(6 H, m), 0.90 (3 H, t); IR (thin film) 3065, 3024, 2959, 2934, 2874, 1495, 1455, 1996 cm^{-1}; MS, *m/e* calcd for $C_{17}H_{23}NO_2$ (M^+) 275.1879, found 275.1885.

[3*R,4α,5β]-4,5-Dihydro-4-methyl-3-(1-methyl-2-phenylethyl)-5-phenylisoxazole (Table I, Entry 8).** Purification was performed by MPLC (10% EtOAc/hexane) to give a partially separable mixture of diastereomers (53%, 91/9 ratio). Recrystallization from 2% EtOAc/hexanes at −4 °C gave crystals of the pure major diastereomer suitable for X-ray diffraction: mp 52–53 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.12 (10 H, m), 4.97 (1 H, d, J = 8.3 Hz), 2.93 (2 H, m), 2.71 (2 H, m), 1.27 (6 H, two overlapping d); IR (thin film); 3029, 2970, 2932, 1653, 1559, 1495, 1456, 750 cm^{-1}; MS, *m/e* calcd for $C_{19}H_{21}NO$ (M^+) 279.1257, found 279.1575.

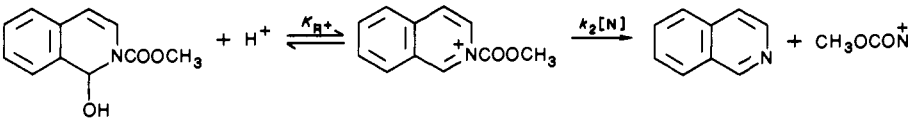
Acknowledgment. We thank the National Institutes of Health (GM 31678) for support of this work. We are especially grateful to Stuart Pharmaceuticals, Merck, and American Cyanamid for unrestricted support.

A Single Transition State in the Transfer of the Methoxycarbonyl Group between Isoquinoline and Substituted Pyridines in Aqueous Solution

Edwin Chrystiuk and Andrew Williams*

Contribution from University Chemical Laboratories, Canterbury, England CT2 7NH.
Received August 15, 1986. Revised Manuscript Received November 22, 1986

Abstract: *N*-Methoxycarbonylisoquinolinium ion reacts with nucleophiles in aqueous solution according to the equation

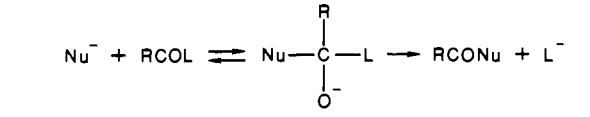


The rate constants, k_2, for attack of substituted pyridines on the isoquinolinium species exhibit a linear Brønsted relationship (β_{nuc} = 0.58) over a range of nucleophile pK_a greater than and less than the pK_a of isoquinoline. The Brønsted data indicate a smaller change in effective charge on nucleophilic nitrogen for formation of a putative tetrahedral intermediate than for its decomposition to product. This is opposite to what is expected for the stepwise process where the largest bonding change to attacking nitrogen is in the addition step. The results are consistent with a single transition state in the transfer of the methoxycarbonyl group between pyridines in aqueous solution; they contrast with those for reaction of pyridines and tertiary amines with neutral acyl derivatives where relatively stable zwitterionic tetrahedral intermediates have been demonstrated. The transition state for transfer between pyridines is symmetrical, and the effective charge on its pyridine nitrogen is consistent with about 40% of a single bond between nitrogen and acyl carbon. An imbalance of effective charge indicates that the MeO–CO component of the transition state has considerable acylium ion character pointing to an almost square-planar structure.

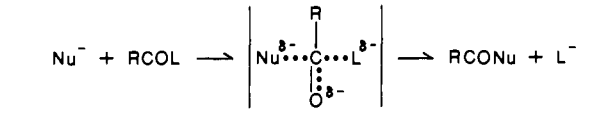
Myron Bender demonstrated in a classical paper that carbonyl oxygen in esters exchanges with solvent oxygen under conditions of alkaline hydrolysis in aqueous solution.[1] The results indicated that hydrolyses of nonactivated esters involve a tetrahedral intermediate.[2] There have now been many fine reports of tetrahedral adducts between acyl functions and nucleophiles,[3,4] and there is no doubt that a stepwise addition–elimination (AE)[5a] mechanism is involved in transfer of an acyl group between strong nucleophiles in polar solvents, especially water.

Scheme I

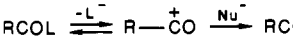
AE



concerted borderline



EA



In recent years, evidence has accumulated for a mechanism of acyl group transfer in water with an elimination–addition (EA)[5a] timing of bond fission and formation and an acylium ion or stabilized acylium ion intermediate. Structural alterations cause the mechanism to swing from one to the other of the mechanistic extremes,[5a] and it is logical to suppose that borderline conditions of structure and solvent could exist where leaving group and

(1) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.
(2) Bender, M. L. *Chem. Rev.* **1960**, *60*, 53.
(3) McClelland, R. A.; Santry, L. J. *Acc. Chem. Res.* **1983**, *16*, 394.
(4) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. *Acc. Chem. Res.* **1981**, *14*, 306.
(5) (a) Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627. (b) We employ Dewar's definition of concertedness[5c] where a reaction occurs in a single step and possesses a single transition state. In other words, the reaction coordinate in the multidimensional potential energy surface does not transverse a minimum energy value except at reactant and product states. Concertedness in this definition does not imply a particular relationship between bond order in forming and breaking bonds in the transition state. The definition is the same as that of Jencks[5d] which states that a concerted mechanism ensues when the intermediate in a two-step mechanism has a lifetime less than a bond vibration period. A synchronous mechanism has both bonds changing in unison and can only have a pathway along the "north-east" diagonal in Figure 1. A concerted mechanism could have a reaction coordinate anywhe.e on the potential energy surface and could traverse paths normally associated with the discrete EA or AE processes. (c) Dewar, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 209. (d) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

