The mechanism for the degradation of Erythromycin A and Erythromycin A 2´-Ethyl Succinate in acidic aqueous solution

Abdolreza Hassanzadeh[1], Jill Barber[1], Gareth A. Morris[2] and Peter Gorry[2]

Schools of Pharmacy and Pharmaceutical Sciences[1] and Chemistry[2], University of Manchester, Oxford Road, Manchester, UK, M13 9PL.

Email: peter.gorry@manchester.ac.uk

Supporting Information

Model II, analytical solutions.

A Mathematica program is given below for the special case of starting with an initial concentration a[0]=a0 and zero b and c, i.e. b[0] = c[0]= 0. In the model below a = [EA], b = [EAEE] and c = [AEA]. A general case with none zero initial concentrations for all species can also be derived.

■ **Equilibrium C <--- A <---> B Literature model**

```
(* kinetic scheme *)

In[1]:= eqns = {
          a'[t] + a[t] * (k1 + k3) - b[t] * k2 == 0,
          b'[t] - a[t] * k1 + b[t] * k2 == 0,
          c'[t] - a[t] * k3 == 0
         };

(* Initial conditions *)

In[2]:= InitialCond = {a[0] → a0, b[0] → 0, c[0] → 0};
```

■ **Laplace transform of kinetic eqns**

```
In[3]:= Lapeqns = LaplaceTransform[eqns, t, s];
```

■ **Solve for Laplace transform for each term**

```
In[4]:= Y[s] = Solve[Lapeqns /. InitialCond,
          {LaplaceTransform[a[t], t, s],
           LaplaceTransform[b[t], t, s],
           LaplaceTransform[c[t], t, s]}]
```

$$\text{Out[4]=}\ \left\{\left\{\text{LaplaceTransform}[c[t],t,s] \to -\frac{a0\,k3\,(k2+s)}{s\,(k1\,k2-(k2+s)\,(k1+k3+s))},\right.\right.$$

$$\text{LaplaceTransform}[a[t],t,s] \to -\frac{a0\,(k2+s)}{k1\,k2-(k2+s)\,(k1+k3+s)},$$

$$\left.\left.\text{LaplaceTransform}[b[t],t,s] \to -\frac{a0\,k1}{k1\,k2-(k2+s)\,(k1+k3+s)}\right\}\right\}$$

■ **Inverse Laplace transform for each term to give solution**

```
In[5]:= sa[t] = InverseLaplaceTransform[Y[s][[1, 2, 1]] /. Y[s], s, t];

In[6]:= sb[t] = InverseLaplaceTransform[Y[s][[1, 3, 1]] /. Y[s], s, t];

In[7]:= sc[t] = InverseLaplaceTransform[Y[s][[1, 1, 1]] /. Y[s], s, t];
```

The solutions obtained in sa[t], sb[t] and sc[t] are somewhat unwieldy and require further manipulations and substitutions within Mathematica using functions such as FullSimplify, Factor, Collect, Expand to produce more compact versions. The final versions are:

$$[EA]_t = [EA]_0\left[\frac{(k_p - k_c)}{2k_p}\left\{e^{-\frac{1}{2}(k_p - k_t)t}\right\} + \frac{(k_p + k_c)}{2k_p}\left\{e^{-\frac{1}{2}(k_p + k_t)t}\right\}\right] \quad \text{(s1)}$$

$$[EAEE]_t = \frac{k_1[EA]_0}{k_p}\left\{e^{-\frac{1}{2}(k_p - k_t)t} - e^{-\frac{1}{2}(k_p + k_t)t}\right\} \quad \text{(s2)}$$

$$[AEA]_t = [EA]_0\left[1 + \frac{(k_d - k_p)}{2k_p}\left\{e^{-\frac{1}{2}(k_p + k_t)t}\right\} - \frac{(k_d + k_p)}{2k_p}\left\{e^{-\frac{1}{2}(k_p - k_t)t}\right\}\right] \quad \text{(s3)}$$

where $k_t = k_1 + k_2 + k_3$, $k_c = k_1 - k_2 + k_3$, $k_d = k_1 + k_2 - k_3$ and $k_p = \sqrt{k_t^2 - 4k_2k_3}$

Hoogmartens data, global fits to both datasets.

