

MACROLIDE RING CLOSURE:

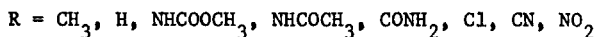
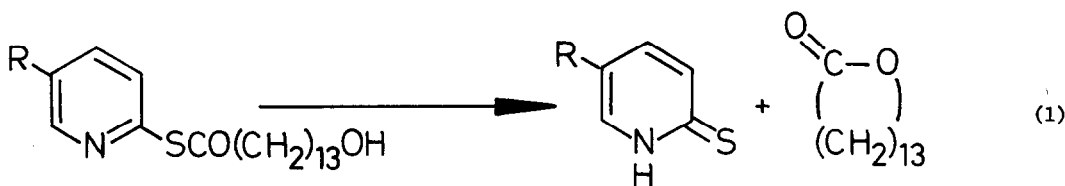
"DOUBLE ACTIVATION" MECHANISM

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Summary: We reinterpret kinetic results of Wollenberg, Nimitz and Gokcek¹ to indicate substantial S-C bond cleavage and N-H bond formation in the transition-state of the rate-limiting step for macrolide ring closure from ω -hydroxy 2-pyridyl thioesters.

A recent report of a study of macrolide ring closure from ω -hydroxy 2-pyridyl thiol esters (equation 1) included data for the rate constants for a series of substituents in the



5-position of the pyridine ring. A non-linear Hammett correlation was interpreted as a change in mechanism from N-H bond formation preceding C-O formation for electron-donating substituents to C-O formation preceding N-H bond formation for electron withdrawing substituents.¹

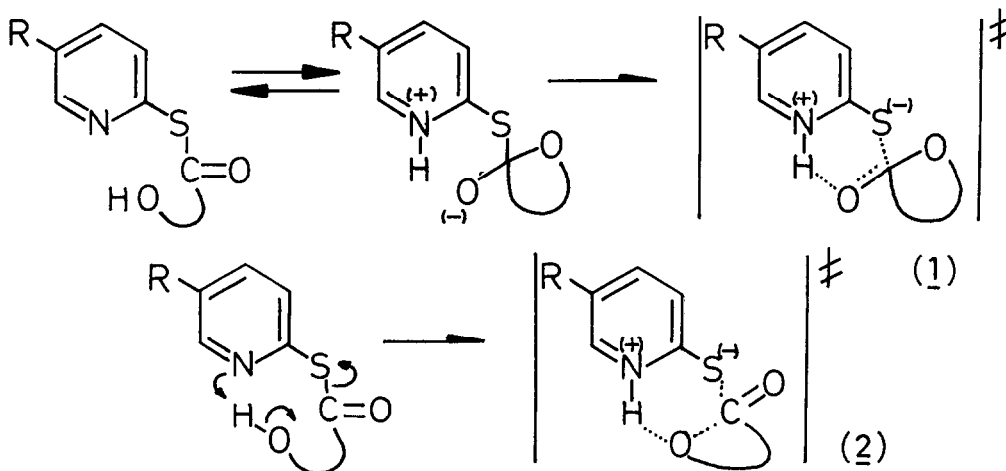
The present paper re-interprets the data of Wollenberg, Nimitz and Gokcek¹ according to Jaffe's method for the effect of substituents on reactions involving two or more side chains on the same ring (equation 2)²; the effects of a substituent on "side chain" nitrogen and on

$$\log k_R/k_H = \sigma_N \rho_N + \sigma_S \rho_S \quad (2)$$

leaving sulphur are independent. It is not surprising that the correlation using two disposable parameters (ρ_S and ρ_N) is superior to that using a single parameter (see figure) but the latter method is not the correct one to use in this case; since both N (*meta*) and S (*para*)

may be involved in the mechanism there is an important problem in the original treatment of the assignment of σ values (σ_m or σ_p). The previous authors¹ chose to use σ_m values but there is no justification for this.

The conclusions that we can draw from the derived ρ_N and ρ_S values (figure) are that the S-C bond is extensively cleaved in the transition-state of the rate-limiting step by comparison of ρ_S (2.76) with the Hammett value for the ionisation of thio-phenols in 95% ethanol/water (3.02);³ we use σ^- values for the substituents *para* to the sulphur. The use of standard Hammett σ values as σ_S gives a marginally poorer correlation (figure). The value of ρ_N (-4.27) is slightly greater than that for the ionisation of substituted pyridines in water (-5.77)⁴ consistent with less than unit positive charge on the nitrogen in the transition-state; this argues for some form of interaction from the reacting centre on the $\ddot{N}H$ group probably by negatively charged oxygen. Reasonable interactions could be with the carbonyl oxygen in a stepwise process (1) from a tetrahedral intermediate or a concerted process (2) where the proton is almost completely transferred from the ω -hydroxyl group.