0002-7863/87/1509-3040$01.50/0

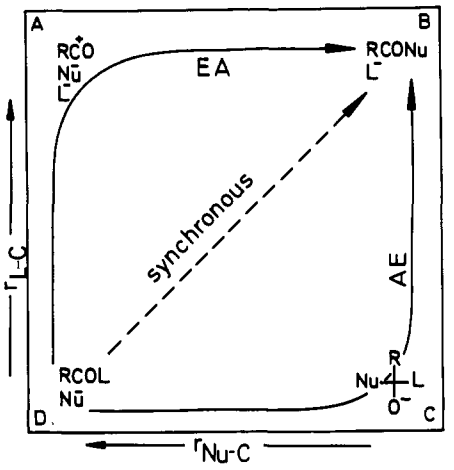
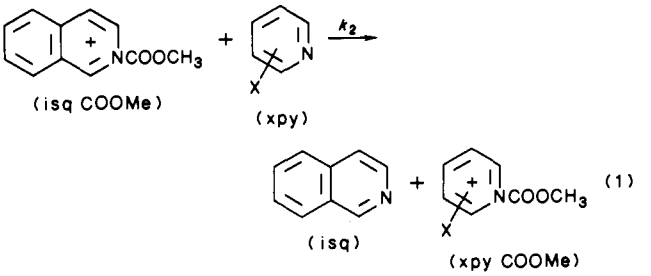


Figure 1. Schematic potential energy diagram for the reaction RCO–L + Nu^- → RCO–Nu + L^-.

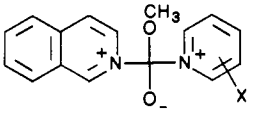
nucleophile break and form their bonds in a concerted[5b] mechanism (Scheme I). These mechanisms may be related by the three-dimensional potential energy diagram illustrated schematically in Figure 1. Increasing the stability of the RCO^+,Nu^-,L corner, for example, by neutralizing the charge on the acylium ion via an "internal" negatively charged nucleophile, is known to favour the EA timing.[5a] It is envisaged that both unstable acylium ion and unstable tetrahedral intermediate could force a concerted path; the same result might be obtained by "tilting" the diagonal A–C in Figure 1 to favor the acylium ion corner and shift the reaction coordinate from an existing "AE"-pathway where the surface is initially "skewed".

Stereochemical probes[6] are not applicable for a study of concertedness in carbonyl group transfer. Polar substituent effects can provide an unequivocal tool for deciding between a stepwise (AE) and a concerted process.[7-10a] The transition state of the rate-limiting step in the stepwise mechanism will suffer a dramatic structural change when the rate-limiting step changes (see Scheme I). The effective charge[10b,c] on the donor or acceptor atom, measured by polar substituent effects, will change significantly in the substituent range where the change in rate-limiting step occurs; the transition states of the two steps will have bonds whose connection with the substituent is substantially different. The resultant free energy relationship will exhibit two linear portions intersecting at the point of change in rate-limiting step. The absence or presence of a break in a free energy relationship is an excellent diagnostic probe for stepwise or concerted mechanisms provided the breakpoint can be predicted.[7-10a] Even if the breakpoint position may not be predicted the observation of a break is compelling evidence that a stepwise process is operating.[11-17]

We decided to study the transfer of the methoxycarbonyl group between pyridine nucleophiles (eq 1) because considerable work has been reported on the kinetics of *N*-(methoxycarbonyl)-pyridinium ion reactions.[12] The methoxycarbonyl group offers a reduction in rate compared with say the acetyl function making



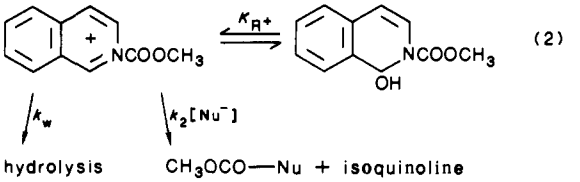
the kinetics more easily followed. Isoquinoline is employed as a leaving group because the favorable spectral change (>300 nm) enables reactions to be followed in relatively high pyridine concentrations. The relatively high steric requirements and the high electrostatic repulsive effect of the pyridine nitrogens in the putative tetrahedral adduct (I) might force a concerted path, and



I

the resonance-stabilizing effect of the methoxyl group on the acylium ion could help to transfer the transition state toward the top left corner in Figure 1. Equation 1 is essentially a symmetrical reaction, and we can therefore predict that decomposition of I forward occurs with the same rate constant as the backward section when the pK_a of the attacking pyridine is the same as that of the leaving isoquinoline; forward and reverse reactions from I will obey the same Brønsted equation.

We show here that the acyl adduct of isoquinoline prepared from methyl chloroformate readily hydrates to form a pseudobase. The reactions of the adduct should therefore be described by eq 2. This equilibrium is advantageous in that it effectively slows



down reactions of the *N*-acylisoquinolinium ions so that the high background hydrolysis rates of regular acylpyridinium species[18,19] do not make the kinetics of reactions with other nucleophiles impossibly difficult to measure.

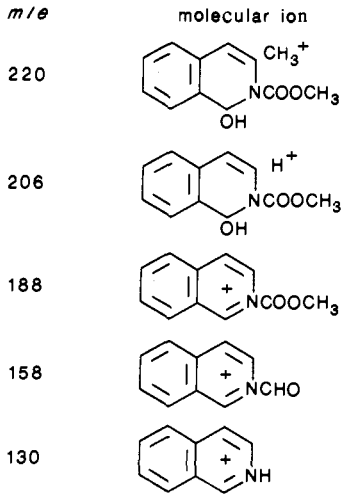
Experimental Section

Materials. Isoquinoline and other pyridines were obtained commercially and recrystallized or redistilled before use. 4-Methoxypyridine and 4-nitropyridine were prepared by reducing the commercially available *N*-oxides with PCl_3 by the method of Ochiai;[20] 3-methoxypyridine was prepared according to the method of Jameson and Lawlor.[22] Other materials were of analytical reagent grade or were redistilled or recrystallized from bench grade products. Acetonitrile was purified by the method of Lewis and Smyth,[23] and water used throughout the kinetic investigation was doubly distilled from glass.

Methods. Solutions of an adduct between isoquinoline and methyl chloroformate were prepared shortly before their use in the kinetic study by mixing a solution of methyl chloroformate (100 μL, 0.02 M in acetonitrile) with isoquinoline (100 μL, 0.02 M in water/acetonitrile (50/50) at pH 4.4). The preparative reaction was shown to be complete in under 2 min by a separate UV-spectral scanning experiment and is similar to the in situ procedure reported by others.[12] The solutions were relatively stable over about 1 h as judged from their further reaction. Similar adducts of methyl chloroformate with other pyridines were likewise prepared, but these solutions are much less stable and are required to be employed within 5 min of their preparation.

