# ERYTHROMYCIN AS A SUPRAMOLECULAR RECEPTOR

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Summary: When Erythromycin A (E) is added to a solution of Rhodamine B base (Z)
dissolved in chloroform, dioxane or DMSO the color disappears immediately and
this effect is attributed to the formation of a Host-Guest complex between Z
and E followed by a fast lactonization of Z.

The study of reactions which involve non-covalent interactions between two
molecules, one which acts as a host and another that acts as a guest, is a
subject of great current interest in fundamental as well as in applied
research.[1] Some antibiotics have been found to interact with very high
selectivity with ions and have been studied as natural ionophores,[2] but to the
best of our knowledge there has not been any study where an antibiotic acts as
a host for an organic molecule. We think that the macrocylic structure of some
of the known antibiotics may be a good receptor for an organic guest and so we
undertake a study of the interaction of some natural antibiotics with dyes. We
wish to report here the remarkable effect of Erythromycin A (**E**) on the
lactonization reaction of Rhodamine B base (**Z**).[3] The zwitterion **Z** exists in
equilibrium with its lactone form **L**, and the position of the equilibrium (eq.1)
depends strongly on the solvent, for instance in water it lies almost completely
on the left whereas in benzene it lies completely on the right.[4] The position
of the equilibrium to the side of the zwitterion is so strongly stabilized by
hydrogen bonding that the single contact of the lactone with celulose produces
the red colour characteristic of **Z**.[5]

E

R=CH₃
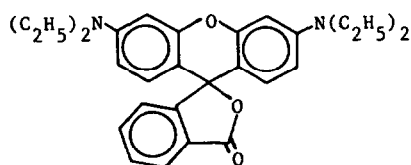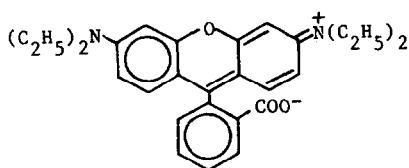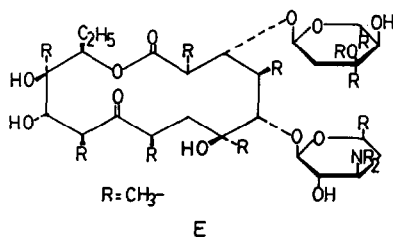
eq.1

Z   L

A 10^{-5}M solution of **Z** in chloroform has a λ_{max} at 551nm and shows an absorption of 0.688 indicating that it is almost completely in the form of **Z**[6]. The addition of **E** in a molar ratio equal to 1:1, produces an instantaneous bleaching of the solution whose optical density decreases to 0.040. A similar observation was done when **E** was added to a solution of **Z** in dioxane or DMSO, but in this case a solution with equal concentration of **Z** and **E** (2.26×10^{-5}M) has no absorption at the λ_{max} of **Z**, 558nm and 564nm in dioxane and DMSO respectively. On the other hand, only a small decrease in optical density is observed when **E** is added to a water solution of **Z**. A plot of Abs. vs [E]/[Z] ratio indicates that the stoichiometry of the interaction is 1:1 (Figure 1).[7] The observed decoloration is reversible since the addition of increasing amounts of ethanol to the solution in chloroform or dioxane leads to the original spectrum (Figure 2).

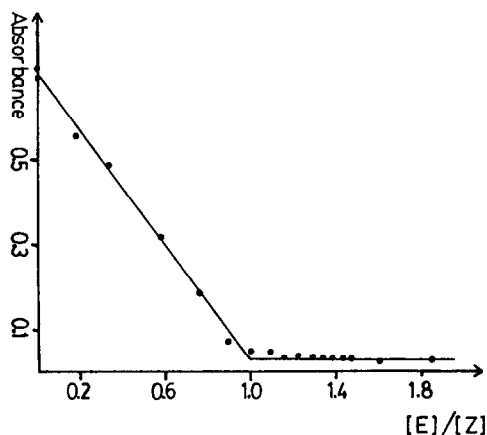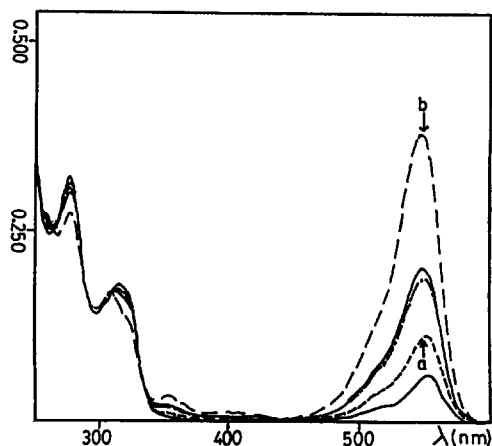FIGURE 1: Plot of absorbance vs. [E]/[Z] ratio in chloroform $[Z]_0 = 1 \times 10^{-5}$M

FIGURE 2: Spectrum of Z and E in chloroform at variable concentration of ethanol: 0.26, 0.51, 0.60 and 1.03 M from a to b.

