The Kinetics and Stereochemistry of the Reaction of Diethyl Maleate and Diethyl Fumarate with Hydrogen Chloride in Acetic Acid

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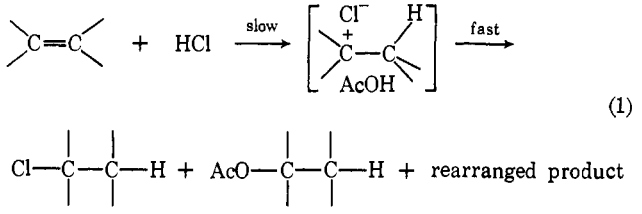
Abstract: Hydrogen chloride in acetic acid adds to diethyl fumarate (DEF) and to diethyl maleate (DEM) according to the rate law: rate = k[olefin][HCl]^2. Values of $\Delta H^{\pm}$ (kilocalories/mole) and $\Delta S^{\pm}$ (entropy units) were determined to be: DEF, 10.9 and −51; DEM, 8 and −52. Experiments in DCl–DOAc showed that there is no kinetic isotope effect upon the rate of addition and nmr analysis of the DCl adducts revealed that anti addition to DEF and DEM occurs to the extent of 90 and 67%, respectively. The study was complicated by the fact that isomerization of DEM and DEF is a competing reaction. The conversion of DEM to DEF was found to be first order in both DEM and HCl with $\Delta H^{\pm}$ = 13.2 kcal/mol and $\Delta S^{\pm}$ = −33 eu. In DCl–DOAc an inverse isotope effect (k_H/k_D = 0.5) was found but no deuterium incorporation accompanied the isomerization. Limited studies of HCl addition to ethyl crotonate indicated that this reaction is also first order in olefin and second order in HCl. Neither the isomerization of DEM nor the addition reactions are subject to catalysis by chloride salt or perchloric acid. The results are interpreted in terms of a mechanism involving 1,4-addition intermediates. Ketonization of the 1,4 adduct by HCl is the slow step in the addition reactions.

This is the fourth in a series of papers concerned with the mechanism involved in the anti addition of acids to olefinic double bonds.[2] In the first paper,[3] we demonstrated that addition of HCl to *tert*-butylethylene and to styrene in acetic acid occurs *via* the well-established Ad_E2 mechanism of eq 1. Such a



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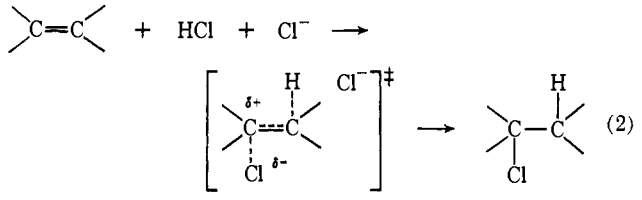
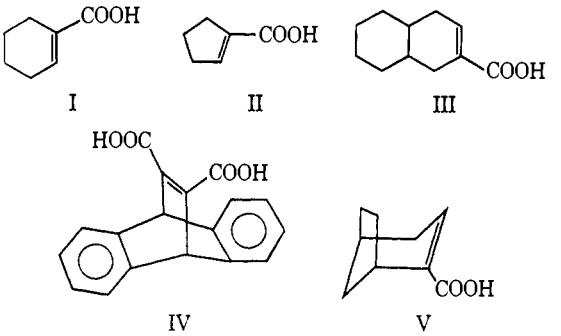
mechanism is consistent with nonstereospecific or preferential syn addition to the double bond but not with stereospecific anti addition. In the second[4] and third[5] papers of this series, we demonstrated that stereospecific anti addition of HCl and of HOAc to cyclohexene occurs by a termolecular mechanism (Ad_E3) of the type illustrated in eq 2 for addition of HCl.[6] In



(2)

this paper, we examine the addition of HCl to diethyl fumarate and to diethyl maleate in acetic acid and show that a still different mechanism is involved in these additions.