(6) Lowe, G. *Acc. Chem. Res.* **1983**, *16*, 244.
(7) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591.
(8) Skoog, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597.
(9) Bourne, N.; Hopkins, A.; Williams, A. *J. Am. Chem. Soc.* **1985**, *107*, 4327.
(10) (a) D'Rozario, P.; Smyth, R. L.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 5027. (b) Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425. (c) Williams, A.; Thea, S. *Chem. Soc. Rev. (London)* **1986**, *15*, 125.
(11) Anderson, B. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1960**, *82*, 1773.
(12) Battye, P. J.; Ihsan, E. M.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 741.
(13) Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939.
(14) (a) Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828. (b) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.
(15) Castro, E. A.; Freudenberg, M. *J. Org. Chem.* **1980**, *45*, 906.
(16) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595.
(17) Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.
(18) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.
(19) Fersht, A. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5442.
(20) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.
(21) Prins, D. A. *Recl. Trav. Chim. Pays-Bas* **1957**, *76*, 58.
(22) Jameson, G. W.; Lawlor, J. M. *J. Chem. Soc. B* **1970**, 53.
(23) Lewis, G. L.; Smyth, C. P. *J. Chem. Phys.* **1939**, *7*, 1085.

Scheme II



Preparative amounts of the adduct between isoquinoline and methyl chloroformate were made from the reagents at alkaline pH by making use of the fact (see later) that the adduct is relatively stable at these pH's. A solution of the methyl chloroformate (2.9 g, 0.03 mol) in CH_2Cl_2 (10 mL) was added to a stirred, cooled suspension of isoquinoline (2.0 g, 0.015 mol) in water (50 mL). The pH of the reaction mixture was kept in the range 6–10 by addition of KOH solution (2 M). The amount of base required was close to the theoretical amount required to neutralize the acid released in the reaction (ca. 15 mL). The solution was extracted with CH_2Cl_2, and the extract was dried with $MgSO_4$ and evaporated to yield a white glass (2.0 g, 63%) which had no characteristic isoquinoline smell. The glass was stable in the deep freeze for up to 4 weeks. Attempts to distill or purify by chromatography led to decomposition and the glass directly from the extraction had the following elemental analysis: C, 65.6; H, 4.6; N, 6.8 (O, 23.0%); $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8 (O, 23.4%). The analysis was carried out by A. J. Fassam of this laboratory with a Carlo Erba analyzer; oxygen is by difference. Chemical ionization (CH_4) mass spectroscopy gave the following peaks consistent with the molecular ions in Scheme II. The glass had IR (thin film, cm^{-1}) 1720 (s), 1640 (m) consistent with carbonyl and olefin bonds; ^1H NMR ($CDCl_3$) δ 4.88 (br, 1 H, O*H*), 3.7 (m, 4 H, OCH_3 and C*H*OH), 7.15 (d, 1 H, CH=C*H*–N=), 5.88 (d, 1 H, —C*H*=CHN=), ca. 7 (m, 4 H, aromatic). The NMR absorbance at δ 4.88 was destroyed by addition of CD_3OD.

Kinetics. Suitable wavelengths for kinetic study were first determined by repetitive UV–spectral scanning with either Pye-Unicam SP800 or Perkin-Elmer Lambda 5 instruments. A typical kinetic experiment consisted of adding an aliquot (20 μL) of a stock solution of the adduct to an aqueous solution of the buffer (2.5 mL) in a silica cell in the thermostated cell compartment of the spectrometer. The absorption (A) at the appropriate wavelength was measured as a function of time, and first-order rate constants were obtained from plots of $A_t - A_\infty$ vs. time on 2-cycle semilogarithmic graph paper. The pH employed in subsequent calculations was that measured in the reaction cell at the completion of the kinetic run. Results of reactions suffering large changes in pH from that in the stock buffer (>092 unit) were discarded. The pH was recorded with a Radiometer PHM 62 digital instrument equipped with a Russell CMAWL CLS combination electrode standardized to ±0.01 pH units with EIL standard buffers.

Solutions of substituted pyridine containing buffers were generally prepared by adding HCl and KCl to produce a half-neutralized stock at 0.5 M ionic strength. These buffers were diluted as required with aqueous KCl of the same ionic strength.

The pK_a values of the pyridines were determined by measuring the pH titration curves, and where a comparison is possible the values obtained are close to literature parameters. The pK_a values of isoquinoline, 3,5-dichloropyridine, 3-cyanopyridine, 4-nitropyridine, and 4-cyanopyridine were obtained by measuring the absorbance at a standard wavelength as a function of pH. Conditions for the measurement of the pK_a values are as given in Tables I–III for the kinetics.

Results

Decomposition of Pyridine–Methyl Chloroformate Adducts in Aqueous Buffers. The isoquinoline–methyl chloroformate adduct releases isoquinoline in aqueous buffers by comparison of the product UV–spectrum with that of an authentic sample of isoquinoline under the same conditions. Scanning of the UV spectrum of the reaction at different pH's demonstrated that the initial spectrum is pH dependent. The degradation of the isoquinoline adduct gives excellent pseudo-first-order kinetics over at least 90% of the total reaction. The rate constant for decomposition of the synthesized glass is identical with that of the material prepared in situ under the same conditions. The data for the hydrolysis over a pH range are illustrated in Figure 2. The rate constants are buffer dependent, and the values quoted in the figure refer to zero buffer concentration. The extrapolated data obey the expression (eq 3) where k_w and pK_{R^+} are 1.4×10^{-2} s^{-1} and 3.52, respectively. There is a small negative deviation from eq 3 at low pH possibly due to decreasing water activity.

$$k_{obsd} = k_w/(1 + 10^{-pK_{R^+}}/10^{-pH}) \quad (3)$$

The pyridine adduct, prepared in acetonitrile/water, hydrolyzed in aqueous buffer, and the buffer-independent rate constants are illustrated in Figure 2 as a function of pH; they fit eq 4 where k_w and k_{OH} are 3.9×10^{-2} s^{-1} and 3.0×10^5 M^{-1} s^{-1}, respectively. Although pyridine buffers were employed in this determination the data from Battye, Ihson, and Moodie[12] indicate that there is no significant buffer catalysis at the concentrations employed in agreement with our results. At low pH there is a deviation from eq 4.