Figures 1 and 2 show the fits to Model II and Model III respectively. The fitting parameters are given in table 1

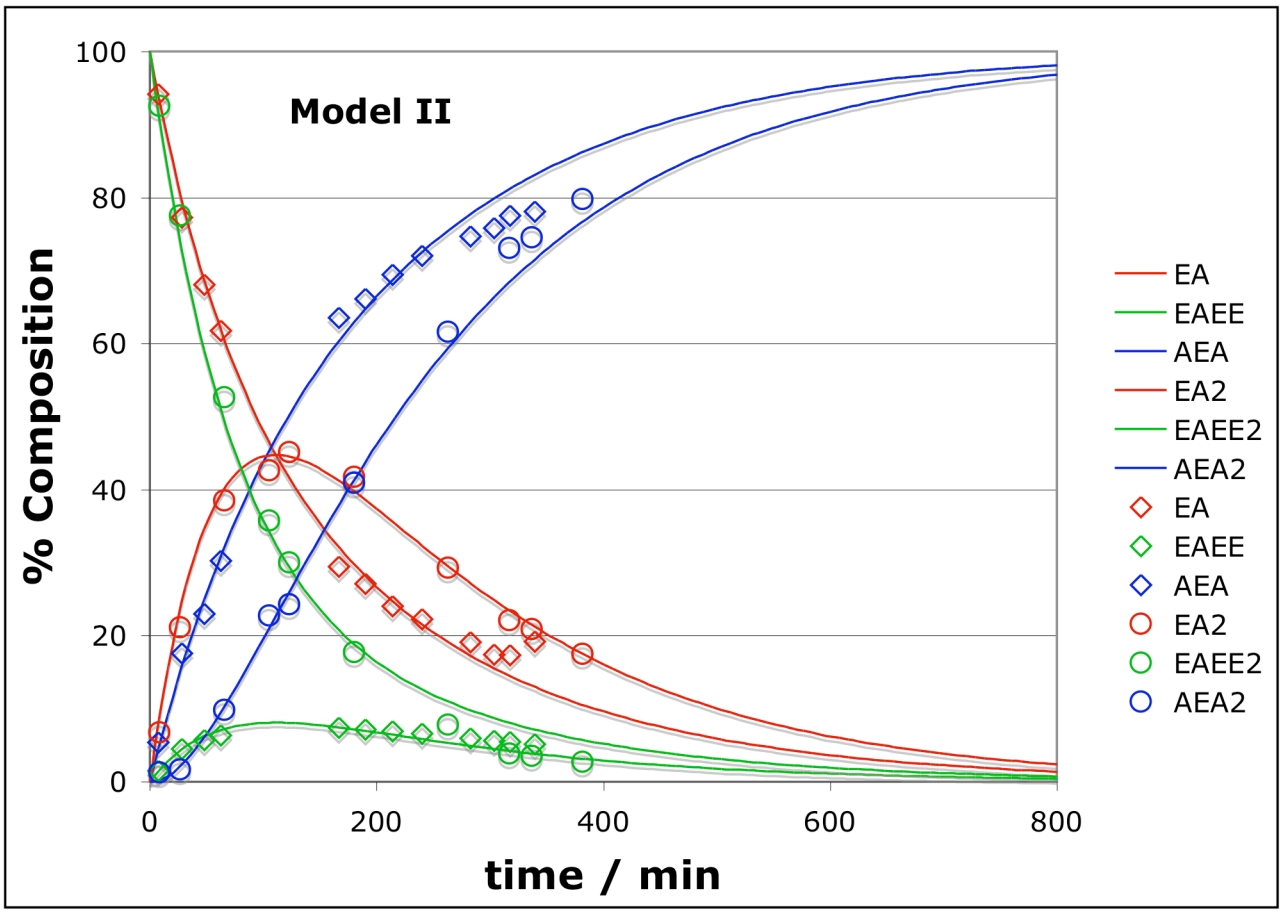


Figure 1. Global fits to Model II for Hogmartens data for EA and EAEE datasets[12].