The literature contains a substantial body of evidence supporting the view that acids add in an anti fashion to α,β-unsaturated carbonyl compounds. Examples include the anti addition of HI to tiglic acid and angelic acid,[7] of HBr to I–V,[8–11] and of HCl to II,[11] IV,[11] and 1-benzoylcyclohexene.[12] The enzyme-catalyzed additions of water to fumaric acid[13] and to *cis*-aconitic acid[14] have also been shown to involve stereospecific anti additions.



Hydrogen halide additions to α,β-unsaturated carbonyl compounds have been most often interpreted in terms of a 1,4 addition followed by stereoselective ketonization of the resulting enol (eq 3).[10,15] The re-

(1) Alfred P. Sloan Foundation Fellow 1966–1968; to whom correspondence should be addressed.

(2) For recent reviews on the mechanism of electrophilic addition reactions see: (a) P. B. D. de la Mare and R. Bolten, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, 1966; (b) R. C. Fahey, *Top. Stereochem.*, 3, 237 (1968).

(3) R. C. Fahey and C. A. McPherson, *J. Amer. Chem. Soc.*, 91, 3865 (1969).

(4) R. C. Fahey, M. W. Monahan, and C. A. McPherson, *ibid.*, 92, 2810 (1970).

(5) R. C. Fahey and M. W. Monahan, *ibid.*, 92, 2816 (1970).

(6) Future papers in this series will provide additional examples of anti addition *via* the termolecular mechanism.

(7) J. Wilicenus and H. P. Talbot, *Ann. Chem.*, 313, 228 (1900); W. G. Young, R. T. Dillon, and H. J. Lucas, *J. Amer. Chem. Soc.*, 51, 2528 (1929).

(8) W. R. Vaughan and K. M. Milton, *ibid.*, 74, 5623 (1952).

(9) W. R. Vaughan, R. L. Craven, R. Q. Little, and A. C. Schoenthaler, *ibid.*, 77, 1594 (1955).

(10) W. R. Vaughan and R. Caple, *ibid.*, 86, 4928 (1964); R. Caple and W. R. Vaughan, *Tetrahedron Lett.*, 4067 (1966).

(11) W. R. Vaughan, R. Caple, J. Csapilla, and P. Scheiner, *J. Amer. Chem. Soc.*, 87, 2204 (1965).

(12) C. Armstrong, J. A. Blair, and J. Homer, *Chem. Commun.*, 103 (1969).

(13) R. A. Alberty, *Enzymes*, 5, 531 (1961).

(14) O. Gawron and K. P. Mahajan, *Biochemistry*, 5, 2343 (1966).

(15) R. E. Lutz and F. N. Wilder, *J. Amer. Chem. Soc.*, 56, 1193 (1934); M. J. S. Dewar and R. C. Fahey, *ibid.*, 85, 2248 (1963).

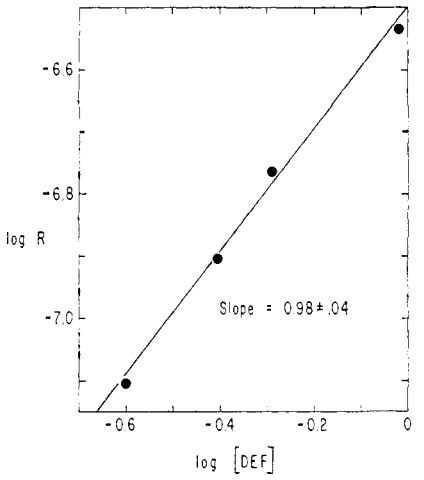
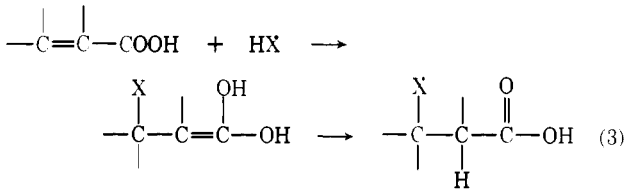


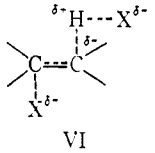
Figure 1. Plot of log R *vs.* log [DEF] at 24.9° with [HCl] = 0.762 M.

sults of kinetic studies of the acid-catalyzed hydration



of mesityl oxide[16] and of the dehydration of 4-phenyl-4-hydroxy-2-butanone[17] were found to be consistent with reaction *via* a 1,4 intermediate but no detailed kinetic studies of hydrogen halide additions have been reported. With respect to hydrogen halide addition it is somewhat difficult to understand why ketonization of the enol intermediate in eq 3 should be a generally stereospecific process, although Vaughan and Caple[10] have presented plausible arguments why anti addition should occur with cyclohexene carboxylic acid derivatives. It seemed to us, however, that a different mechanism might be involved for anti addition of hydrogen halides to α,β-unsaturated carbonyl compounds.

