Reaction of a Highly Spiro-activated Electrophilic Cyclopropane with Pyridines. The Substituent Effect on the Reaction Rate

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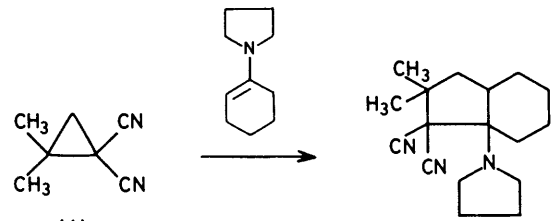
The kinetics of the reactions of 3,3,10,10-tetramethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (7) with a series of substituted pyridines were investigated. The compound underwent well behaved second-order reactions with nucleophiles to afford the polar zwitterionic products (9). Values of log k in acetonitrile fall on a straight line when plotted against the pK_a values of a series of 3- or 4-substituted pyridines and exhibit a Brønsted slope of 0.24. Methyl substitution in the neighbourhood of the reaction centre in the substrate or a nucleophile produced a fall in reactivity to some degree (1/2—1/10) These results together with an unusual solvent effect are interpreted by a preassociative mechanism in which a polar encounter complex is formed prior to the cyclopropane ring opening to give the final product (9).

ABOUT a century ago, Bone and Perkin observed a homo-Michael type reaction between 1,1-bisethoxycarbonylcyclopropane (1) and diethyl malonate (2) under drastic, basic conditions.[1] In 1970, Mattson and his co-workers[2] reinvestigated the chemistry of the cyclopropane derivatives with a number of electron-withdrawing groups. They synthesized the hydrate (3) of a tetraketone and studied several nucleophilic reactions with (3). Since then, both synthetic applications[3] and mechanistic studies[4] have been published from several laboratories.

Highly reactive cyclopropanes with powerful electron-attracting groups are termed ' activated ' cyclopropanes. Most reactions of these activated cyclopropanes with nucleophiles may be regarded as either homo-Michael additions or nucleophilic substitutions. However it was shown by Danishefsky[5] that a nucleophile preferentially attacked the more hindered (substituted) ring carbon in such activated cyclopropanes. Cram suggested[4] that unimolecular heterolytic ring opening of

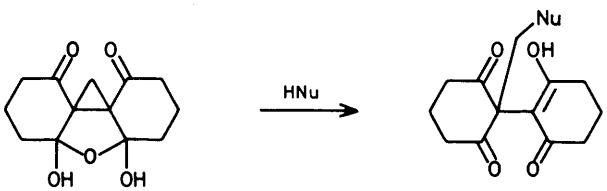


(4)

R^1,R^2 = CH_3
X, Y = CN

a cyclopropane took place prior to the reaction to afford a zwitterionic intermediate. On the other hand, Berkowitz and Grenetz demonstrated that the cycloaddition of an enamine to the activated cyclopropane (4) proceeds by an S_N2 route rather than by way of a zwitterionic intermediate.[6]

(2)



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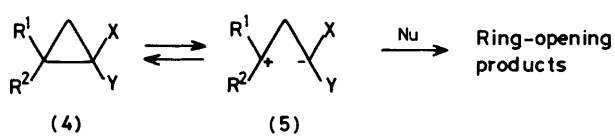
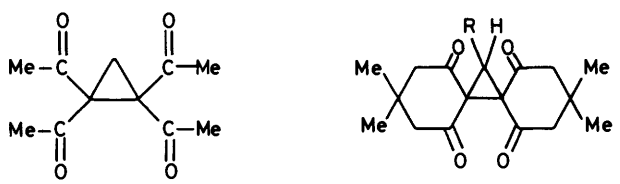


(4) (5)

R^1,R^2 = vinyl, aryl
X, Y = CN, CO_2R



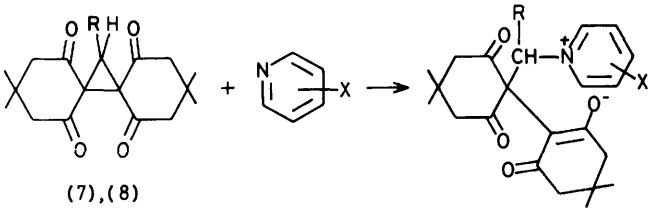
(6) (7) R = H (8) R = Me

Previously we reported novel photochemical syntheses of spiro-activated cyclopropanes (7) and (8) and 1,1,2,2,-tetra-acetylcyclopropane (6).[7,8a] Also, the ready formation of the intramolecular charge-transfer pyridinium β-keto-enolates in the reaction of (7) with pyridines was reported.[9] However, tetra-acetylcyclopropane (6) did not react with pyridine even under forced conditions. This kind of spiro-activation was also noted in the reaction of the spiroacylal of Meldrum's acid.[8b]

In this paper, we describe a kinetic investigation of the reaction of (7) and (8) with a series of substituted pyridines for the purpose of elucidating the reaction mechanism.

