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MECHANISTIC AND SYNTHETIC ASPECTS OF MACROLIDE RING CLOSURE

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Summary: Kinetic studies have substantiated the idea of a "double-activation" mechanism for macrolide ring closure from relatively electron-rich 2-pyridyl thiolesters while a change of mechanism is observed for electron-poor 2-pyridyl thiolesters. Mechanistic and synthetic aspects of the ion-assisted cyclization are also discussed.

We wish to report our kinetic studies of macrolide ring closure from ω-hydroxy 2-pyridyl thiolesters. The large accelerating effect of the pyridine ring (and similar heterocycles) has been attributed to a "double-activation" mechanism.[1] This mechanism is consistent with several reported observations, including the absence of acid or base catalysis, the low reactivity of the isomeric ω-hydroxy 4-pyridyl thiolesters, and certain labeling studies which eliminate intermediate ketene-type structures.[2] The electronic character of the pyridine ring should have a signigicant influence on the degree of interaction for the speculated proton chelate structure (Figure 3, X = H) and this should be reflected in the rate of macrolide cyclization.

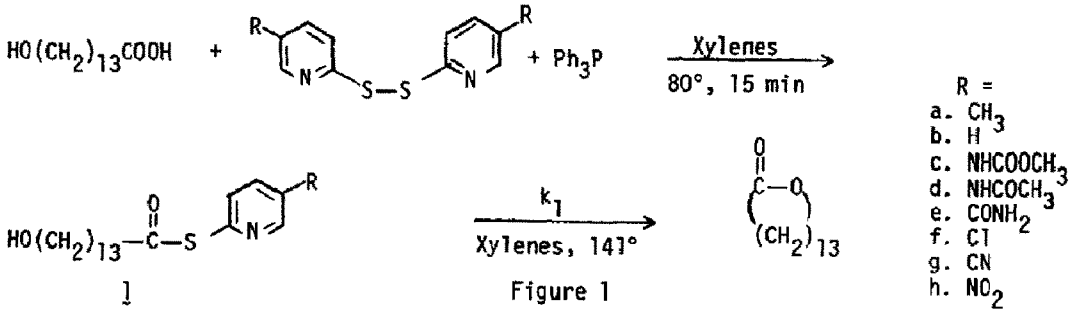

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Figure 1

In particular, it was our desire to determine the influence of basicity[3] versus leaving-group ability for various 2-pyridinethiolates (Figure 1). A series of symmetrically substituted 2,2'-dipyridyl disulfides was synthesized and the cyclization rates for ring closure of 14-hydroxytetradecanoic acid were studied for comparison.[4] For each thiolester 1a-h the cyclization reaction showed excellent first-order kinetics. Least-squares fitting of the data to the equation $\ln(C/A) = k_1 t$ gave the first-order rate constants k_1 with correlation

coefficients r = 0.998 to 0.999 for 4 to 7 points in each case. A plot of log (k_1) *versus* σ_m reveals a striking change in mechanism in the region of σ_m = 0.12 (Figure 2).

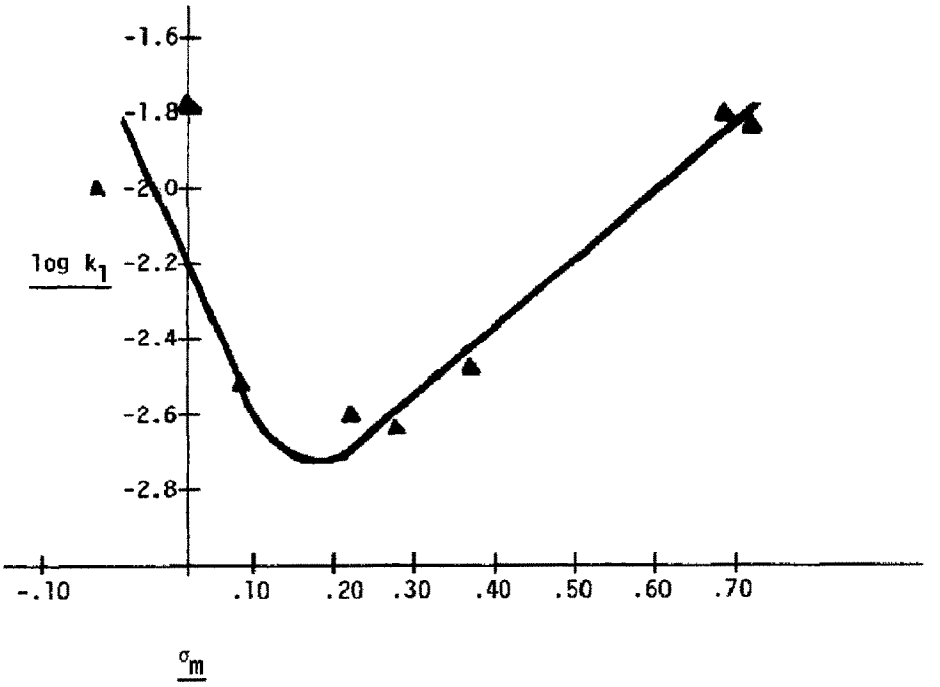
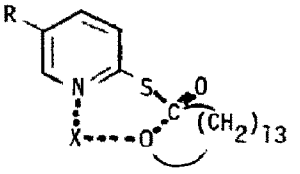


