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NUCLEOPHILIC CLEAVAGE OF SPIROACTIVATED CYCLOPROPANES.1. KINETIC AND THERMODYNAMIC PARAMETERS FOR REACTION OF 6,6-DIMETHYL-2-PHENYL-5,7-DIOXASPIRO[2,5]OCTANE-4,8-DIONE (2) WITH PYRIDINE.

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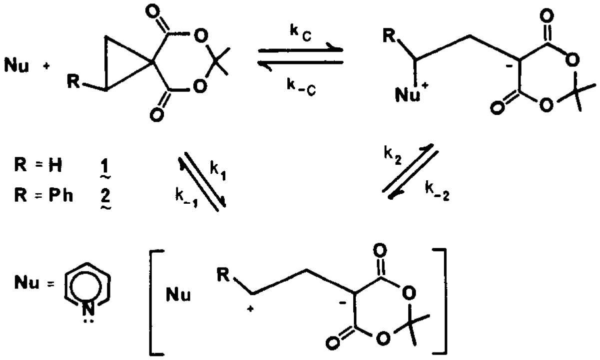
SUMMARY: Reaction of the title spiroactivated cyclopropane(2) with pyridine in acetonitrite yields a zwitterionic addition product. The reaction is reversible which provides conditions under which rates and equilibria constants can be obtained along with the derived activation and thermodynamic parameters of reaction. An extended Bronsted treatment affords a β_{nuc} value for the reaction of 2 with substituted pyridines.

Nucleophilic opening of electron-deficient cyclopropanes has found application in organic synthesis[1], the utility being greatly enhanced by the increased reactivity of spiroactivated cyclopropyl ring systems[2]. Mechanistically the reaction is of fundamental importance being related to the Michael reaction of activated alkenes[3,4] and nucleophilic substitution at saturated carbon[5]. For this reason we began a comprehensive kinetic investigation of the nucleophilic cleavage of spiroactivated cyclopropanes. We report here some of our initial findings. Previous mechanistic studies have been carried out by Cram[6] utilizing simple diactivated cyclopropanes and by Hanafusa[7] in an interesting dispiroactivated system.

The reaction systems chosen for our initial studies are shown below in Scheme I.



Scheme I

The ring opening reaction with nucleophiles can proceed by way of a concerted pathway (k_c) or in a stepwise fashion involving two different transition states. The parent substrate (R = H, 1) was found by Danishefsky[2] to react at room temperature (48 h) with pyridine to yield a yellow betaine product. Indeed under pseudo-first-order conditions, we have found the reaction of 1 with pyridine (10^{-3} M 1, 0.6 M pyr) in acetonitrite occurs slowly at 25°C, $t_{\frac{1}{2}}$ = 31 h.[8] The reaction is second order ($k_c = 1.04 \times 10^{-5}\ M^{-1}\ s^{-1}$) and irreversible.[9]

The reaction of **2** with pyridine in acetonitrile proceeds nearly two orders of magnitude faster than the reaction of **1**. A plot of the pseudo-first-order rate constant, k_{obs}, versus the concentration of pyridine yields a straight line with a slope equal to the bimolecular rate constant, k_c (Figure 1).

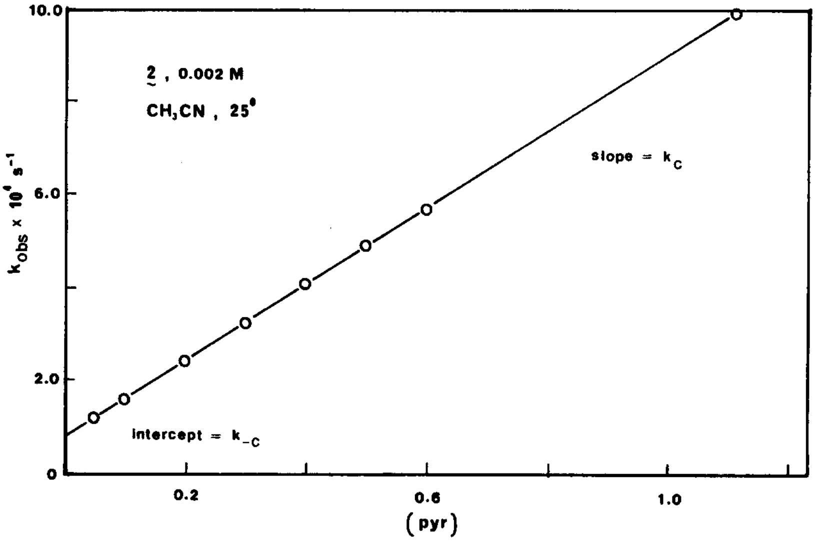


Figure 1.

The non-zero intercept of the plot yields a unimolecular rate which could correspond to the forward rate process, k_1, or the rate of reclosure of the cyclopropyl ring, k_{-c}. The latter was found to be the case since the ring opening-ring closure equilibrium can be approached from both sides of the equilibrium. This was shown by the time dependence of approach to equilibrium plotted in Figure 2. Thus under one set of reaction conditions reliable values for rates and equilibria constants can be obtained along with the derived activation and thermodynamic parameters of reaction.