RESULTS AND DISCUSSION

Product and Kinetic Studies.—3,3,10,10-Tetramethyldispiro[5.0.5.1]trideca-1,5,8,12-tetraone (TACP) (7) and its related methyl derivative Me-TACP (8) were prepared by the method previously described.[7] The reaction of TACP with a series of substitued pyridines gave rise to zwitterionic products (9) which displayed an absorption maximum in the visible region.[8a,9] Detailed considerations of the structures of these products were reported previously.[9] The reaction can be regarded as a nucleophilic substitution at the methylene carbon in the cyclopropane ring, the leaving group being an enolate anion of the 1,3-diketone. Therefore, this reaction may be described as either a homo-Michael type or a Menschutkin type reaction.



(7),(8)

(9) R = H
(10) R = Me

The pseudo-first-order rate constants, k_{obs}, for reactions in the presence of a large excess of the nucleophilic reagent were determined spectrophotometrically by measuring the appearance of the betaines (9) and (10) in acetonitrile as the solvent. Under these conditions good first-order behaviour was observed for at least 2.5 half-lives (Figure 1). The k_{obs} values increased with increasing concentration of added pyridine. The data for the reaction of TACP with pyridine are shown in Table 1.

TABLE 1

Pseudo-first-order rate constants for reaction of TACP (7) with pyridine in acetonitrile at 25.0 °C

10^3[TACP]/ M	10^3-[Pyridine]/ M	[Pyridine]/ [TACP]	$10^6k_{obs}/s^{-1}$	10^5k_2/ l mol^{-1} s^{-1}
2.00	100	50	8.00	8.00
1.00	100	100	8.01	8.01
0.50	100	200	8.02	8.02
1.00	50.1	50.1	0.390	7.80
1.00	200	200	1.64	8.20
1.00	300	300	2.52	8.40
1.00	2.00	2.0		8.6 [a]

[a] The value is calculated by using second-order kinetics.

By changing the concentration of the nucleophilic reagent, second-order rate constants were obtained from the plot shown in Figure 2. Second-order rate constants k_2 for the reaction of TACP with a series of substituted pyridines and Me-TACP with pyridine were obtained

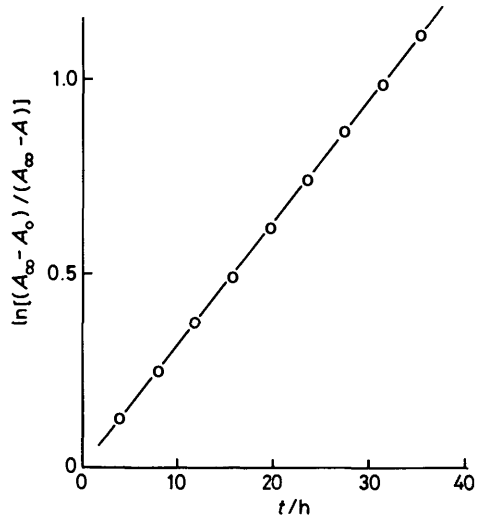


FIGURE 1 A plot of $\ln[(A_\infty - A_0)/(A_\infty - A)]$ *versus* t for the reaction of TACP (7) (0.001M) with pyridine (0.1M) at 25 °C in acetonitrile

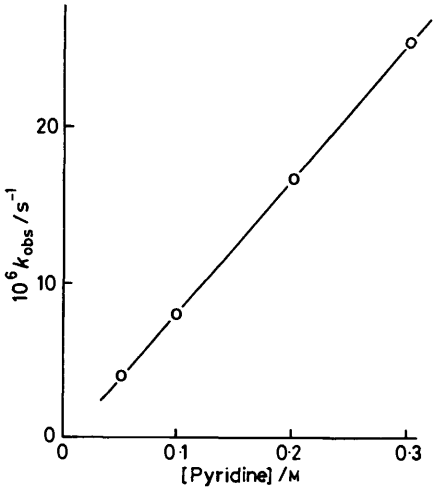


FIGURE 2 Pseudo-first-order rate constants for the reaction of TACP (7) (0.001M) with pyridine at 25 °C in acetonitrile

from the slope of plots in Figure 2 or from dividing k_{obs} by the concentration of nucleophile. The values summarized in Table 2 are an average of two kinetic runs.

