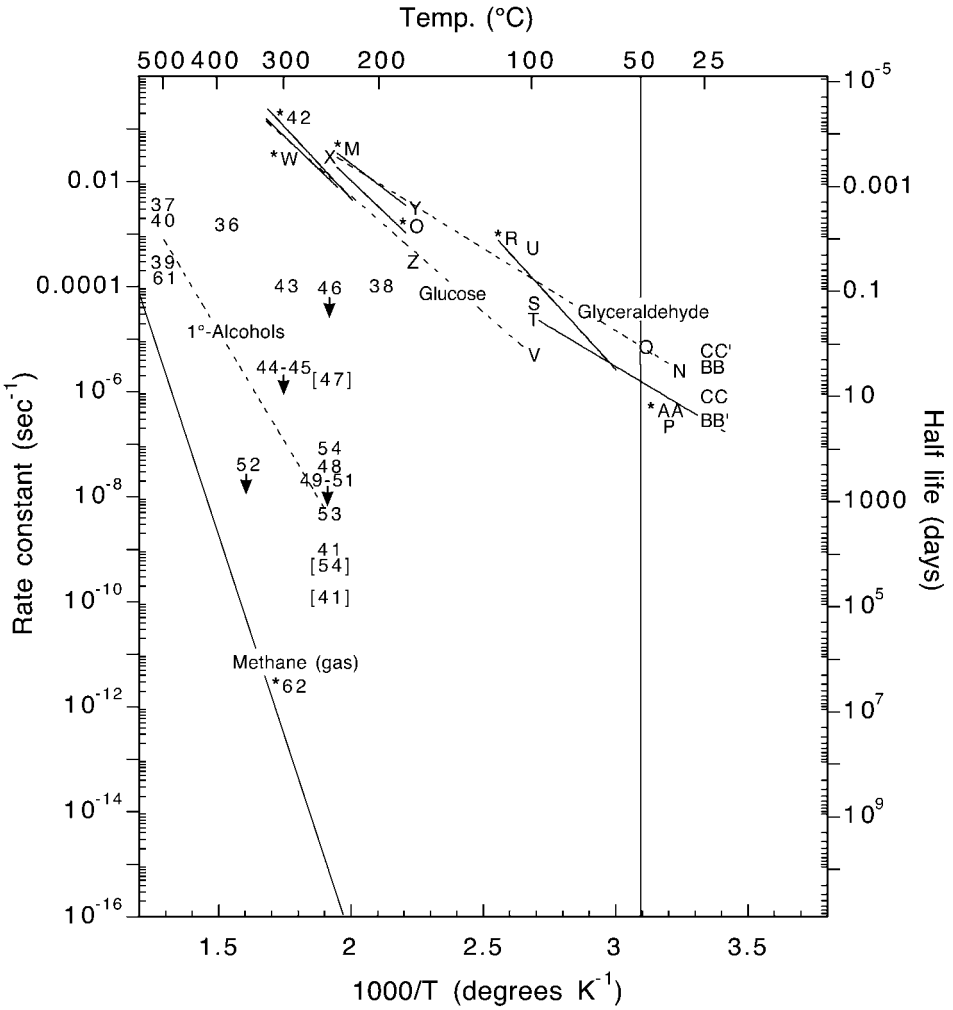

Figure 3. Arrhenius plots of the reactions of alcohols, sugars, and hydrocarbons in which the logarithms of the rate constants are plotted as a function of the reciprocal of the absolute temperature multiplied by 1000. The plotted rate constant of each reaction is marked by the number given that reaction in Tables I and II. Reactions carried out at several temperatures are plotted as solid lines identified by adjacent asterisked numbers. Bimolecular reactions have bracketed numbers. Rate constant upper limits of unreactive molecules have a downward arrow below their numbers.

decomposition involves only decarboxylation (Reaction (R1)) with half-lifes at 50 °C from 0.007–3 days (Abeles *et al.*, 1992b; Clark, 1969; Jencks, 1987c).

$$\text{R–COOH} \rightarrow \text{R–H} + \text{CO}_2\,. \qquad \text{(R1)}$$

α-Carbonyl-carboxylic acids [pyruvate (3,4), glyoxylate (5)] apparently decompose as rapidly as β-carbonyl-carboxylic acids. However, pyruvate decomposition is not simple decarboxylation because it yields acetic acid instead of acetaldehyde

(Belsky *et al.*, 1999). Also, the glyoxylate study used amine buffers that could catalyze its decomposition (Halliwell and Butt, 1972). These uncertainties indicate that the decomposition of pyruvate and glyoxylate should be reexamined under milder conditions (50 °C to 150 °C).