$$k_{obsd} = k_w + k_{OH}[OH^-] \quad (4)$$

The rate constants, k_w, for substituted pyridine adducts are recorded in Table I and agree with those determined by other workers.[12]

Table I. Hydrolysis of *N*-(Methoxycarbonyl)pyridinium Ions[a]

pyridine	pK_a^{xpy}	$10^3 k_w{}^b/s^{-1}$ [lit.[12] value]	pH[c]	λ[d]/nm	N[e]
parent	5.31	39 (2) [35][12]	2.02–4.98	275	8
isoquinoline	5.46	14 (0.1)	1–12	f	15
3-Me	5.82	23 (1)	5.65	280	8
4-Me	6.14	17 (2) [12.5][12]	5.66	270	12
3,5-Me_2	6.14	23 (0.4)	5.60	290	14
3,4-Me_2	6.45	8.8 (1)	5.79	273	9
4-MeO	6.71	3.6 (0.1) [2.06][12]	5.52	270	6

[a] 25 °C, ionic strength maintained at 0.5 M with KCl [b] uncertainties (total range) in parentheses. [c] Where a single pH is given this is the average over a narrow range and indicates that essentially only one pH value was employed. [d] Wavelength for kinetics. [e] Number of data points not including duplicate runs. [f] Wavelengths 245, 285, and 290 nm were employed; higher wavelengths for the higher pH's.

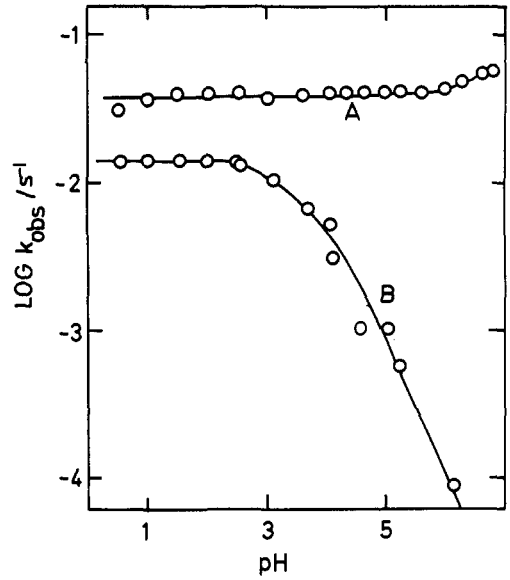


Figure 2. Dependence on pH (25 °C, ionic strength maintained at 0.5 M with KCl) of the hydrolysis of the adducts between methyl chloroformate with pyridine (A) and isoquinoline (B). Acetate buffers were employed above pH 3, and the results were extrapolated to zero buffer concentration; above pH 5.5 phosphate buffers were employed. The lines are calculated from eq 3 and 4 and parameters are given in the text.

Table II. Reactions of Substituted Pyridines and Other Nucleophiles with *N*-(Methoxycarbonyl)isoquinolinium Ion[a]

substituent	pK_a^{xpy}	$k_2^b/M^{-1}\ s^{-1}$	pH[c]	$10^2[Nu]^f/M$	λ^d/nm	N^e
pyridines						
1. 3,5-Cl_2	0.51	0.044 (0.006)	0.07	1–10	360	9
2. 3-CN	1.85	0.14 (0.017)	1.84	1–10	360	8
3. 4-NO_2	1.86	0.51 (0.05)	3.68	2–10	380	8
4. 4-CN	2.19	0.36 (0.024)	2.21	1–8	360	7
5. 3-Br	3.05	6.7 (0.64)	3.07	2–8	360	4
6. 3-MeOCO	3.25	4.5 (0.19)	3.29	1–5	365	5
7. 3-$CONH_2$	3.37	5.6 (0.27)	3.44	1–5	360	5
8. 4-MeOCO	3.40	7.6 (0.7)	3.44	1–4	348	4
9. 3-Ac	3.43	5.0 (0.1)	3.45	1–5	360	5
10. 3-CH_2CN	3.49	8.9 (0.08)	3.54	2–8	364	4
11. 4-$CONH_2$	3.55	9.3 (0.07)	3.64	0.5–4	360	4
12. 3-CHO	3.60	7.3 (0.47)	3.65	0.4–2	360	5
13. 4-Ac	3.64	8.1 (0.22)	3.65	1–4	360	4
14. 3-MeO	4.94	20 (1.9)	4.94	1–8	310	5
15. parent	5.31	31 (0.1)	4.92–6.37	1–10	280	38
16. 3-Me	5.82	52 (3.7)	5.76	2–10	290	5
17. 2-Me	5.92	1.0 (0.01)	5.76	2–10	290	5
18. 4-Me	6.14	54 (3.4)	6.04	4–10	280	7
19. 3,5-Me_2	6.14	110 (1)	6.12	2–10	290	5
20. 3,4-Me_2	6.45	200 (5.5)	6.52	2–10	290	5
21. 4-MeO	6.71	140 (16)	6.7	1–7	290	5
22. 2,6-Me_2	6.77	3.3 (0.03)	6.80	2–10	300	3
23. 2,4,6-Me_3	7.48	3.3 (0.8)	6.81	2–10	300	5
24. 4-NH_2	9.21	9100 (700)	9.12	1–10	300	7
25. 4-NMe_2	9.68	39000 (3000)	9.63	2–10	318	6
other nucleophiles						
26. $CH_3CO_2^-$	4.76	4.7 (0.03)	4.04–5.2	0.5–5	245, 285	25
27. HPO_4^{2-}	7.21	55 (7)	6.12–7.14	0.5–5	290	8

[a] 25 °C ionic strength made up to 0.5 M with KCl. [b] Uncertainty range in parentheses. [c] Where a single pH is given this is the average over a narrow range. [d] Wavelength for kinetics. [e] Number of data points not including duplicate runs. [f] Maximum and minimum total concentration range of the nucleophile.