Substituent Effects on Reaction Rate.—It will be convenient to compare the reaction of TACP with some

TABLE 2

Second-order rate constants for reaction of TACP (7) and Me-TACP (8) with pyridines at 25.0 °C

Activated cyclopropane	Substituent in pyridine	Solvent	10^5k_2/ l mol^{-1} s^{-1}	Relative rate
(7)	H	C_6H_6	24.4	3.1
(7)	H	CH_3CN	8.00	1
(7)	4-Me	CH_3CN	16.0	2.0
(7)	3-Me	CH_3CN	11.4	1.4
(7)	4-CO_2Me	CH_3CN	2.44	0.31
(7)	4-CN	CH_3CN	0.611	7.6×10^{-2}
(7)	2-Me	CH_3CN	0.79	9.9×10^{-2}
(8)	H	CH_3CN	3.78	0.47
(8)	H	C_6H_6	6.10	0.76

related Menschutkin reactions, which are typical bimolecular nucleophilic substitution reactions and afford polar products from neutral reactants (alkyl halide and pyridine). Table 3 presents a comparison of (a) the effect of an α-methyl substituent at the reaction centre ($k_{\alpha\text{-Me}}/k_2$), (b) the effect of a 2-methyl substituent in the nucleophile ($k_{2\text{-Me}}/k_2$), (c) the Brønsted slope (β), and (d) the solvent effect on the reactivity $[(k_2)_{CH_3CN}/(k_2)_{C_6H_6}]$.

TABLE 3

Behaviour of highly spiro-activated cyclopropane (TACP) and primary alkyl halide in the nucleophilic reaction

Reactions	Characteristic parameters [a]	Reactions	Characteristic parameters [a]
		Steric influence	
Me-TACP–TACP with pyridine in CH_3CN	$k_{\alpha\text{-Me}}/k_2$ 0.47	$(CH_3)_2CHI$–CH_3CH_2I with pyridine in $C_6H_5NO_2$	$k_{\alpha\text{-Me}}/k_2$ 0.051 [b]
2-Me-pyridine–pyridine with TACP in CH_3CN	$k_{2\text{-Me}}/k_2$ 0.10	2-Me-pyridine–pyridine with CH_3CH_2I in $C_6H_5NO_2$	$k_{2\text{-Me}}/k_2$ 0.25 [b]
		2-Me-pyridine–pyridine with CH_3I in CH_3CN	$k_{2\text{-Me}}/k_2$ 0.50 [c]
		Brønsted correlations	
TACP–substituted pyridine in CH_3CN	β 0.24	CH_3I–substituted pyridine in CH_3CN	β 0.35 [c]
		Allyl bromide–substituted pyridine in CH_3NO_2	β 0.37 [d]
		Solvent effect	
TACP–pyridine	$(k_2)_{CH_3CN}/(k_2)_{C_6H_6}$ 0.3	$BrCH_2CO_2Et$–Et_3N	$(k_2)_{CH_3CN}/(k_2)_{C_6H_6}$ 26 [e]
		$ClCH_2CH_2C_6H_5$–1,4-diazabicyclo[2.2.2]octane	$(k_2)_{CH_3CN}/(k_2)_{C_6H_6}$ 53 [f]

[a] $k_{\alpha\text{-Me}}/k_2$, $k_{2\text{-Me}}/k_2$, and $(k_2)_{CH_3CN}/(k_2)_{C_6H_6}$ are the rate ratios under described conditions. β is the Brønsted slope. [b] Ref. 10. [c] Ref. 11. [d] Ref. 12. [e] Ref. 13. [f] Ref. 14.

Examination of Table 3 shows that, in many respects, TACP seems to be different from a primary alkyl halide in the reactions with pyridines. The replacement of hydrogen at the reaction site of TACP, the methylene carbon in the cyclopropane ring, by a methyl group produced little change in the reactivity ($k_{\alpha\text{-Me}}/k_2$ 0.47). But the rate ratio between a primary alkyl halide and a secondary substrate is reported to be 0.051 for reactions with pyridine.[10] In addition, the reactivity of TACP was decreased by changing pyridine to 2-methylpyridine ($k_{2\text{-Me}}/k_2$ 0.10). This rate ratio is smaller than the value (0.50) reported in the reaction of methyl iodide with pyridines. The influence of the methyl substitution in the neighbourhood of the reaction site can be attributed to primary steric hindrance during association of these reactants.