Two other possible transition-state structures consistent with the present conclusions of large positive charge on N and extensive S-C bond fission involve rate limiting S \rightarrow N transfer of the ω -hydroxy acyl group⁵ and an E1cB mechanism⁶ but these are excluded on other grounds.^{5,6} The essentially complete proton transfer (from ground- to transition-state) to nitrogen is consistent with the values of k_H/k_D ($0.5 < k_H/k_D < 1.6$) found previously.¹ The absence of a break in the extended Hammett plot is indicative of a single mechanism throughout the substituent range.

Since the reactions which we use as Hammett parameter standards were carried out in solvents different from that used in the ring closure reactions (xylenes) we are not able to estimate reliable "effective charges" for the transition-state and our measures of the extent of bond cleavage and formation are only qualitative. The stepwise mechanism with (1) as the transition-state from decomposition of a tetrahedral intermediate requires S-C fission to be

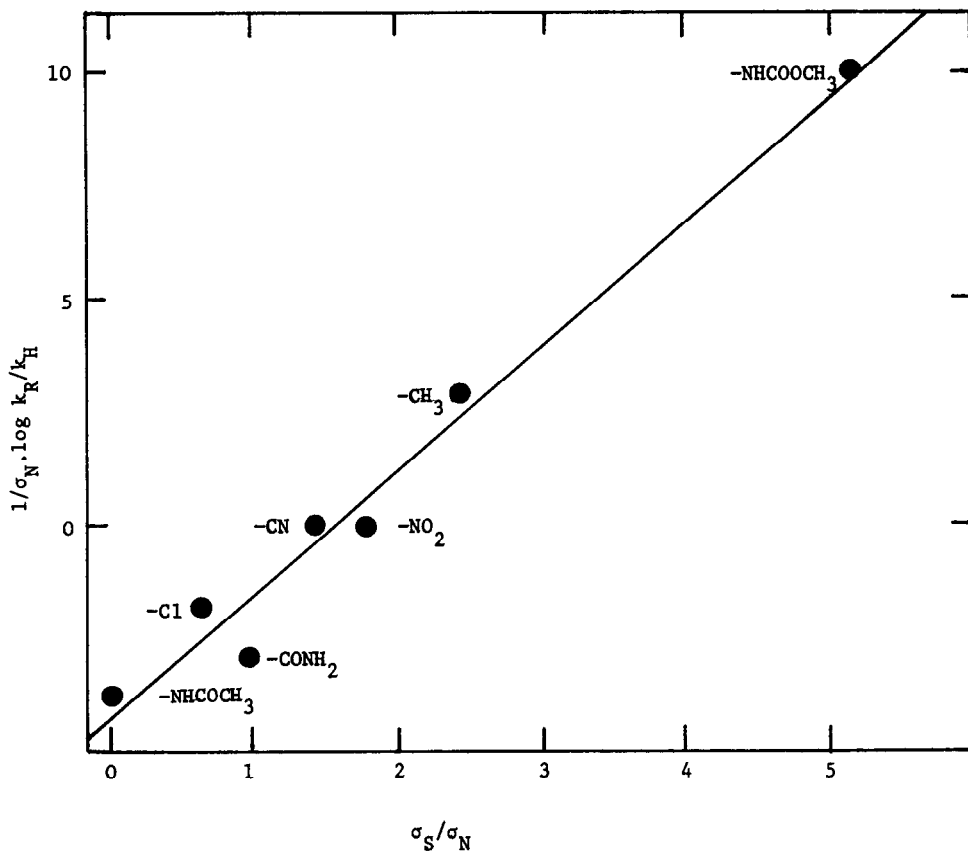


Figure: Hammett σ^- Correlation

- Rate constant data are taken from Wollenberg, Nimitz and Gokcek¹
- Values of σ_S (σ_p^-) and σ_N (σ_m^-) are derived from tables of Barlin and Perrin.⁷ The amido group value for σ_S is obtained from Jaffé and Doak;⁸ the values of σ_N and σ_S for $-\text{NHC(=O)OCH}_3$ are from pK values for the corresponding benzoic acid and the parent measured under the same conditions using 0.1M ionic strength at 25° (4- NHC(=O)OCH_3 , 4.39; 3- NHC(=O)OCH_3 , 4.10; parent, 4.03).
- Line is theoretical for the Hammett σ^- correlation:

$$1/\sigma_N \cdot \log k_R/k_H = -4.27 + 2.76 \sigma_S/\sigma_N \quad (r = 0.988).$$

The equation for the standard Hammett correlation is:

$$1/\sigma_N \cdot \log k_R/k_H = -3.77 + 2.69 \sigma_S/\sigma_N \quad (r = 0.982).$$

rate limiting if extensive S-C fission is to be observed. It is expected, however, that decomposition of the intermediate via departure of the 2-mercapto-pyridine would be faster than the return to reactants involving an oxyanion leaving group. The non-polar solvent for the reaction would favour mechanism (2).

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