Figure 1 also shows that the carboxylic acids (7–17) without an α- or β-carbonyl group are very stable with half-lifes that range from 10^5 years for β-hydroxyacids to 10^{20} years for acetic acid. Only oxalic acid (1–2), malonic acid (18–20), and formic acid (55–57) are moderately reactive. β-Hydroxyacids [β-hydroxybutyric acid (22)] decompose primarily by dehydration (Reaction (R2)). The somewhat more stable α-hydroxyacids [lactic acid (7)] decompose by decarboxylation, dehydration, and to a lesser extent decarbonylation (Reaction (R3)) (Knozinger, 1971; Lira and McCrackin, 1993; Mok *et al.*, 1989). Simple alkyl acids could be more stable than estimated because reaction vessel walls probably catalyze their decomposition (Bell *et al.*, 1994; Belsky *et al.*, 1999).

$$\text{R–CHOH–CH}_2\text{–COOH} \rightarrow \text{R–CH=CH–COOH} + \text{H}_2\text{O} \tag{R2}$$

$$\text{R–CHOH–COOH} \rightarrow \text{R–CHO} + \text{CO} + \text{H}_2\text{O}. \tag{R3}$$

3.2. Transformation rates of aldehydes and ketones

Figure 2 depicts Arrhenius plots of the decomposition reactions of mono- and dicarbonyl compounds. Carbonyl compounds undergo unimolecular reactions and bimolecular reactions involving either intermolecular reduction-oxidation (Reaction (R4)) or self-aldolization (Reaction (R5)) (Abeles *et al.*, 1992c; House, 1972; Reeves, 1966). The most reactive molecules have a carbonyl group in the α- or β-position with respect to a second oxygen-containing group. These carbonyl-activated substances that have half-lifes from 1–300 days are: α-ketoaldehydes [glyoxal (24), pyruvaldehyde (25–26), phenylglyoxal (27)] that undergo intramolecular reduction-oxidation (Reaction (R6)), hydroxyaldehydes [glycolaldehyde (28)] that undergo self-aldolization yielding larger sugars (Reaction (R5)), and β-diketones [acetylacetone (K), 5-methyl-2,4-hexanedione (L)] that undergo hydrolytic deacylation (Reaction (R7)) (Bonn *et al.*, 1985; Weber, 2001a; Calmon and Maroni, 1968).

$$2\,\text{R–CHO} + \text{H}_2\text{O} \rightarrow \text{R–CH}_2\text{OH} + \text{R–COOH} \tag{R4}$$

$$2\,\text{CHR}_2\text{–CHO} \rightarrow \text{CHR}_2\text{–CHOH–CR}_2\text{–CHO} \tag{R5}$$

$$\text{R–CO–CHO} + \text{H}_2\text{O} \rightarrow \text{R–CHOH–COOH} \tag{R6}$$

$$\text{R–CO–CH}_2\text{–CO–R}' + \text{H}_2\text{O} \rightarrow \text{R–COOH} + \text{CH}_3\text{–CO–R}'. \tag{R7}$$

The remaining aldehydes and ketones are very stable with half-lifes probably several orders of magnitude greater than the 10^4 year half-life of the simplest aldehyde, formaldehyde. Simple hydrocarbon ketones [2-decanone (29), cyclohexylphenyl-ketone (30), acetophenone (31)] show no unimolecular decomposition after 5 days at 250 °C and a slow self-aldolization with a half-life of about 175 years at 0.01 M. Simple hydrocarbon aldehydes [acetaldehyde (32), decanal (33)] are less stable than the ketones because they undergo, not only self-aldolization, but also intermolecular reduction-oxidation (Reaction (R4)), and decarbonylation (Reaction (R8)) (Swain *et al.*, 1979; Schubert and Kintner, 1966).