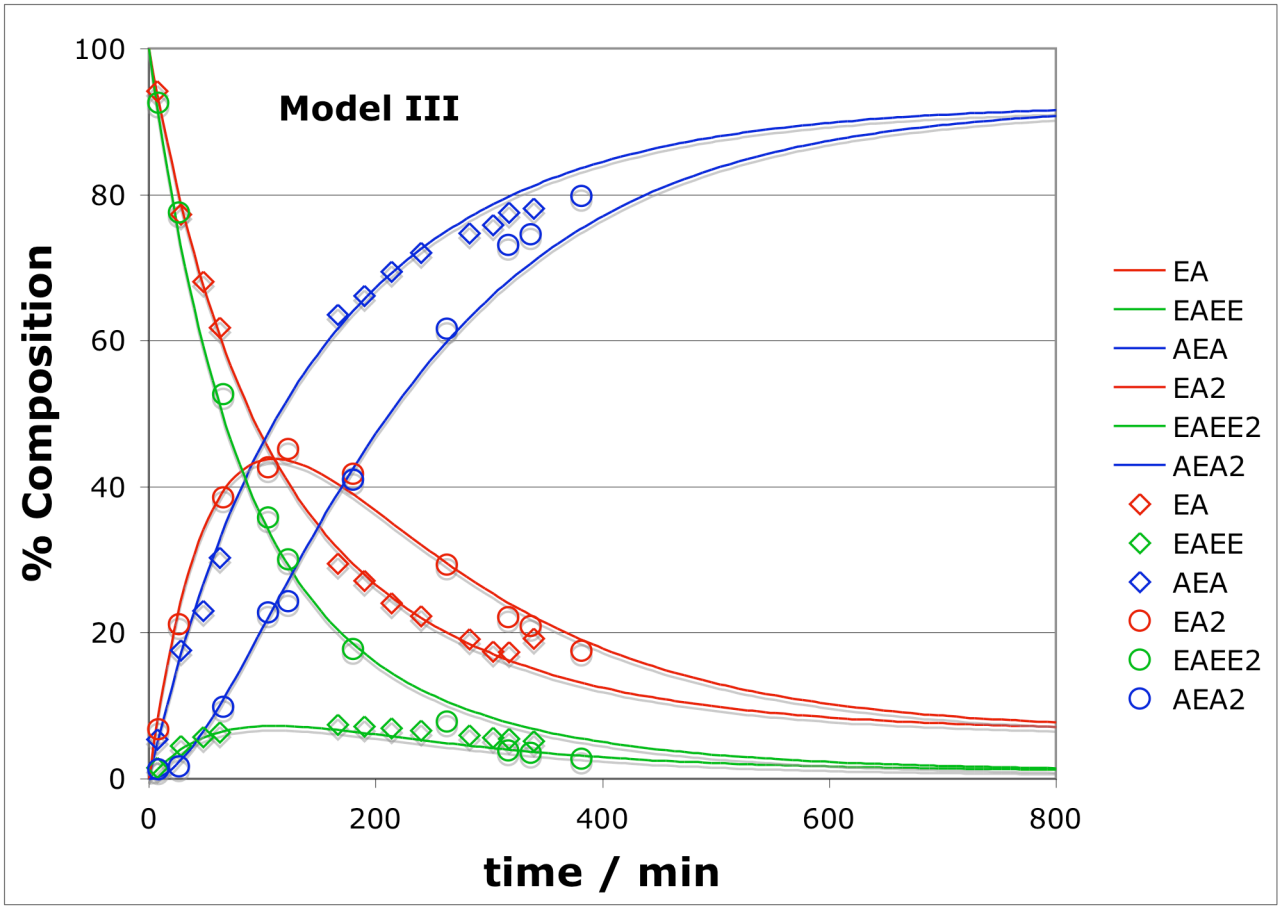


Figure 2. Global fits to Model III for Hogmartens data for EA and EAEE datasets[12].

	Model	*SS*	$k_1/10^{-3}$ min^{-1}	$k_2/10^{-2}$ min^{-1}	$k_3/10^{-3}$ min^{-1}	$k_4/10^{-3}$ min^{-1}
Original analysis*	II	–	2.1± 0.39	1.1 ± 0.22	6.6 ± 0.1	–
This paper	II	0.0319	2.1 ± 0.20	1.16 ± 0.03	6.3 ± 0.10	–
This paper	III	0.0266	1.9 ± 0.2	1.14 ± 0.03	6.85 ± 0.14	0.48 ± 0.14

Table 1. Fitting parameters to Hoogmartens EA and EAEE datasets.[12,] The quoted errors are half those of equation 6 for consistency with the original paper. *Constrained k_1 value.