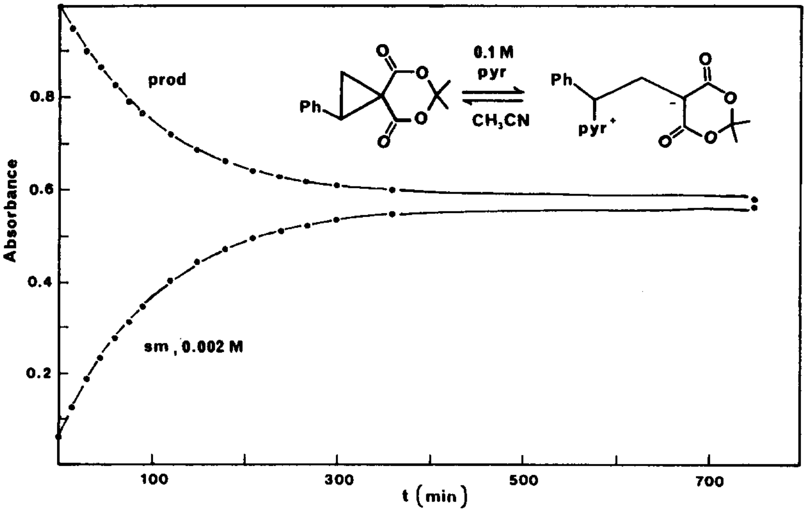


Figure 2.

These are listed in Table I. Equilibria have been measured for only a few organic reactions. The Menschutkin reaction[10,11], methyl transfer[12], and the direct reaction of carbocations with carbanions[13] are some pertinent examples.

Table I. Rates of Reaction and Derived Activation and Thermodynamic Parameters for Reaction of 2 with Pyridine in Acetonitrile at 25°C.

	ΔH(kcal/mol)	ΔS(eu)	ΔG(kcal/mol)
k_c (8.27×10^{-4} M^{-1} s^{-1})[a]	13.5	-27.3	21.6
k_{-c} (7.51×10^{-5} s^{-1})[b]	24.8	5.7	23.1
K (11 M^{-1})[c]	-11.9	-33.0	-1.5

[a] Obtained from the slope of a plot of k_{obs} vs [pyr]. [b] Obtained as the intercept of a plot of k_{obs} vs [pyr]. [c] $K = k_c/k_{-c}$

The activation parameters for reaction of 2 with pyridine are remarkably similar to those reported for the reaction of substituted pyridines with alkyl halides, the Menschutkin reaction.[10] The large negative entropy of activation (-32 eu) observed in the Menschutkin reaction has been attributed to solvent reorganization around the halide ion leaving group. Similar solvent ordering at the negative end of the zwitterionic transition state in our system produces a substantial negative entropy of activation(-27 eu).

The reverse process (k_{-c}) exhibits a relatively modest enthalpy of activation (24.8 kcal/mol) suggesting a low degree of ring formation, ring strain, in the cyclization transition state. The positive entropy of activation (5.7 eu) is also indicative of an open transition state. This favorable entropy factor is crucial in allowing the ring formation to be competitive with the bimolecular ring cleavage. The activation parameters found for the ring closure reaction are comparable to those recently reported for the cyclization of a bis-sulfonyl stabilized carbanion to a three membered ring.[14]

Further insight into the transition state structure for the reversible reaction system under study was gained from an extended Bronsted treatment. A Bronsted correlation for the k_c process employing eight substituted pyridines is shown in Figure 3. The β_{nuc} derived from this correlation is 0.26. Thus, although solvent reorganization at the transition state appears to be well advanced, as evidenced by the entropy of activation charge development on the pyridinium nitrogen appears less complete. This is again reminiscent of the Menschutkin reaction transition state where β_{nuc}

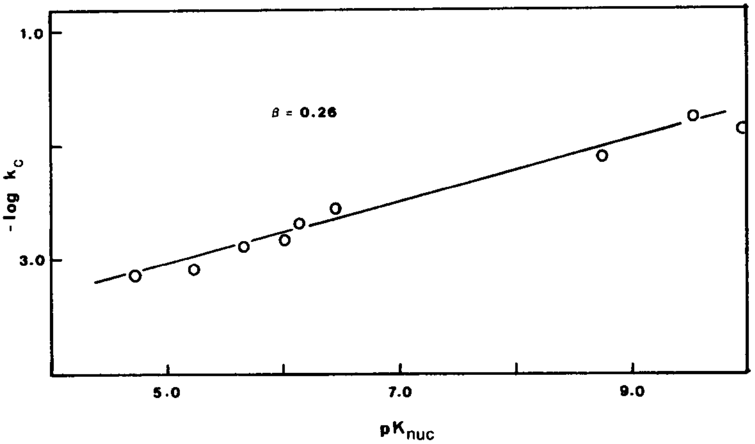


Figure 3.

values of around 0.3 are typically observed.[10] A β_{nuc} of 0.24 was observed for the nucleophilic cleavage by a series of substituted pyridines of the dispiroactivated cyclopropyl system studied by Hanafusa.[7]

In summary, we have shown that the nucleophilic cleavage of spiroactivated cyclopropanes provides a unique opportunity for obtaining the rates and equilibria constants derived from elementary bimolecular and unimolecular processes. Further studies will explore the structure-reactivity relationships provided by these systems as well as the effects solvent polarity and nucleophilicity have on the rates of reaction and position of equilibrium.

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