$$\text{R–CHO} \rightarrow \text{R–H} + \text{CO}. \tag{R8}$$

3.3. Transformation rates of alcohols, sugars and hydrocarbons

Figure 3 shows Arrhenius plots of the decomposition of sugars, alcohols, and hydrocarbons. As observed previously for carboxylic acids, aldehydes, and ketones, reactants with a carbonyl group in the α- or β-position with respect to a second oxygen-bearing group are the most reactive. Carbonyl-activated alcohols [sugars (M–Z), β-hydroxyaldehydes (AA–CC)] have half-lifes from 1–100 days. Sugar transformations generally begin by either aldo-keto isomerization (Reaction (R9)), or by β-dehydration followed by enol-keto isomerization (Reaction (R10)) and redox rearrangement (Reaction (R11)) (Pigman and Anet, 1972; Feather and Harris, 1973; Speck, 1958; Anet, 1964). Small acyclic sugars undergo self-aldolization yielding larger sugars (Mizuno and Weiss, 1974). β-Hydroxyaldehydes, like 3-hydroxypropanal (AA), undergo both β-dehydration and dealdolization.

$$\text{R–CHOH–CHO} \rightarrow \text{R–CO–CH}_2\text{OH} \tag{R9}$$

$$\begin{aligned}\text{R–CHOH–CHOH–CHO} &\rightarrow \text{H}_2\text{O} + \text{R–CH=COH–CHO} \\ &\rightarrow \text{R–CH}_2\text{–CO–CHO}\end{aligned} \tag{R10}$$

$$\text{R–CH}_2\text{–CO–CHO} + \text{H}_2\text{O} \rightarrow \text{R–CH}_2\text{–CHOH–COOH}. \tag{R11}$$

Hydrocarbons and alcohols lacking a carbonyl substituent are very stable, except for t-butanol (42) and phenylethane-1,2-diol (38) that have dehydration half-lifes at 50 °C of 1500 and 0.01 days, respectively. Primary monoalcohols [ethanol (39), n-propanol (40), 1-decanol (41) and 2-phenylethanol (48)] are extremely stable with their combined Arrhenius plot indicating a half-life of 10^{10} years at 50 °C. Secondary alcohols [cyclohexanol (43) ethyleneglycol (36), and glycerol (37)] are less stable than primary monoalcohols with half-lifes that probably exceed 10^6 years at 50 °C. Most hydrocarbons are extremely stable and did not react during aquathermolysis at 250 °C for 5 days. Cyclohexane is so stable it is used as a thermolysis solvent (Siskin and Katritzky, 2001). The extrapolated Arrhenius

plot of methane gas (62) measured at 800–1000 °C gives an estimated half-life of 10^{19} years at 50 °C.

3.4. Influence of functional groups on organic transformation rates

Table III lists the estimated half-lifes at 50 °C of specific types of organic transformations. Hydrocarbons are not listed because their stability towards aquathermolysis prevented measurement of their decomposition rates. As shown in Table III compounds containing only one oxygenated carbon group are very stable. The only exception is t-butanol, a tertiary alcohol, with an unusually rapid dehydration half-life at 50 °C of 10^8 seconds (3 years). Comparison of the half-lifes in Table III also shows that the rates of organic transformations are strongly enhanced by a second oxygenated carbon group in α- and β-position. In decarboxylation the β-carbonyl group has the strongest accelerating effect – an extraordinary 10^{24}-fold increase in the decarboxylation rate of acetoacetic acid compared to acetic acid. The decarboxylation rate is also increased by other groups: 10^{24}-fold by the α-carbonyl group (pyruvic acid, see earlier discussion of pathway uncertainty), 10^{21}-fold by the β-carboxylic acid group (malonic acid), 10^{17}-fold by the α-carboxylic acid group (oxalic acid), 10^{14}-fold by the α-alcohol group (lactic acid), and 10^{24}-fold by the α-alcohol-β-carbonyl group (tartronate semialdehyde). The β-carbonyl group also has the strongest activating effect on alcohol dehydration – a 10^{12}-fold increase in the dehydration of 3-hydroxypropanal compared to primary alkyl alcohols. The dehydration rate is also enhanced 10^5-fold by the β-carboxylic acid group (β-hydroxy acids), 10^4-fold by the α-carboxylic acid group (lactic acid), and 10^{12}-fold by the α-alcohol-β-carbonyl (glyceraldehyde).