Table III. Reaction of Pyridine with *N*-Methoxycarbonyl-Substituted Pyridinium Ions[a]

leaving pyridine	pK_a^{xpy}	$k_2^b/M^{-1}\ s^{-1}$	pH[c]	10^3[xpy], M[f]	λ^d/nm	N^e
1. isoquinoline	5.46	31 (0.1)	(from Table II)			
2. 4-Me	6.14	2.7 (0.5)	5.66	2–10	270	12
3. 3,5-Me_2	6.14	2.3 (0.3)	5.60	2–10	290	14
4. 3,4-Me_2	6.45	1.1 (0.05)	5.79	2–10	273	9
5. 4-MeO	6.71	1.5 (0.01)	5.52	2–10	270	9

[a–f] Footnotes as in Table II.

Reaction of Nucleophiles with *N*-(Methoxycarbonyl)pyridinium Ions in Aqueous Buffers. Kinetics of the decay of the spectra of the pyridine adducts in aqueous buffers are pseudo-first order and obey the kinetic eq 5. A study against pH and nucleophile concentration was carried out for *N*-(methoxycarbonyl)isoquinolinium ion with pyridine as a model, and the rate constants obey eq 6; the data for pyridine are illustrated in Figure 3.

$$k_{obsd} = k_w + k_2'[\text{total nucleophile concn}] \quad (5)$$

$$k_{obsd} = k_w + k_2[py]/(1 + 10^{-3.52}/10^{-pH}) \quad (6)$$

In order to demonstrate that the rate constants obtained are for nucleophilic attack of pyridines on the (methoxycarbonyl)-pyridinium ions we carried out the following experiments. The 4-methoxypyridine–methyl chloroformate adduct in acetonitrile/water was added to isoquinoline buffer at pH 5.84. The product of this reaction hydrolyzed to isoquinoline with a rate constant ($3.3 \times 10^{-3}\ s^{-1}$) close to that obtained from *N*-(methoxycarbonyl)isoquinolinium ion prepared from the methyl chloroformate ($3.2 \times 10^{-3}\ s^{-1}$ under identical conditions including the same amount of 4-methoxypyridine). The UV spectrum of the product (before it decomposed to isoquinoline) was also similar to that of the directly prepared isoquinoline adduct at the same pH. The formation and decay of the intermediate isoquinoline adduct was directly observed by following the absorbance at 291 nm (Figure 4). The adduct between pyridine and methyl chloroformate in acetonitrile/water reacted with 4-aminopyridine in aqueous solution to give a species which decomposed (as followed by the spectral decay at 292 nm) with a rate constant ($4.73 \times 10^3\ s^{-1}$) close to that for the decay of material prepared with 4-aminopyridine and methyl chloroformate under the same conditions ($4.60 \times 10^{-3}\ s^{-1}$), including the same concentration of

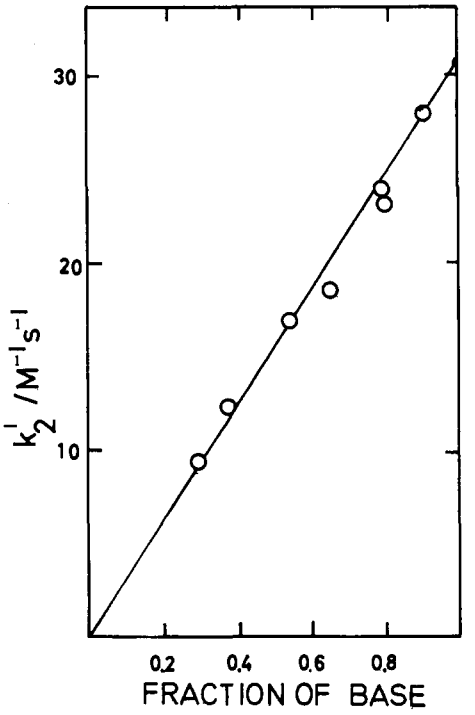


Figure 3. Plot of k_2' vs. the fraction of base (FB) of pyridine for the decomposition of the methyl chloroformate–isoquinoline adduct in pyridine buffers at 25 °C and ionic strength maintained at 0.5 M with KCl. The line is calculated from eq 5 and 6 and parameters are given in Table II.

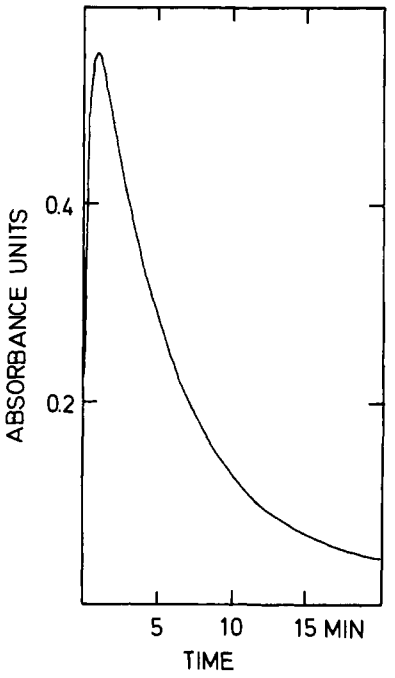


Figure 4. Time dependence of the absorption at 291 nm of the reaction of *N*-(methoxycarbonyl)-4-methoxypyridinium ion (8×10^{-3} M) with buffer containing isoquinoline (10^{-2} M) at 25 °C and ionic strength maintained at 0.5 M with KCl. The pH is kept at 5.84 with sodium acetate (0.1 M).

pyridine. The addition of (methoxycarbonyl)pyridine to the 4-aminopyridine buffer was also characterized by an increase and decay of the absorbance at 292 nm.

Reactivities of the isoquinoline–methyl chloroformate adduct with acetate and phosphate ions were obtained from data employed in determining the hydrolysis rate constant at zero buffer concentration in the pH 4–7 region. These derived rate constants are recorded in Table II. Reaction with pyridine nucleophiles was, except for the parent pyridine, carried out at a single fraction of pyridine base, and the kinetic data were analyzed according to the established rate law for pyridine (eq 6). The data are recorded in Table II. Unfortunately 4-morpholinopyridine did not give a significant UV-absorption change in its reaction with the methyl chloroformate–isoquinoline adduct so that we are unable to present data for k_2 for this nucleophile.