It is well known that α,β-unsaturated carbonyl compounds undergo nucleophilic additions to the carbon–carbon double bond. Recent studies of the addition of ammonia[18] and of water[19] to fumarate indicate that these reactions occur *via* rate-limiting nucleophilic attack at the double bond to form a planar carbanion intermediate. In the case of the addition of ammonia, it was shown that addition is nonstereospecific.[18] Since α,β-unsaturated carbonyl compounds are subject to nucleophilic attack, a mechanism involving simultaneous anti attack by halide ion and proton *via* a transition state resembling VI seemed a reasonable



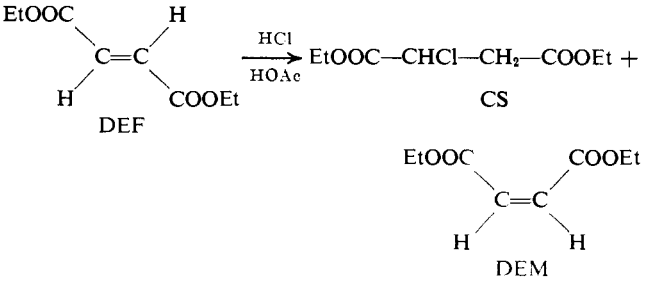
VI

alternative to the mechanism of eq 3 for explaining anti addition of hydrogen halides. The stereospecific enzyme-catalyzed anti additions of water to fumaric acid and to aconitic acid might be understood in terms of a similar mechanism[14] and it was therefore of some interest to establish whether such a mechanism does operate for nonenzymatic additions. The present studies were undertaken with this objective.

The diethyl esters of fumaric and maleic acid, rather than the free acids, were chosen for study owing to their greater solubility in organic solvents and in order to avoid the complications resulting from the existence of various ionized forms of the acids. The same reaction conditions, hydrogen chloride in acetic acid, as used in the previous studies were chosen so that the results obtained would be directly comparable to the earlier results.

Results

Reaction of Diethyl Fumarate (DEF). The reaction of DEF with hydrogen chloride in acetic acid yields primarily diethyl chlorosuccinate (CS) but careful analysis by glpc revealed that approximately 0.1% of diethyl maleate (DEM) is also formed. It was shown that CS is stable to the reaction conditions. Reaction rates



were studied as a function of reactant concentration, reaction medium, and temperature. Initial rates, $R = \Delta[CS]/\Delta t$, were determined at less than 10% conversion and were based on the glpc analyses of three or more samples for each run. The work-up procedure and glpc analysis were checked with known mixtures.

The rate law was established from studies of the dependence of R upon reactant concentrations. Figure 1 shows a plot of log R *vs.* log [DEF] at constant hydrogen chloride concentration. The unit slope establishes a first-order dependence upon DEF A plot of log R *vs.* log [HCl] at constant [DEF] (Figure 2) has slope 2.0 demonstrating a second-order dependence upon HCl. Thus, the rate law for addition to DEF is given by

$$-d[DEF]/dt = d[CS]/dt = k_F[DEF][HCl]^2 \quad (4)$$

In five runs followed to over 50% conversion (see Table I), third-order rate constants calculated from the in-

Table I. Rate Constants for Addition of HCl to DEF

T, °C	$k_F \times 10^7$, M^{-2} sec^{-1} (no. runs) From initial rates	From integrated rate law
24.9	5.1 ± 0.1 (8) 4.9 ± 0.3[a] (3)	4.75 ± 0.2 (3)
50.4	23.8 (1)	24.8 (1)
79.9	107 (1)	113 (1)

[a] From runs in 0.44, 0.65, and 1.1 M DCl in DOAc.