The half-lifes in Table III also show that the β-carbonyl group strongly enhances hydrolytic deacylation. Acetylacetone deacylates at 50 °C with a half-life of 9 days, but 2-decanone does not deacylate when heated at 250 °C for 5 days. In addition aldo-keto isomerization and self-aldolization of aldehydes and ketones are increased by an α-alcohol group. For example, glyceraldehyde isomerizes at 50 °C with a half-life of 58 days, but 2-decanone does not isomerize when heated at 250 °C for 5 days; glycolaldehyde self-aldolizes at a rate at 50 °C that is comparable to the rate of 2-decanone at 250 °C.

4. Discussion

4.1. Chemical activation and the structure of metabolism

The above survey of organic reactivity shows that oxygenated carbon groups strongly accelerate chemical transformation of nearby functional groups. These rate accelerations, that can reach 10^{24} for β-positioned carbonyl groups (aldehydes, ketones), exceed the known maximum catalytic power of 10^{17} of modern enzymes

TABLE III

Effect of adjacent carbon groups on the rate of organic transformations [a]

Decarboxylation of a carboxylic acid, R–COOH or R–COO^-		Dehydration of an alcohol, R–CR′R″–OH		Deacylation, isomerization and aldolization of a ketone or aldehyde, R_2>C=O or R–CHO	
Substance	Estimated $t_{1/2}$–50 °C	Substance	Estimated $t_{1/2}$–50 °C	Substance	Estimated $t_{1/2}$–50 °C
acetic acid	3×10^{27} s	1°-alcohol (ethanol, propanol,	[1×10^{18} s] [g]	2-decanone (deacyl., isomer.)	no react. (250 °C)
acetate	2×10^{25} s	decanol, phenylethanol)		decanal (0.01 M aldoliz.)	2×10^{6} s (250 °C)
		3°-alcohol (t-butanol)	1×10^{8} s	2-decanone (0.01 M aldoliz.)	4×10^{7} s (250 °C)
acetoacetic acid	4×10^{3} s	3-hydroxy-propanal	5×10^{5} s	acetylacetone (deacylation)	8×10^{5} s
acetoacetate	2×10^{5} s				
lactic acid	2×10^{13} s [b]	ethylene glycol	insuff, data	glyceraldehyde (isomerization)	5×10^{6} s
lactate	[2×10^{13} s] [c]			glycolaldehyde (0.01 M aldoliz.)	2×10^{7} s
tartronate semialdehyde	[10^{3} s] [d]	glyceraldehyde	9×10^{5} s	α-hydroxymalonaldehyde	no data found
pyruvic acid	1×10^{4} s [e]	glycolaldehyde	aldolizes	glyoxal (intramolec. redox)	3×10^{6} s
pyruvate	6×10^{5} s [e]			pyruvaldehyde (intramolec. redox)	2×10^{6} s
oxalic acid	6×10^{9} s	lactic acid	2×10^{13} s [b]	glyoxylate	decarboxylates
oxalate^{-2}	[6×10^{11} s] [f]	lactate	[2×10^{13} s] [c]		
malonic acid	4×10^{6} s	β-hydroxy acids (β-hydroxybutyric		malonic semialdehyde	no data found
malonate^{-1}	6×10^{6} s	acid, malate^{-1}, 2-deoxygluconic acid)	[6×10^{12} s] [h]		

[a] Unbracketed half-lifes were estimated by extrapolation using Arrhenius plots. Bracketed half-lifes were estimated by extrapolation using the Arrhenius plot slope of a related reaction (reactions noted below).

[b] Half-life was estimated using the most recent study indicating an 1/1 ratio of decarboxylation to dehydration (Lira and McCrackin, 1993).

[c] Half-life of lactate was estimated using the slope of the Arrhenius plot of lactic acid (Lira and McCrackin, 1993).

[d] Half-life of tartronate semialdehyde^{-1} was estimated using the slope of the Arrhenius plot of related β-ketoacids.

[e] Pyruvic acid decarboxylation yielded acetate instead of the expected acetaldehyde (see discussion in text).

[f] Half-life of oxalate^{-2} was estimated using the slope of the Arrhenius plot of oxalic acid.

[g] Half-life of 1°-alcohols was estimated from the joint Arrhenius plot of the alcohols listed.

[h] Half-life of β-hydroxy acids was estimated from the joint Arrhenius plot of the acids listed.