The least-square fitting error *SS* is still smaller for Model III than Model II, but the datasets display some internal inconsistency. In particular the EAEE data from set 2 (starting from EAEE) falls towards zero much more quickly than for set 1 (starting from EA). This means that neither model can hope to fully fit the experimental data, hence the larger value of SS.

EA and AEA datasets – Model III fits from our earlier study[19]

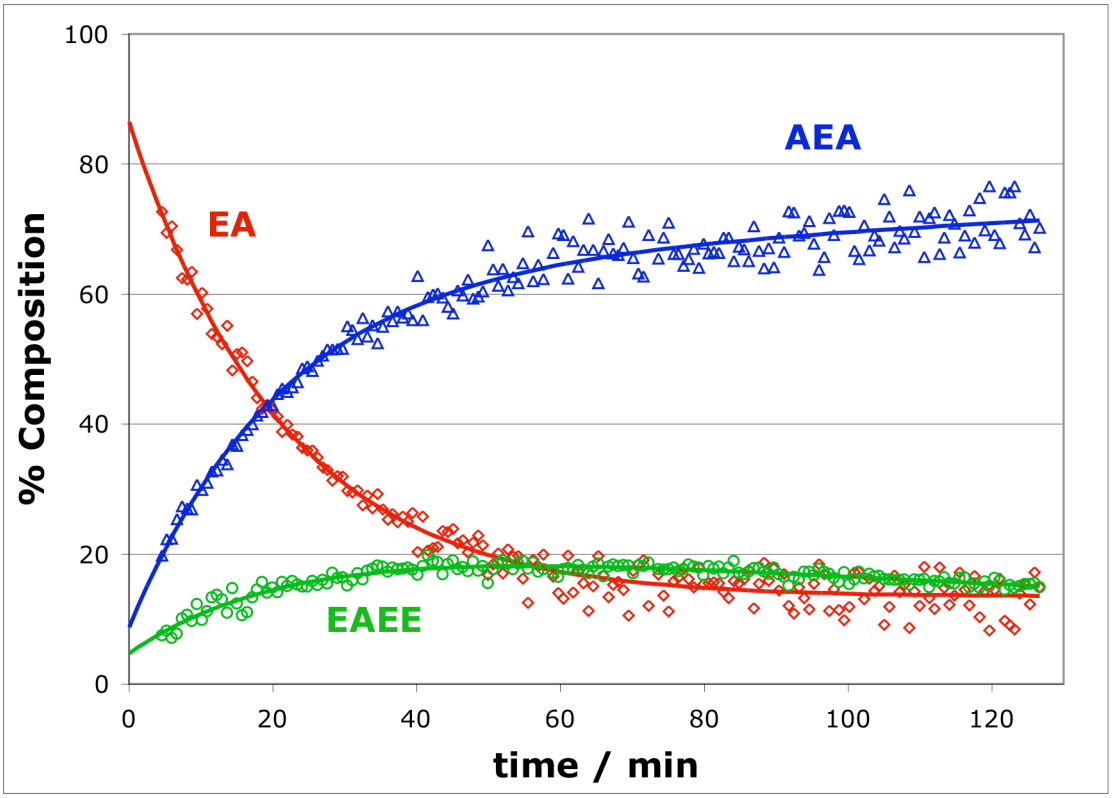


Figure 3. The degradation of erythromycin A in deuteriated phosphate buffer (0.2 M) at apparent pH 3**,** 37 °C. Fits are to Model III.[19]