(16) R. P. Bell, J. Preston, and R. B. Whitney, *J. Chem. Soc.*, 1166 (1962).
(17) D. S. Noyce and W. L. Reed, *J. Amer. Chem. Soc.*, 80, 5539 (1958).
(18) J. L. Bada and S. L. Miller, *ibid.*, 91, 3946 (1969).
(19) J. L. Bada and S. L. Miller, *ibid.*, 91, 3948 (1969).

tegrated form of eq 4[20] decreased less than 10% from the average value and yielded an average value within 6% of that determined from initial rate studies. In contrast, second-order rate constants calculated from the integrated second-order rate law, first order in both DEF and HCl, decreased to 60% of their average value by completion of the run.

Rate studies in DCl–DOAc (Table I) allow an evaluation of the isotope effect (k_H/k_D = 1.0) and the variation of k_F with temperature leads to the apparent activation parameters $\Delta H_F^{\ddagger}$ = 10.9 kcal/mol and $\Delta S_F^{\ddagger}$ = −51 eu.

The effect of changing the reaction medium in various ways was studied and the results are summarized in Table II. Neither the presence of hydroquinone or

Table II. The Effect of Salts and Diluents upon the Rate of Addition to DEF (0.965 *M*) at 25°

Compd	Concn, *M*	[HCl], *M*	$k_F \times 10^7$, M^{-2} sec^{-1} [a]
Hydroquinone	0.02	0.80	4.5
$(PhCO_2)_2$	0.02	0.93	4.7
Light[b]		0.89	5.2
Cyclohexane	0.9	0.53	4.7
HCOOH	1.1	0.53	5.0
CF_3COOH	1.1	0.81	5.2
H_2O	0.1	0.52	4.8
	1.0	0.53	~0.8[c]
DMF	0.52	0.53	~0.4
$HClO_4$	0.12	0.49	5.0
	0.20	0.49	5.3
	0.32	0.49	5.8
$LiClO_4$	0.12	0.49	4.9
	0.20	0.49	4.6
	0.32	0.49	4.5
LiCl	*0.53*	*0.53*	4.2
$(CH_3)_4NCl$	0.21	0.32	4.5
	0.71	0.32	3.0

[a] Calculated from initial rate assuming eq 4 to be valid. [b] Irradiation with a G.E. sunlamp. [c] Substantial amounts of ethyl acetate and fumaric acid observed.

of benzoyl peroxide nor irradiation of the reaction mixture with light had a significant effect upon the reaction rate which shows that free-radical processes are not involved. Cyclohexane, formic acid, and trifluoroacetic acid each have negligible effects upon the reaction when present at 1 *M* concentration. Water at low concentrations (0.1 *M*) has little effect but seems to retard the reaction at higher concentrations and causes substantial side reaction. The more basic diluent dimethylformamide has a decided rate-retarding effect. Perchloric acid, a far stronger acid than hydrogen chloride in acetic acid,[21] has only a minor rate-enhancing effect while lithium perchlorate has an opposite effect. Similarly, lithium chloride and tetramethylammonium chloride decrease the rate.

Reaction of Diethyl Maleate (DEM). Treatment of DEM with hydrogen chloride in acetic acid gives CS and much DEF, the ratio of CS to DEF increasing with the HCl concentration. The reaction was studied in two ways: (1) by sampling and glpc analysis as described above for DEF and (2) by direct nmr measurements on the reaction mixtures. The first method

(20) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 21.

(21) I. M. Kolthoff and S. Bruckenstein, *J. Amer. Chem. Soc.*, 78, 1 (1956).