Values of k_2 (except for points 17, 22, 23, 26, and 27 in Table II) were fitted to eq 7 of the same form as that derived by other workers[12] for a two-step process (eq 8) where β's refer to the Brønsted exponents of the individual rate constants, $\Delta\beta = \beta_{-1} - \beta_2$ and $\Delta pK = pK_a^{xpy} - pK_a^{isq}$. The parameters were derived by a "grid-search" program which scanned values of $\Delta\beta$ from −0.3

$$k_2 = k_2^0 \times 10^{\Delta pK\beta_1}/(1 + 10^{\Delta pK\Delta\beta}) \quad (7)$$

$$\text{isq-COOMe} + \text{xpy} \underset{\beta_{-1}}{\overset{\beta_1}{\rightleftharpoons}} \text{I} \xrightarrow{\beta_2} \text{xpy-COOMe} + \text{isq} \quad (8)$$

to 0 in units of 0.05, β_1 from 0.4 to 0.9 in units of 0.05, and log k_2^0 from 1.6 to 2.4 in units of 0.05. The set of parameters giving the minimum sum of the squares of the residuals is $\Delta\beta = 0$, $\beta_1 = 0.6$, and log $k_2^\circ = 2.1$. The line corresponding to the best parameters is shown in Figure 5 which also records a plot of the residuals (log k_2 − log $k_{2\text{calcd}}$). The fit of best parameters is illustrated by the plots of the lines for the two "next best" sets of parameters (see Figure 5). The data also fitted a linear Brønsted eq 9. This equation is almost the same as that for the best fit to eq 7 ($k_2 = 0.5 \times 10^{2.1} \times 10^{0.6\Delta pK}$) derived from the grid search method; the slight difference is due to the use by the grid search program of a fixed array of possible parameters.

$$\log k_2 = (0.58 \pm 0.03)pK^{xpy} - 1.41 \pm 0.14 \quad (n = 22,\ r = 0.978) \quad (9)$$

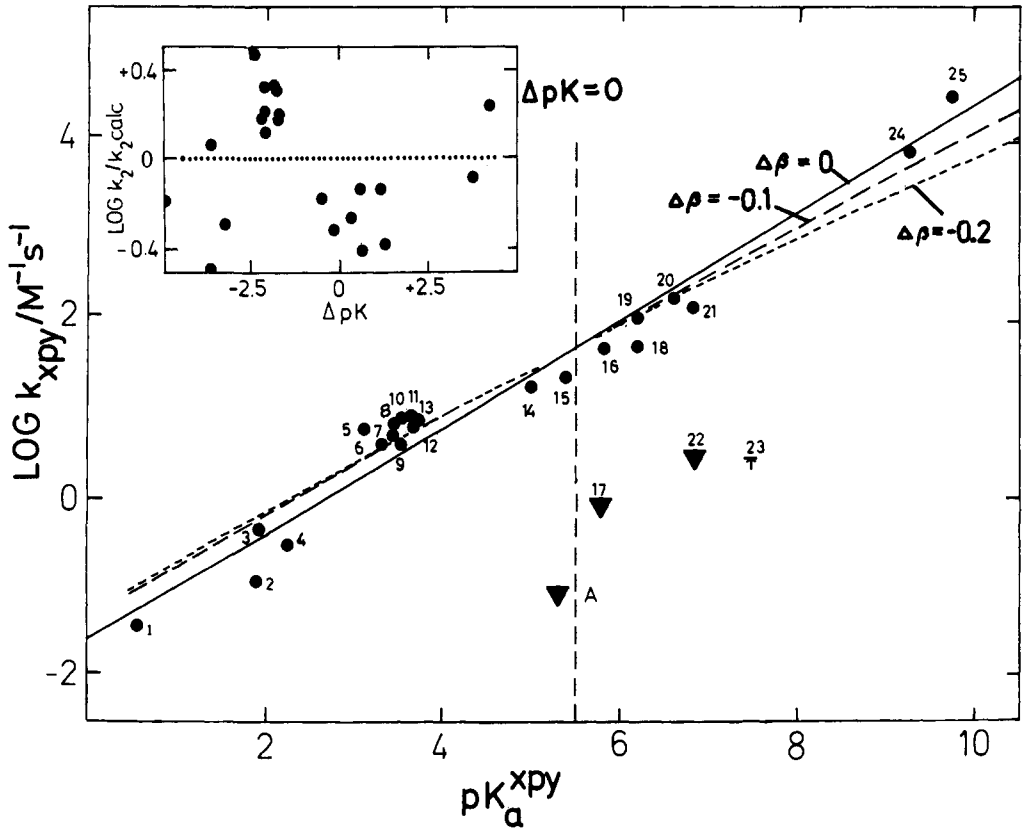


Figure 5. Brønsted dependence of k_2 for the attack of substituted pyridines on *N*-(methoxycarbonyl)isoquinolinium ion. Line is calculated from eq 9 and is not distinguishable from the best fit to eq 7. Data and identity numbers are from Table II; the inset shows the plot of the residuals for the best fit; the dashed lines in the main figure represent the two next best fits of the data to eq 7 (see text). Conditions are given in Table II. Point A is for pyridine with *N*-(methoxycarbonyl)pyridine.[12]

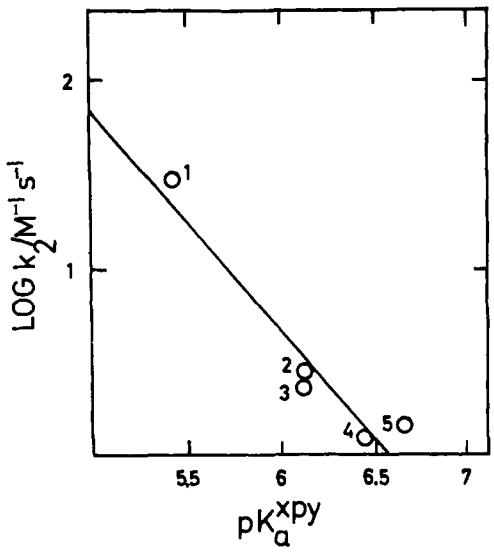


Figure 6. Brønsted plot of k_2 for the attack of pyridine on *N*-methoxycarbonyl-substituted pyridinium ions. Data and conditions are from Table III, and the line is calculated from eq 10.