Figure 2

For σ_m >.12, ρ = 1.77 (5 points, r = .984), implying a transition state with negative charge on or near the pyridine ring. For σ_m <.12, however, ρ = -4.34 (3 points, r = .64), indicating that for electron-donating groups, the transition state involves a positively charged (i.e. protonated) pyridine ring. These data suggest that the transition state resemb that shown in Figure 3, where electron-donating substituents lead to significant N-H bond for tion before C-O bond formation, whereas for electron-withdrawing substituents, C-O bond forma tion precedes N-H bond formation.

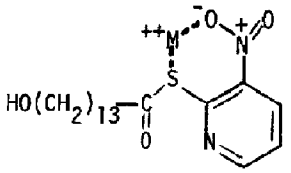


X = H, D

Figure 3

On the basis of this mechanism, deuterium labeling of the hydroxyl group of thiolesters 1 was expected to have opposite effects on the rates of cyclization for thiolesters with electron-donating versus electron-withdrawing groups. For 2,2'-dipyridyl disulfide (1b) a primary isotope effect is expected with $k_H/k_D > 1$.[5] Experimentally, the ratio was found to be 1.68. On the other hand, strong electron-withdrawing groups should lead to a secondary isotope effect with $k_H/k_D < 1$.[6] For 2,2'-bis(5-nitropyridyl) disulfide (1h) the ratio k_H/k_D was determined to be 0.58, consistent with expectation.

A substantial increase in the rate of macrolide cyclization from thiolesters in the presence of metal ions has been previously noted.[7] Presumably, this acceleration results from metal-sulfur coordination leading to a more electrophilic carbonyl center. Our additional finding that a nitro substituent on the pyridine nucleus substantially accelerates ω-hydroxy thiolester cyclization prompted our investigation of metal-assisted ring closure of 3-nitro-2-pyridyl thiolesters. In this case bidentate metal chelation (2) was expected to greatly accelerate the rate of lactone formation.[8] In the presence of excess mercuric chloride cyclization of the thiolester from 14-hydroxytetradecanoic acid undergoes rapid cyclization at room temperature (82%). On the other hand, the rate of cyclization from thiolester 3 was significantly slower in the presence of various metal ions compared to the analogous thermal process. Thus, bidentate metal binding to the phenanthroline ring (3), although making the thiolate a better leaving group, greatly decreases the basicity of the ring nitrogens and retards the reaction. This is in agreement with the results of our Hammett study of substituted 2-pyridyl thiolesters, which shows that either high basicity of the nitrogen or good leaving-group ability of the thiolate led to high rates of cyclization, while lower rates were obtained when both factors were intermediate.



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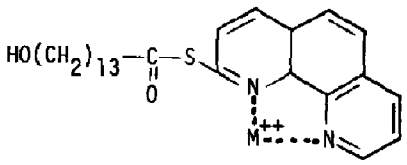

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References and Notes

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4. The experiments were conducted as follows: Triphenylphosphine (32.2 mg, .123 mmol, 1.5 eq) 14-hydroxytetradecanoic acid (ref. 3, 20.0 mg, .082 mmol, 1.0 eq) and the substituted dipyridyl disulfide (.123 mmol, 1.5 eq) were stirred under nitrogen in xylenes (3 ml, freshly distilled from sodium metal) at 80° for 15 min to form the thiolester. The solution was diluted to 19.0 ml with xylenes, and 1.00 ml of a standard solution of hexadecane in xylenes was added as a gas chromatographic internal standard. The mixture was brought to reflux by immersion in a pre-heated 160° bath. Aliquots were removed at intervals and cooled in dry ice until analyzed by gas chromatography. GC analysis: 2 m, 2 mm i.d. glass column packed with 3% OV-17 on 80/100 Chromosorb W-HP, programmed from 130° to 200°. All runs were repeated and k values were reproducible within 2%.
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8. 2,2'-Bis(3-nitropyridyl) disulfide was prepared from commercially available 2-chloro-3-nitropyridine. Procedure: Sodium sulfide nonahydrate (3.41 g, 0.75 eq) was refluxed in 95 ethanol (150 ml) for 10 min; then sulfur (0.46 g, 0.75 eq) was added and the resulting dark green solution was refluxed 15 min to form Na_2S_2. This hot solution was added in portions to a solution of 2-chloro-3-nitropyridine (3.00 g, 1.00 eq) in 95% ethanol (100 ml), and the red solution was refluxed for 2 hr. The precipitate was collected by filtering the hot solution and recrystallized from benzene to give 2,2'-bis-(3-nitropyridyl) disulfide (II), MP 241-243° (1.20 g, 41%).

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