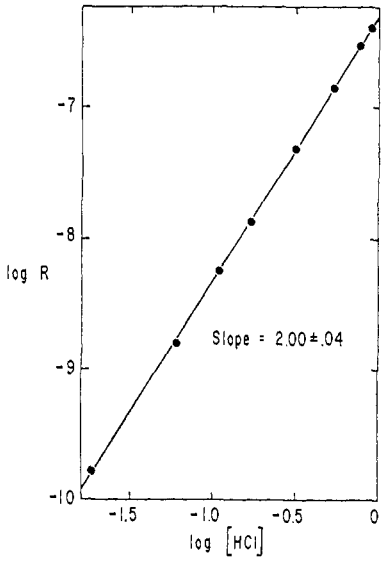


Figure 2. Plot of log *R vs.* log [HCl] at 24.9° with [DEF] = 0.965 *M*.

proved satisfactory for studying the appearance of CS but was unsatisfactory for following DEF owing to the fact that DEM partially isomerizes to DEF in the work-up procedure. The nmr method could be used to study the appearance of DEF but CS could be detected only at high conversion of DEM.

The conversion of DEM to DEF was followed by inspection of the olefinic proton signals in the nmr spectrum. Plots of log [DEM] *vs.* time gave straight lines for low initial concentrations of hydrogen chloride or for the first stage of reaction at higher acid concentrations. A plot of the pseudo-first-order rates, k_1, obtained from these slopes *vs.* log [HCl] has a slope of 1.08 while an analogous plot *vs.* log *A*, *A* being an acidity function for HCl–HOAc solutions similar to the Hammett h_0 function for aqueous media,[22] has a slope of 0.9. These results suggest that the main isomerization reaction is kinetically first order in hydrogen chloride; the apparent observed deviation from a strictly first-order dependence can be attributed to deviations of HCl activity from concentration in the concentration region studied or to a small component of the reaction (<10%) occurring with greater than first-order dependence on HCl. The data can be fit empirically to the rate expression

$$d[DEF]/dt = k_i[DEM][HCl]^{1.08} \quad (5)$$

with the calculated values of k_i remaining constant for the range of acid concentrations studied (Table III).

The rate of isomerization was studied as a function of the reaction conditions (Table III). The rate is greater for reaction in DCl–DOAc than in HCl–HOAc showing that the reaction involves an inverse isotope effect (k_H/k_D = 0.5). Recovery and nmr analysis of DEM and DEF demonstrated that neither incorporate deuterium during the course of the reaction. The effects of salts and various diluents upon the rate are quite similar to those reported above for addition to DEF.

The appearance of CS was followed by glpc analysis using the same procedure as described above for addi-

(22) D. P. N. Satchell, *J. Chem. Soc.*, 1916 (1958); R. C. Fahey and D.-J. Lee, *J. Amer. Chem. Soc.*, 90, 2124 (1968).

Table III. Isomerization of DEM at 25.0° and [DEM] = 0.212 M

[HCl], M	Salt or diluent	Concn, M	10^5k_i, sec^{-1}	10^5k_i, sec^{-1} $M^{-1.08}$
0.075	None		0.49	7.9
0.225	None		1.55	7.8
0.36	None		2.59	7.8
0.50	None		3.8	8.1
0.212[a]	None		2.95	15.5
0.495	Inhibitor[b]	0.01	3.8	8.1
0.225	Cyclohexane	0.90	1.64	8.2
0.225	DMF	0.52	0.12	0.6
0.225	H_2O	0.10	1.55	7.7
0.225	$HClO_4$	0.10	1.43	7.2
0.225	$LiClO_4$	0.10	1.43	7.2
0.225	TMAC	0.52	1.3	6.5

[a] For DCl in DOAc. [b] 2,6-Di-*tert*-butyl-*p*-cresol.

tion to DEF. Initial rates were determined at <10% DEM conversion (0–3% CS formation) and employed to calculate third-order rate constants, k_M, for addition to DEM. The ratio CS/DEF was determined from the observed fraction of CS and the integrated form of eq 5 (assuming [HCl] constant) at ≤5% HCl conversion (up to 80% DEM conversion in some runs). Values of k_M calculated indirectly from these ratios using k_i = 7.9×10^{-5} M^{-1} sec^{-1} are included in Table IV. The