Similar reversibility is observed when water is added to the dioxane or DMSO solution. It is important to note that the effect of the addition of water is more important in dioxane than in DMSO (Table).

It has been reported that in non protic solvents the equilibrium constant determined when **Z** is dissolved in the solvent is different from that measured starting from a solution of **L**[5]. We observed that a solution of **L**[8] in dioxane, chloroform or DMSO has no absorption at the λ_{max} of the **Z** form, which indicates that the rate of equilibration of eq.1 is very slow in these solvents. On the other hand, when **Z** is dissolved in DMSO and the solution is heated at 70°C its absorbance decreases slowly because of the transformation into **L**. The rate constant of this reaction which is estimated from initial rate measurements is $1 \times 10^{-5} s^{-1}$, thus the fact that in the presence of **E** the lactonization reaction occurs at a rate higher than 0.1 s^{-1} [9] at 25°C, indicates that **E** is acting as a

TABLE: Absorption of solutions of **Z** and **E** in dioxane or DMSO in the presence of different concentration of water or ethanol. $[Z]_o = [E]_o = 2.26 \times 10^{-5} M$.

Water or Ethanol, M.	Absorption		
	Dioxane		DMSO
	Water	Ethanol	Water
1.8	0.030	0.004	0.008
2.6	0.067	0.014	0.012
3.4	0.104	0.042	0.023
5.1	0.254	0.154	0.038

very efficient catalyst for this reaction. Since **E** has five -OH groups it might stabilize **Z** through hydrogen bonding as other hydrogen bond donors do, but as indicated above the effect of the addition of **E** is the opposite, namely the equilibrium shown in eq.1 is driven to the right. This result would indicate that a host-guest complex is formed between **Z** and **E** and that the binding energy contributes to decrease the free energy of activation for the intramolecular reaction. This probably means that in the process of binding there is a change in the geometry of **Z** especially around the central carbon favoring its transformation from a sp^2 into a sp^3 hidridized carbon. Besides, as the geometrical distortion proceeds, the carboxylate group must be directed toward the electrophilic central carbon so as to stabilize it until it reaches an appropriate position to form the C-O bond of the lactone. Similar interpretation has been given to the catalysis by cyclodextrin of the lactonization of phenolphthalein.[10] Studies are under way in order to determine the structure of the host-guest complex formed.

REFERENCES AND NOTES

(1) a) Lehn, J.M. Science (Washington D.C.) 1985, 227, 849-856.

    b) "Host-Guest Complex Chemistry Macrocycles" Vögtle F.; Weber E.; Ed. Springer-Verlag, Berlin, Heilderberg, 1985.

(2) Reference 1b, p.43.

(3) Rhodamine B base and Erythromycin A were purchased from Aldrich and Sigma respectively and were used without further purification.

(4) Ramette R.W., Sandell E.B., J.Amer.Chem.Soc. 1956, 78, 4872-4878.

(5) Rosenthal I.; Peretz P.; Muszkat K.A.; J.Phys.Chem., 1979, 83, 350-353.

(6) The solutions for all this study were prepared immediately before use and protected from light since it produces a fast decoloration. Besides the absorbance of solutions of identical concentration shows a variation of optical density in values as hight as 20% which may be attributed to adsortion of Z by the silica surface of the glassware as was observed with other dyes (see Stork, W.H.J., de Hasseth, P.L., Shippers, W.B., Kormeling, C.M., Mandel, M. J.Phys.Chem., 1973, 77, 1772).

(7) Ayres, G.H., Quantitative Chemical Analysis; Harper & Row: New York, 1968. Análisis Químico Cuantitativo; Ed. del Castillo: Madrid, 1970, p.494.

(8) To prepare L , 50 mg of Z where refluxed with 30 ml of benzene during 1 hour. This procedure was repeated twice and the combined benzene solutions yielded, after evaporation, 40 mg of pure lactone. The purity was checked by IR and UV spectra.

(9) This is the highest first order rate constant that we can measure and decoloration of the solution of Z when E is added occurs at least 10 times faster.

(10) Taguchi L., J.Amer.Chem.Soc., 1986, 108, 2705-2709.