Figure 3 shows the relationship of the logarithms of the rate constants for the reaction of TACP with a series of substituted pyridines against the pK_a values of the conjugate acid of pyridines. There is observed a nice, linear log k_2 *versus* pK_a relationship with a slope β of 0.24 in acetonitrile. This Brønsted slope is smaller than the reported values of 0.35—0.43 for bimolecular nucleophilic substitution reactions of pyridines.[11] This small sensitivity to basicity of the attacking pyridine suggests a small amount of charge development in the transition state.

Although the reaction of TACP with pyridines gave rise to the polar zwitterionic products (9), a large acceleration could not be observed in acetonitrile compared with that in benzene solution.

Mechanistic Considerations.—At least three types of mechanism can be visualized for the reaction of highly spiro-activated TACP with pyridine. First, we can assume that a classical S_N2 mechanism (concerted mechanism) holds, with covalent bond-making aiding bond-breaking in the usual manner, as mentioned by Berkowitz and Grenetz.[6] Although the second-order kinetics and the substituent effect can be qualitatively explained by this mechanism, it does not account very well for the unusual solvent effects in the appearance of

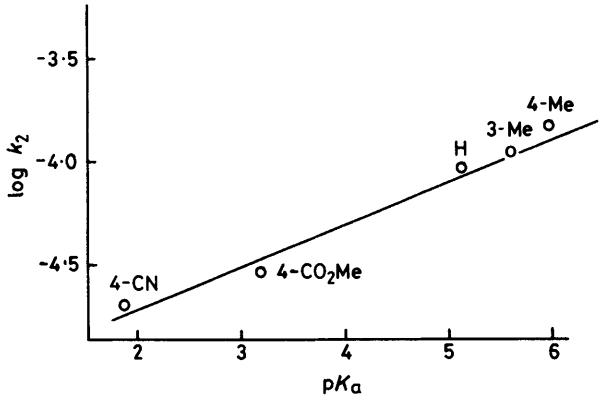
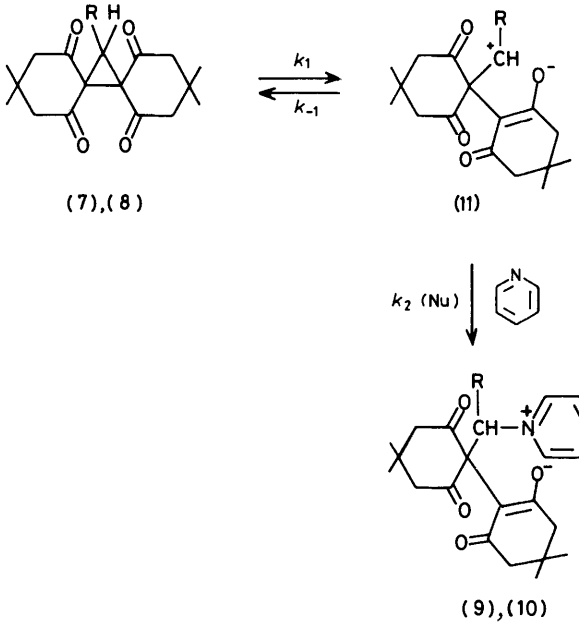


FIGURE 3 Second-order rate constants for reactions of pyridines with TACP (7) at 25 °C plotted against the pK_a of the attacking pyridines

the zwitterionic product (9). Secondly, we can assume that the mechanism involves bimolecular nucleophilic substitution toward the zwitterionic intermediate (11) by a nucleophile as suggested by Cram and Danishefsky.[3] In this mechanism the cyclopropyl ring is opened heterolytically and reversibly in a preliminary step without participation of a nucleophile. In addition, k_{-1}

is greater than k_2 because this reaction obeyed good second-order kinetics as mentioned above. The reaction is then completed by attack of the nucleophile on this intermediate ion pair. Cram and his co-workers noted that as the medium became more polar, optically active