Table IV. The Reaction of HCl with DEM (0.212 M) at 25.0°

[HCl], M	10^7R,[a] M sec^{-1}	10^5k_M,[b] M^{-2} sec^{-1}	CS/DEF[c]	10^5k_M,[d] M^{-2} sec^{-1}
0.038			0.025 ± 0.01	4.0
0.206	3.5	3.9	0.12 ± 0.02	4.1
0.493	23	4.3	0.29 ± 0.03	4.4
0.495			0.23 ± 0.04	3.5
0.93		3.8	0.50 ± 0.08	4.2

[a] Determined at <10% DEM conversion. [b] Calculated from initial rate. [c] CS determined at ≤5% HCl conversion; DEF calculated from data in Table III. [d] Calculated from $k_M = k_i(CS/DEF)/[HCl]^{0.92}$.

calculated values of k_M do not vary with the HCl concentration implying that addition to DEM follows the same third-order rate law found for addition to DEF but with a rate constant, $k_M = 4.0 \pm 0.2 \times 10^{-5}$ M^{-2} sec^{-1}, about 80 times k_F.

The values of k_i and the ratio of CS to DEF were determined as a function of temperature (Table V).

Table V. The Effect of Temperature Upon the Reaction of HCl (0.502 M) with DEM (0.212 M)

T, °C	10^5k_i, M^{-1} sec^{-1}	CS/DEF
25.0	7.9	0.26
50.0	55	0.18
80	380	0.07
125	2300	0.03

For isomerization of DEM to DEF the apparent activation parameters are $\Delta H_i^{\pm} = 13.2$ kcal/mol and $\Delta S_i^{\pm} = -33$ eu. From the variation of the ratio of CS to DEF the differences in activation parameters for isomerization of and addition to DEM may be estimated. The values, calculated for 1.0 M HCl, are $\Delta H_i^{\pm} - \Delta H_M^{\pm} =$ 5 kcal/mol and $\Delta S_i^{\pm} - \Delta S_m^{\pm} = 19$ eu. The apparent activation parameters for addition to DEM are thus $\Delta H_M^{\pm} = 9.0$ kcal/mol and $\Delta S_M^{\pm} = -52$ eu.

The Equilibrium Constant for Isomerization of DEF and DEM. The equilibrium constant, K_i, for interconversion of DEF and DEM was determined directly by isomerization of DEM (0.5 M) in acetic acid catalyzed by KSCN (0.316 M). The ratio of DEF to DEM was determined by glpc analysis and was found to approach a constant value of 650 after reaction for 30 half-lives.

An independent evaluation of K_i was possible through determination of k_{-i} for isomerization of DEF to DEM. As pointed out above, the reaction of DEF with HCl yields mainly CS but small steady-state quantities of DEM were also detected. By the principle of microscopic reversibility, the rate law for isomerization of DEF to DEM must be the same as that for isomerization of DEM to DEF. The latter was shown to follow eq 5. If we assume a first-order dependence (rather than the observed apparent order of 1.08) upon [HCl], we obtain

$$d[DEM]/dt = -k_M[DEM][HCl] - k_i[DEM][HCl] + k_{-i}[DEF][HCl] \quad (6)$$

and application of the steady-state assumption, $d[DEM]/dt = 0$, gives

$$k_{-i} = ([DEM]/[DEF])(k_i + k_M[HCl]) \quad (7)$$

The conditions under which the steady-state assumption is valid can be derived by integration of eq 6 under the assumption that [HCl] is constant (less than 10% addition) leading to eq 8

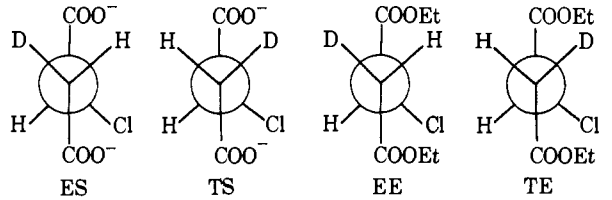
$$k_{-i} = (\alpha[DEM]/[DEF])(1 - e^{-\alpha t[HCl]})^{-1} \quad (8)$$

where $\alpha \equiv k_i + k_M[HCl]$. Comparison of eq 7 and 8 shows that eq 7 is valid for reaction times $t \geq 4/(\alpha \cdot [HCl])$. For three runs (0.965 M DEF; 0.187, 0.53, and 0.894 M HCl) at 25° measurements of [DEM]/[DEF] under the steady-state conditions gave values ranging from 0.0009 to 0.0017 from which application of eq 7 yielded $k_{-i} = 1.3 \pm 0.3 \times 10^{-7}$. K_i is calculated to be 600 ± 200, which accords with the value of K_i determined by direct isomerization of DEM.