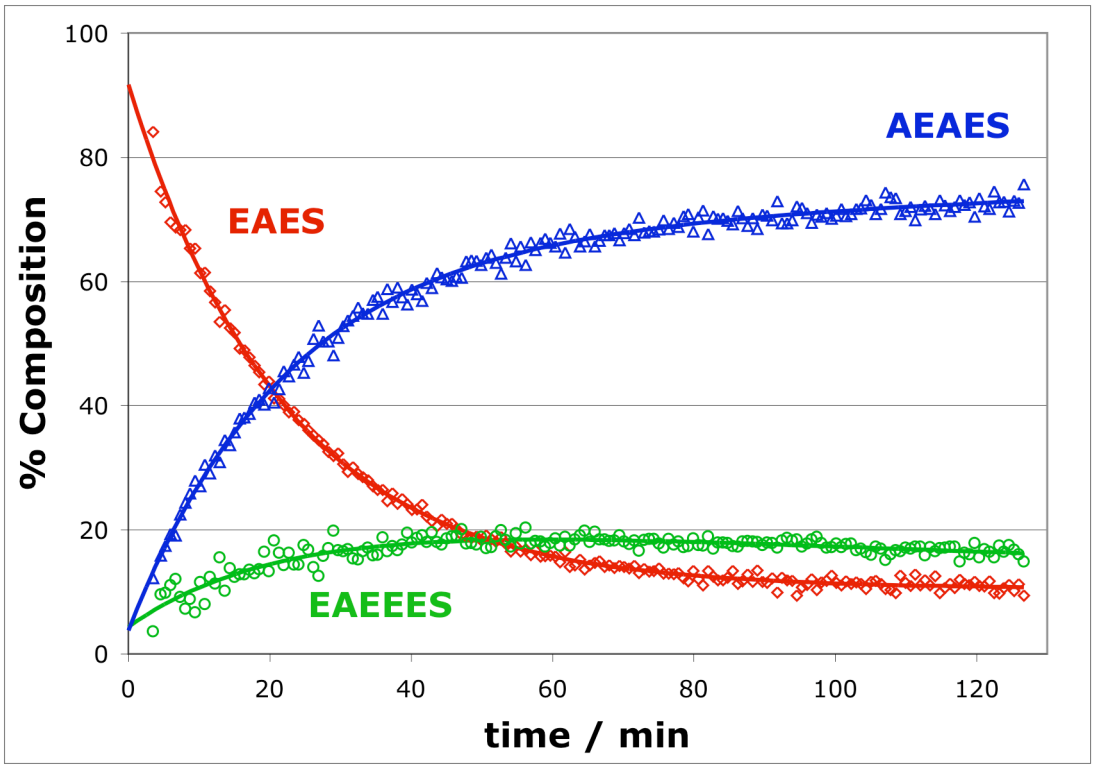
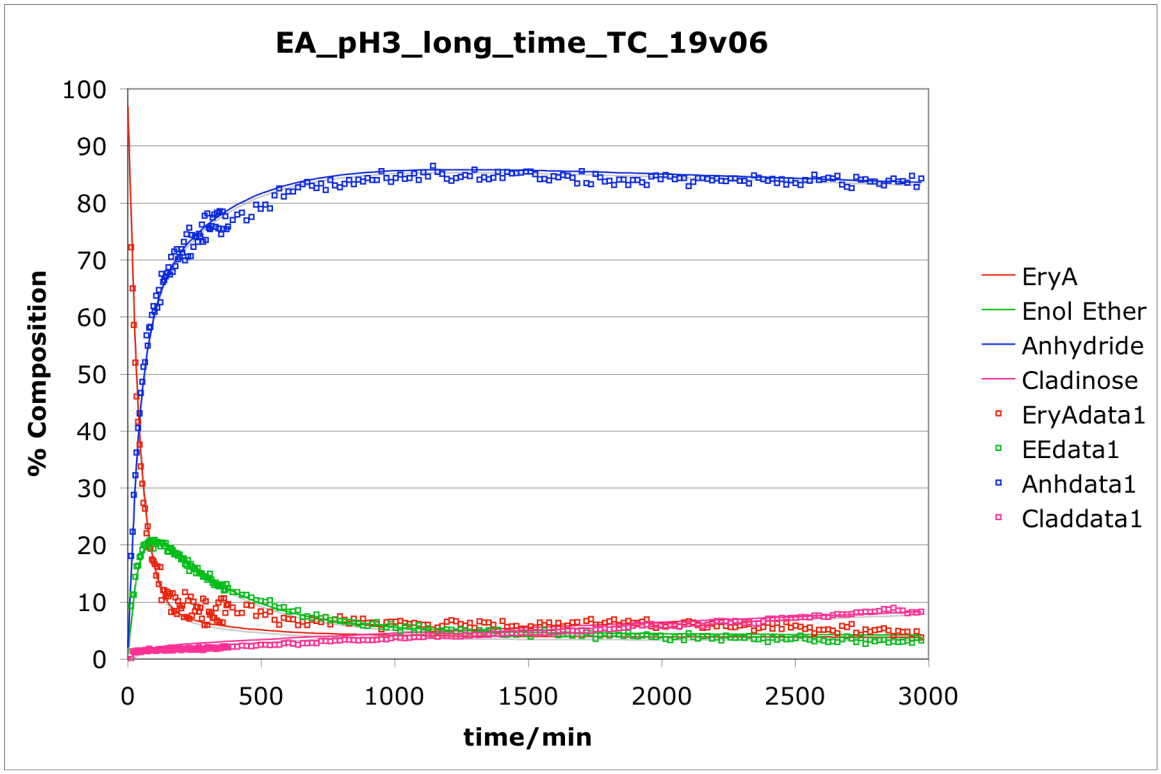
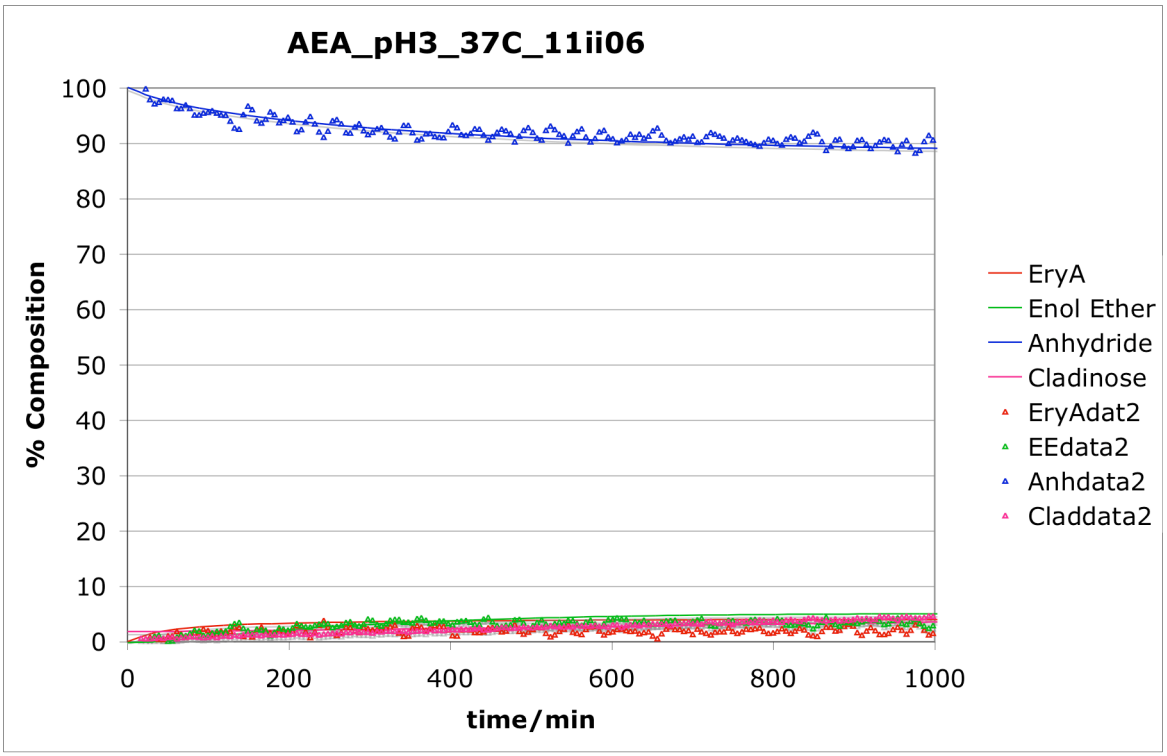


Figure 4. The degradation of erythromycin A 2´-ethyl succinate in deuteriated phosphate buffer (0.2 M) at apparent pH3**,** 37 °C. Fits are to Model III.[19]

EA and AEA datasets – separated versions of paper figure 4





EAES and AEAES datasets – separated versions of paper figure 5