(Radzicka and Wolfenden, 1995). Life has exploited this powerful chemical activation by using metabolic intermediates containing α- and β-carbonyl groups, and the β-acyl group of thioesters that mimics the β-carbonyl group. These groups not only enhance the reactivity of nearby groups towards decarboxylation, dehydration, aldolization, and hydrolytic deacylation, but also provide groups capable of reduction-oxidation, aldolization, and isomerization. Furthermore, carbonyl groups readily bind to groups in enzyme active sites as covalent hemiacetal, hemithioacetal, carbinolamine, and imine adducts (Hine and Yeh, 1967; Kallen and Jencks, 1966; Ogata and Kawasaki, 1970). The widespread use of carbonyl-activated intermediates in modern metabolism suggests either that the use of chemical-activation confers a strong competitive advantage, or that enzymes lack the catalytic power needed to transform many substrates that are not chemically activated. In either case, chemical activation provides such a strong kinetic advantage that metabolism is probably forced to use activated intermediates. Furthermore, the synthesis and use of these activated intermediates must be achieved in a context of fixed group transformation energies (Weber, 2002) that control the direction of chemical transformations. Taken together these kinetic and thermodynamic chemical constraints undoubtedly are a major determinant of the structure of intermediary metabolism.

4.2. Constraints on the chemistry of primitive autocatalytic processes

If life is viewed as a chemical process (metabolism and biopolymer synthesis) that is catalytically controlled by its products (proteins and nucleic acids) in a way that enhances the perpetuation of the entire system, then the origin of life was most likely a prebiotic chemical process that became increasingly controlled by the catalytic action of its products. This view that stresses autocatalysis restricts the chemistry of the origin of life to processes that (1) generate autocatalytic products, (2) take place in a small 'one-pot' domain where close proximity allows autocatalysts to act on intermediates of the process, and (3) occur in the presence of liquid water needed for delivery of a primary organic substrate(s) from the environment. Furthermore, the autocatalysts and their reaction intermediates had to be confined in order to prevent their dissolution in the surrounding aqueous environment.

Containment of reaction intermediates is especially important at the earliest stage in the origin of life when catalysis was weak. In fact, for the rate of a two-step process to equal the escape rate of C,H,O-intermediates from a lipid vesicle, the process had to be catalyzed and use the most reactive intermediates. Containment, catalysis, and reactive intermediates are required, because the escape of small C,H,O-intermediates from a lipid vesicle is fast compared to the rates of organic transformations. For example, the most reactive C,H,O-molecules have transformation half-lifes at 50 °C of 10^4–10^7 seconds, but a small organic molecule (i.e. glycerol) at 50 °C takes only 0.25 seconds to diffuse from the center to the surface of a spherical aqueous domain with a 0.005 cm radius (see Methods for

all calculations). Even escape from a bilayer lipid vesicle of the same size is fast with a half-life of 19 seconds. Therefore, a membrane-enclosed primitive catalytic domain of this size or smaller had to use the most reactive carbonyl-containing organic intermediates ($t_{1/2}$-50 °C $\approx 10^4$–10^7 sec); and catalyze their reactions 10^3–10^6-fold in order for the transformation rate to be comparable to the vesicle escape rate ($t_{1/2}$-50 °C = 19 sec). It is important to note that this analysis of the escape behavior of small C,H,O,-intermediates does not apply to large or charged organic molecules (like phosphoesters and amino acids) that are more strongly retained by membranes (Chakrabarti and Deamer, 1992; Chakrabarti and Deamer, 1994).

The required degree of catalysis could have been less, if binding of reaction intermediates to catalytic sites reduced their rate of diffusion. This seems likely for carbonyl-containing molecules that form reversible covalent linkages to hydroxyl, sulfhydryl, and amino groups yielding hemiacetal, hemithioacetal, carbinolamine, and imine adducts, respectively (Hine and Koser, 1971; Kallen and Jencks, 1966; Ogata and Kawasaki, 1970). Assuming 0.1 M binding sites and an equilibrium constant of about 100 M^{-1} (Hine and Koser, 1971; Kallen and Jencks, 1966; Ogata and Kawasaki, 1970), then about 10% of the intermediates would be freely diffusible and their escape half-life would increase 10-fold. As a result, only a catalytic acceleration of 10^2–10^5-fold is needed to make the transformation rate of carbonyl-activated intermediates comparable to their escape rate from a 0.005 cm vesicle. Since a 10^3–10^4-fold rate enhancement has been observed for amine-catalyzed sugar transformations (Weber, 2001a, b), a primitive lipid vesicle of this size would be marginally capable of carrying out a multi-step process based on sugar transformations.