It is evident from the foregoing considerations that the observed rate for addition to DEF contains a component (~10% of the total rate for addition) which involves isomerization of DEF to DEM followed by addition to DEM.

The Stereochemistry of Addition to DEF and DEM. The stereochemistry of addition of DCl to DEF and DEM was determined by nmr analysis of the products of addition. The nmr spectrum of CS exhibits an ABX pattern for the resonance of the C-2 and C-3 protons. Analysis of the ABX pattern gave values of $J_{AX} = 6.5$ Hz, $J_{BX} = 8.0$ Hz, and $J_{AB} = -16.9$ Hz. Addition of DCl to DEF yielded a product exhibiting two C-3 proton doublets, $J = 6.2$ and 8.0 Hz under conditions of deuterium decoupling, with the former being more intense. Addition of DCl to DEM gave a product exhibiting the same two C-3 proton doublets but with the latter being more intense. When the product from DEF was hydrolyzed and converted to the disodium salt, the corresponding C-3 proton doublets had splittings of 9.95 and 4.2 Hz with the former being most

intense; the latter doublet was more intense in the salt derived from DEM. It is known that the salts exist primarily in conformations with the two carboxylate groups anti and the well-established variation of vicinal coupling constants with dihedral angle[23] allows the assignment of the salt derived from DEF as primarily the erythro isomer ES, while that from DEM is primarily the threo isomer TS.[24] The main product from addition of DCl to DEF is thus diethyl *d,l-erythro*-2-



chlorosuccinate-*3-d* (EE) and that to DEM is diethyl *d,l,-threo*-2-chlorosuccinate-*3-d* (TE), each corresponding to anti addition across the respective olefinic double bond. The relevant nmr data obtained from these compounds are summarized in Table VI. It is of inter-

Table VI. Nmr Spectral Data for Derivatives of Chlorosuccinic Acid

Compd	δ, ppm	Mult[a]	*J*, Hz	Area	Assignment
EE[b]	0.92	t	7	6	CH_3
	2.65	d	6.2	1	CDH
	3.89	q	7	2	CH_2
	3.95	q	7	2	CH_2
	4.54	d	6.2	1	CHCl
TE[b]	2.99	d	8.0	1	CDH
	4.54	d	8.0	1	CHCl
ES[c]	0.264	d	4.2	1	CDH
TS[c]	0.563	d	9.9	1	CDH

[a] d, doublet; t, triplet; q, quartet. [b] 10–20% wt/v in benzene with δ measured downfield from TMS as internal standard. [c] ~10% wt/v in D_2O with δ measured upfield from $(CH_3)_4NBr$ as internal standard.

est to note that the relative magnitudes of the vicinal coupling constants become reversed in going from the ester to the salt which indicates that the conformation with the two carboethoxy groups anti is *not* the most stable conformation for the esters.

With the stereochemical assignments thus established, the stereochemistry of the reaction was determined from the nmr spectra of the addition products under a variety of reaction conditions (Table VII). No significant

Table VII. The Stereochemistry of Addition of DCl to DEM and DEF at 25°

Substrate[a]	[DCl], *M*	% addn	% EE[b] Obsd	% EE[b] Corr
DEM	0.69[c]	9	33.5	
	0.88[d]	12	32	
	1.1	12	34.5	
DEF	0.88	10	81	89
		26	83	91
	0.88[d]	10	81	89
		25	81	89
	1.3	35	86	94.5

[a] 1.0 *M* except as noted. [b] ±2%. [c] 0.58 *M* DEM. [d] With 0.1 *M* $HClO_4$.