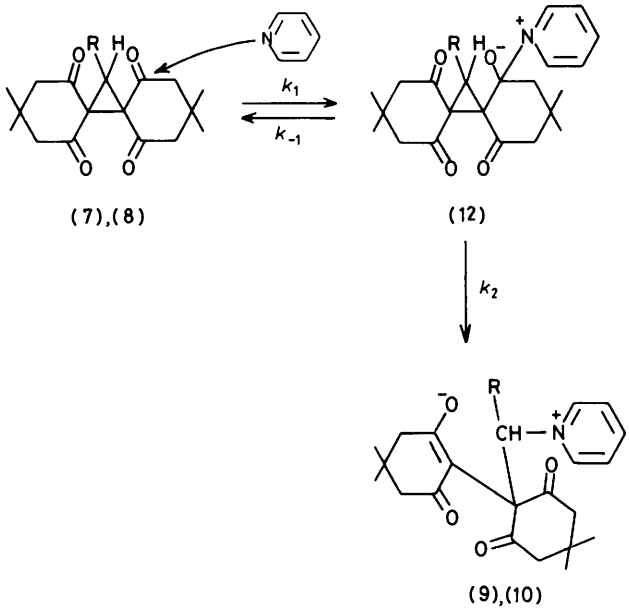


species were racemized more rapidly by way of cyclopropyl ring cleavage.[4] Thus, the rate in methanol was 20 times faster than that in benzene. In contrast, the small opposite dependence of reactivity on changing solvent polarity cannot support the existence of an ionic intermediate in the rate-controlling stages of the reaction of TACP with pyridine. This ion-pair mechanism, therefore, does not account for the unusual solvent effect as well as the rate deceleration effect upon methyl substitution in the cyclopropyl ring.

A third possibility is that the nucleophile participates in the ion pair as proposed by Bordwell *et al.* They suggested that the S_N2^I ion-pair mechanism can apply to the reaction of a suitably substituted tertiary allylic bromide, *p*-$MeC_6H_4SO_2CH{=}CHC(Br)Me_2$, with nucleophiles.[16] The similar mechanism can be applied to the reaction of TACP with pyridine after some modifications as follows.

The nucleophile is involved in the formation of the intermediate (12). The reaction is initiated by the entrance of a pyridine molecule into the solvent shell of TACP, resulting in a solvated polar encounter complex prior to cyclopropane ring opening. As shown above (Table 3), the presence of an α-methyl group in TACP decreases the nucleophilic reactivity of pyridine to a certain extent. However, its steric influence becomes less sensitive than that of a simple alkyl iodide.

On the basis of these results, it can be considered that a pyridine molecule approaches a site other than the methylene carbon in the cyclopropane ring, for example, one of the carbonyl carbons, and then rearranges to the methylene carbon resulting in ring opening to give the zwitterionic product. In other words, we consider that TACP reacts with pyridine by a preassociation mechanism in which a polar encounter complex with the nucleophile is formed before collapsing to the product. Recently, the existence of zwitterionic adducts between highly electrophilic ketones and tertiary amines has been reported. This complements Bordwell's suggestion, particularly in the reaction of carbonyl compounds with amines.[17] By this mechanism, all the experimentally observed effects, such as the less retarding effect ($k_{\alpha\text{-Me}}/k_2$), the smaller value ($k_{2\text{-Me}}/k_2$), the Brønsted slope (β), and the unusual solvent effect, may be reasonably explained. A detailed account of the solvation in which TACP becomes desolvated and covalently bonded to pyridine must await further investigation on the influence of solvents.



As a consequence of these considerations, it seems that the mechanism of the reaction of activated cyclopropane varies capriciously, depending on the substituents on the cyclopropane ring and the nature of the nucleophile.

EXPERIMENTAL

Materials.—TACP (7) and its methyl derivative, (8), were prepared by a previously described method.[7] The substituted pyridines were purified by distillation after being dried with potassium hydroxide. The solvents were purified by the method described previously.[9]

Kinetic Measurements. General Procedure.—A Hitachi 124 u.v.–visible spectrophotometer with a thermostatted cell block was used for all absorption measurements. A stock solution of TACP (0.01M) was prepared by dissolving a carefully weighed amount of pure sample (7) into purified solvent. A stock solution of pyridine (1.00M) was also prepared by the same method. A measured volume (1.00 ml) of TACP solution and the same volume of pyridine solution were placed in a 10 ml volumetric flask which was

subsequently filled to the mark with the same solvent (TACP/pyridine = 0.001M/0.1M). The desired amount of the TACP–pyridine solution (*ca.* 4 ml) was placed in 1 cm stoppered cell which was immersed into a constant-temperature bath (±0.03 °C).

After an appropriate interval (30 min), the initial absorbance (A_0) of the solution at an appropriate wavelength (390 nm) in the charge transfer-band was measured. To follow the reaction the increase in the absorbance (A) of the solution with time at the same wavelength was then monitored. The final absorbance (A_∞) was determined after approximately 10 half-lives. The first-order rate constants, k_{obs}, were calculated from the slope of the linear plots of $\ln(A_\infty - A_0/A_\infty - A)$ *versus* time (t) using the least-squares method. The second-order rate constants, k_2, were evaluated by division of the pseudo-first-order rate constants by the pyridine concentrations or by linear regression analysis of the pseudo-first-order rate constant and nucleophile concentration data. In all cases the progress of the reaction was followed to *ca.* 2.5 half-lives. Two different techniques were used to measure the rate of the same reaction.

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