In several respects, viscose liquid spherules possibly formed by aggregation of a prebiotic oligomer appear to provide a more attractive microenvironment than lipid vesicles for the earliest autocatalytic process. First, the synthesis of a viscous spherule is simpler, requiring only the synthesis of a self-associating autocatalyst without extra need to synthesize a membrane lipid. Second, viscous spherules are not as susceptible as lipid vesicles to disruption by osmotic gradients, divalent cations, and phase changes dependent on pH, temperature, and concentration (Enoch and Strittmatter, 1979; Gruner, 1985, 1987; Hargreaves and Deamer, 1978).

Finally, small viscose spherules are orders of magnitude better than lipid vesicles at reducing rate of escape of C,H,O-reaction intermediates. For example, a small neutral molecule (i.e. glycerol) has an escape half-life of 40,600 seconds from a spherule with a 0.005 cm radius that has a viscosity equivalent to liquid glycerol at –20 °C (a slowly pourable liquid with a viscosity of 1.34×10^5 cp). This escape half-life of 40,600 seconds is 2100-times slower than that of a lipid vesicle of the same size. Consequently, autocatalytic viscous spherules require less catalytic power than lipid vesicles to alleviate the detrimental effect of escape of reaction intermediates. Although the matrix of a viscous liquid domain could have unpredictable effects on catalysis by organic functional groups, the slower diffusion of intermediates due to viscosity is not expected to significantly reduce

catalyzed reaction rates, since the expected rate of a primitive weakly catalyzed reaction in a viscose spherule would be much slower than its diffusion-controlled reaction rate. For example, at 25 °C and 1 M catalyst, the rate of a diffusion-controlled catalytic reaction in the viscous spherule above is estimated to be 1680-times faster than a primitive catalyzed reaction that has a half-life of 0.0001 day (8.6 sec). In general, viscosities of the order of 10^5 cp would not be expected to slow primitive catalyzed reactions with half-lifes of 10^{-6} days and longer.

Although viscous spherules are an attractive container for a primitive weakly autocatalytic process, they are not the best container for an evolved powerful catalytic system because the diffusion of intermediates would be rate-limiting. Lipid vesicles with their low viscosity aqueous interiors would be a better environment for a powerful autocatalytic process, especially for catalysts that can phosphorylate and thereby trap metabolic intermediates (Davis, 1958; Westheimer, 1987). The first lipid vesicles could have used fatty acids that were synthesized using simpler, chemically more spontaneous pathways than the modern fatty acid biosynthesis (Weber, 1991).

If the first autocatalytic biogenic process was based on C,H,O-organic transformations, then the above kinetic considerations indicate it most likely used reactive carbonyl-containing substrates that yielded autocatalysts having weak but significant catalytic power. Of all the possible carbonyl-containing substrates, small 3- and 4-carbon sugars have several properties that make them very attractive substrates for the earliest autocatalytic process. First, sugars carry the largest amount of self-transformation energy per carbon (Weber, 1997, 2000, 2002). Combined with the reactivity conferred on sugars by their carbonyl group, this high self-transformation energy allows sugars to spontaneously react with ammonia to give catalytic products – amines and carboxylic acids that have been shown to catalyze sugar transformation reactions (Weber, 2001a, b). Sugar transformations do not require coupling to an energy source. In addition, sugars can be synthesized under mild aqueous conditions (Schwartz and de Graaf, 1993) from formaldehyde, a one-carbon plausible prebiotic substrate that has been synthesized under a variety of prebiotic conditions (Aurian-Blajeni *et al.*, 1980; Bar-Nun A and Hartman, 1978; Canuto *et al.*, 1983; Chittenden and Schwartz, 1981; Ferris and Chen, 1975; Halmann *et al.*, 1981; Hubbard *et al.*, 1971; Kasting and Pollack, 1984; Miller and Schlesinger, 1984; Pinto *et al.*, 1980). Consequently, a sugar-based autocatalytic process would have had access to a reliable and constantly replenished supply of carbon and energy. Finally, a primitive autocatalytic process that used sugar substrates could develop in a straightforward manner into the sugar-based metabolism of contemporary life (Weber, 1991, 1997, 1998, 2000, 2001a, 2002).

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