The reaction of pyridine with *N*-methoxycarbonyl-substituted pyridinium ions was measured and the data recorded in Table III; the Brønsted plot of the data is relatively scattered (Figure 6) as it proved difficult to measure k_2 except for the isoquinoline point. The uncertainty in the measurements is reflected in the deviations from the linear regression of k_2 with pK of the leaving pyridine (eq 10).

$$\log k_2 = (-1.14 \pm 0.3)pK^{xpy} + 7.58 \pm 1.61 \quad (n = 5, r = 0.933) \quad (10)$$

Discussion

Hydration of *N*-(Methoxycarbonyl)isoquinolinium Ion. The hydrolysis of the adduct between isoquinoline and methyl chloroformate obeys a rate law consistent with the equilibrium of eq 2. This mechanism is confirmed by (a) the isolation of material at alkaline pH from the non-hydrolyzed solution having structural characteristics of the pseudo-base and (b) the closeness of k_w (1.4×10^{-2} s^{-1} in eq 3) to the value of k_w (3.5×10^{-2} s^{-1}) determined for the hydrolysis of the similar and bona fide *N*-(methoxycarbonyl)pyridine.[12]

The value of pK_{R^+} for the methoxycarbonyl adduct (3.52) is comparable with that for *N*-cyanoisoquinolinium ion (−2)[24] and with that estimated for the *N*-methylisoquinolinium ion (15.3)[25] and is consistent with electron-withdrawing substituents stabilizing the pseudo-base. Pyridines, with no fused benzene rings, do not appear to form pseudo-bases with methyl chloroformate whereas the quinoline series forms pseudo-bases relatively easily; this is presumably due to the complete loss of resonance energy with pyridines not seen with quinolines or isoquinolines. There is no evidence for pseudo-base formation in *N*-sulfuryl- or *N*-phosphorylisoquinoline in earlier work.[7-9] The reason for this is possibly due to the weaker electron-withdrawing power of these substituents compared with that of the acyl group; the effective charges induced by the PO_3^{2-} and SO_3^{2-} groups are much lower than those by the carbonyl functions.[10b,c]

Reaction of the Isoquinoline–Methyl Chloroformate Adduct with Nucleophiles. The kinetics of reaction of nucleophiles with the isoquinoline–methyl chloroformate adduct in water can be reasonably interpreted as attack on the *N*-(methoxycarbonyl)isoquinolinium ion to give the acyl nucleophile followed by hydrolysis as indicated in the Results section. The attack of substituted pyridines follows a good linear Brønsted relationship over a wide pK_a range (Figure 5). A two-step (AE) mechanism with two transition states predicates a "break" in the Brønsted plot at the pK_a of isoquinoline (5.46). Linearity over a range of pK_a's above and below the predicted breakpoint is prima facie evidence for only one transition state and thus for a concerted process.

Studies of reactions where the substituted pyridines act as nucleophiles indicate deviation of the isoquinoline only within the limits expected of microscopic medium effects in linear free energy relationships.[7,9,26] Reference to Figure 5 indicates that the 4-(dimethylamino)- and 4-aminopyridines are quite important in defining the line. That the observed values of k_2 for these nucleophiles do not include gross complexation effects[8,27] is confirmed by (a) the absence of large deviations elsewhere in the pyridine range and (b) the low concentrations of nucleophile employed in the kinetics and the absence of curvature in the concentration ranges employed. There is undoubtedly some "complexing" effect as the Brønsted plot is not precisely smooth; this effect has been seen with other studies of pyridines acting as nucleophiles[7-9,26] and has been carefully investigated both here and elsewhere[7-9] and shown not to be due to error. We attribute the effect to the preassociation step required, prior to chemical reaction, where slight variations in solvent organization in the complex could result between the two processes being compared (addition of proton and addition of acylisoquininium ion).

That k_2 for reaction of the adduct in pyridine buffers is nucleophilic is further confirmed by the observation that ortho substituents greatly inhibit the rate constant (Figure 5). The rate constant for the bona fide general base catalysis of hydrolysis of *N*-(methoxycarbonyl)pyridinium ion[12] is well below those rate constants thought to represent nucleophilic attack (Figure 5). Observations of intermediates in reactions of pyridines with *N*-(methoxycarbonyl)pyridinium ions, as indicated in the results section, provide excellent evidence for pyridinolysis.

The plot of the error residuals in the correlation with eq 9 shows that the best fit has a random distribution. Conservatively, we should say that the Brønsted plot is linear within an uncertainty limit of less than 0.1 unit of $\Delta\beta$ between the two putative lines represented, and this is illustrated in Figure 5 by the lines of best fit next to that of eq 7.

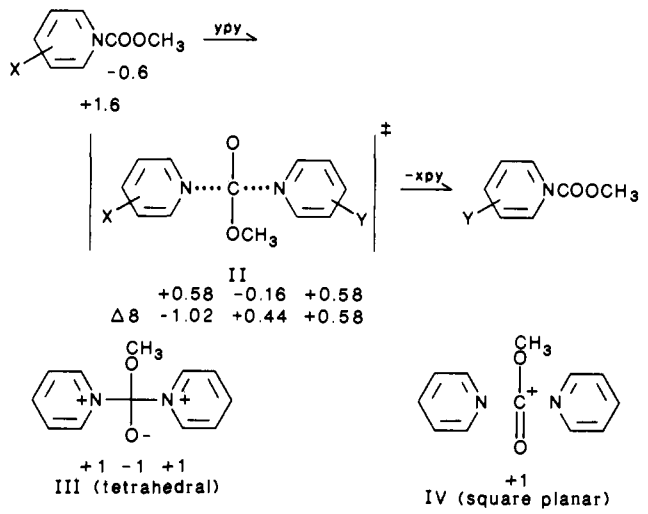
A second argument from the data of Figure 5 indicates a single transition state for the pyridinolysis. The value of β_{nuc} is approximately 0.6 for attack of substituted pyridines on *N*-(methoxycarbonyl)isoquinolinium ion when the second step of the putative two-step process (eq 8) is rate limiting. Since k_{xpy} under these conditions is k_1k_2/k_{-1} the β_{eq} for formation of the tetrahedral intermediate (k_1/k_{-1}) must be less than 0.6. Since the overall β_{eq} for formation of product is 1.6 the β_{eq} for formation of product from putative tetrahedral intermediate must be greater than 1.0. It is not conceivable that the second step is more sensitive to substituents on the attacking nucleophile than is the first step where the substituent effect is directly linked to the changing bond. These conclusions are not consistent with a stepwise process but can be explained by a concerted one.

The value of β_{eq} (1.6)[18,19] for the overall reaction is estimated to be the same or very close to that for acetyl group transfer between pyridines (1.6);[18,19] β_{eq} for acyl group transfer is relatively insensitive to change in the side chain R group provided there is no change in gross electrostatic charge.[10c] We may then calculate β_{-2} (1.0) from β_{nuc} ($\beta_1 + \beta_2 - \beta_{-1}$) and β_{eq}. This value is close to that measured for attack of pyridine on *N*-methoxycarbonyl-substituted pyridinium ions.

Charge Distribution in the Transition State. Since the reaction is a symmetrical one the effective charge on entering and departing nucleophiles must be the same. The charge distribution (Scheme III) may be deduced from the overall β_{eq} and the β_{nuc} value; the quantity $\Delta\epsilon$ is the change in effective charge from ground to transition state. The increase in positive charge on the MeO–CO group of atoms of +0.44 unit indicates some acylium ion character in the transition state. The electrostatic repulsion between the

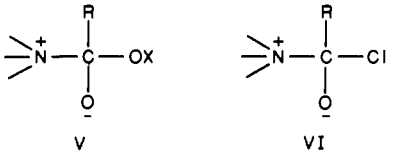
(24) Huckings, J.; Johnson, M. D. *J. Chem. Soc.* **1964**, 5371.
(25) Bunting, J. W.; Meathrel, W. G. *Can. J. Chem.* **1972**, *50*, 917.
(26) Hopkins, A.; Day, R. A.; Williams, A. *J. Am. Chem. Soc.* **1983**, *105*, 6062. (b) Fischer, A.; Galloway, V. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591, 3596.
(27) (a) Kancko, C.; Shiba, F.; Fujii, H. *Heterocycles* **1981**, *15*, 1195. (b) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3209.

Scheme III



positively charged nitrogens in III would tend to distort a tetrahedral stereochemistry toward a square-planar one, and a transition state with full acylium ion character would be square planar (IV).

Concertedness in Acyl Group Transfer Reactions. This study has direct relevance to the tetrahedral intermediates V and VI demonstrated unequivocally in the pyridinolysis of acetic anhydride,[13] methyl chloroformate,[14] aryl acetates,[15] aryl benzoates,[16] and carbonates[17] and in the aminolysis of anhydrides[28] and carbamate esters.[29] It is an immediate problem as to why the



V VI

intermediate I or III should be less stable than the above species and why V and VI should have any stability at all in view of estimates for the lifetimes of tetrahedral adducts with good leaving groups.[30-33]

Those tetrahedral intermediates which have been demonstrated kinetically for interaction of pyridines and amines with neutral acyl compounds[13-17,28,29] possess a zwitterionic form (V and VI); it is our contention that the electrostatic interaction is sufficient to stabilize the adduct to give an energy "well" in the potential energy surface of the acyl transfer reaction. The stabilization afforded by the electrostatic interaction in the zwitterion is about 14 kcal/mol if the microscopic dielectric constant is taken as 10.

Acyl group transfer with a single transition state has been proposed for several systems in polar solvents; the cases studied involve donor and acceptor groups which therefore possess considerable leaving ability. The solvolysis of benzoyl chloride has been demonstrated to involve competing stepwise and concerted mechanisms by use of a free energy correlation with the solvolysis of adamantyl chloride in the same solvents.[34] Reaction of aryl oxide ions with 2-aryloxazolin-5-ones exhibits bond formation which is balanced by a similar amount of endocyclic bond fission as measured by the change in effective charges on the entering and leaving atoms.[30] This behavior is explained by a concerted mechanism, and it is argued that the acylium ion is stabilized electrostatically forcing the transition state "north-west" along the diagonal A-C in the potential energy surface of the reaction (Figure 1).

Arguments based on estimated rate constants for decay of tetrahedral adducts too great to support a stepwise process have been advanced to indicate that concerted acyl group transfer could occur with weakly basic acceptors and donors.[30,32] Ritchie, Van Verth, and Virtanen[31] estimated that the decomposition of the adduct between ethanethiol and 2,4-dinitrophenyl acetate has a rate constant greater than 10^{13} s^{-1} in water and about 10^{19} s^{-1} in dimethyl sulfoxide. The cyanide adduct may exist in water but not in dimethyl sulfoxide.

Acknowledgment. We are grateful to the SERC for a research studentship (EC) and to Dr. R. B. Moodie for helpful advice.

(28) Hall, W. E.; Higuchi, T.; Pitman, I. H.; Hekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153.
(29) (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (b) Gresser, M. J.; Jencks, W. P. *Ibid.* **1977**, *99*, 6970.
(30) Curran, T. C.; Farrar, C. R.; Niazy, O.; Williams, A. *J. Am. Chem. Soc.* **1980**, *102*, 6828.
(31) Ritchie, C. D.; Van Verth, J. E.; Virtanen, P. O. *J. Am. Chem. Soc.* **1982**, *104*, 3491.
(32) McClelland, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7579.
(33) Bender, M. L.; Thomas, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4189.
(34) (a) Bentley, T. W.; Carter, G. E.; Harris, H. C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 983. (b) Bentley, T. W.; Harris, H. C. *Ibid.* **1986**, 619.

Kinetic and Stereochemical Effect of a Fluorine Substituent on the Cope and the Homodienyl 1,5-Hydrogen Shift Rearrangements

William R. Dolbier, Jr.,* Adam C. Alty, and Otto Phanstiel, IV

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32611. *Received November 3, 1986*

Abstract: The kinetics and stereochemical outcome for the thermal rearrangements of 3-fluoro-1,5-hexadiene and 1-(fluoromethyl)-2-vinylcyclopropane have been investigated. The relative proportions of *Z* and *E* products in each case reflected their relative stability, thus indicating the lack of any dramatic kinetic effects due to the presence of the fluorine substituents in contrast to the very dramatic effects of this nature observed in cyclobutene-butadiene interconversions.

The recently reported dramatic kinetic effect of substituents, particularly fluorine substituents, upon electrocyclic cyclobutene-butadiene interconversions,[1,2] combined with the subsequent theoretical explanation for these effects,[2,3] induced us to

0002-7863/87/1509-3046$01.50/0