(23) A. A. Bothner-By, *Advan. Magn. Resonance*, 1, 195 (1965).
(24) The observed values of J_{AX} and J_{BX} and their assignments are in general agreement with earlier studies of the disodium salt of chlorosuccinic acid [*cf.* L. E. Erickson, *J. Amer. Chem. Soc.*, 87, 1867 (1965)].

variation in the observed stereochemistry was found with per cent conversion at 25° indicating that isomerization of the products is unimportant under these reaction conditions. At a higher temperature (125°) some change in the stereochemistry of the adducts with reaction time was observed and appreciable isotopic exchange occurred; accurate results could not be obtained under these conditions. There appears to be no marked variation in the stereochemistry of addition with DCl concentration although one run with DEM at 3.5 *M* HCl carried out in a sealed ampoule between 0 and 25° did give somewhat more anti adduct than was observed at 25° and lower HCl concentrations. The presence of perchloric acid (0.1 *M*) had no effect upon the stereochemistry of addition to either DEF or DEM, but the presence of a proton source led to some competing HCl addition in these reactions.

Consideration of the relative rates of addition and the average ratio of [DEF] to [DEM] present during addition to DEM shows that at most about 2% of the DCl adduct formed is derived from addition to DEF. Corrections for this do not change the observed results for addition to DEM within experimental error and have therefore been neglected.

For addition to DEF, however, it is necessary to correct for that fraction of the reaction proceeding *via* DEM. The fraction of the reaction of DEF which yields EE by direct addition to DEM is given by

$$f_{\mathrm{DEM}}^{\mathrm{EE}} = \frac{nk_{\mathrm{M}}[\mathrm{DEM}]}{k_{\mathrm{F}}[\mathrm{DEF}]} \tag{9}$$

where *n* is the observed fraction of EE formed from reaction of DEM (*n* = 0.34, Table VII). For greater than about 1% conversion the steady-state condition is valid and [DEM] is given by eq 7. Combination of eq 7 and 9 gives

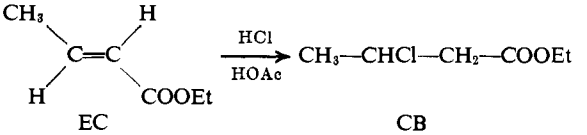
$$f_{\mathrm{DEM}}^{\mathrm{EE}} = \frac{nk_{\mathrm{M}}k_{-\mathrm{i}}}{k_{\mathrm{F}}(k_{\mathrm{i}} + k_{\mathrm{M}}[\mathrm{DCl}])} \tag{10}$$

Since there is no isotope effect upon k_{F} it is reasonable to assume that there is none upon k_{M}; however, both k_{i} and $k_{-\mathrm{i}}$ are subject to a twofold inverse isotope effect. Substitution of the appropriate values in eq 10 allows the calculation of $f_{\mathrm{DEM}}^{\mathrm{EE}}$. The corresponding fraction of TE formed in the reaction is given by

$$f_{\mathrm{DEM}}^{\mathrm{TE}} = \frac{(1-n)}{n} f_{\mathrm{DEM}}^{\mathrm{EE}}$$

and from these values it is a simple matter to correct the observed fraction of EE formed in the addition to DEF to that which would be found in the absence of competing addition to DEM. The corrected values are included in Table VII.

Addition to Ethyl Crotonate. A limited study was made of the addition of HCl to ethyl crotonate (EC). The sole product was the ethyl β-chlorobutyrate (CB) characterized by its nmr spectrum. The reaction was



studied in the same general fashion as described above for addition to DEF. Third-order rate constants, k_3,

were calculated from the observed initial rates and were found to be roughly constant over a 20-fold change in HCl concentration (Table VIII). Neither tetramethyl-

Table VIII. Addition of HCl to Ethyl Crotonate (0.785 *M*) in Acetic Acid at 25°

[HCl], *M*	10^5R, *M* sec^{-1}	10^6k_3, *M*$^{-2}$ sec^{-1}
0.049	0.98	5.1
0.162	19	9.5
0.425	117	8.3
1.12	490	5.0
		Av = 7 ± 2
0.425[a]	105	7.4
0.425[b]	115	8.1

[a] With 0.125 *M* $(CH_3)_4NCl$. [b] With 0.10 *M* $HClO_4$.

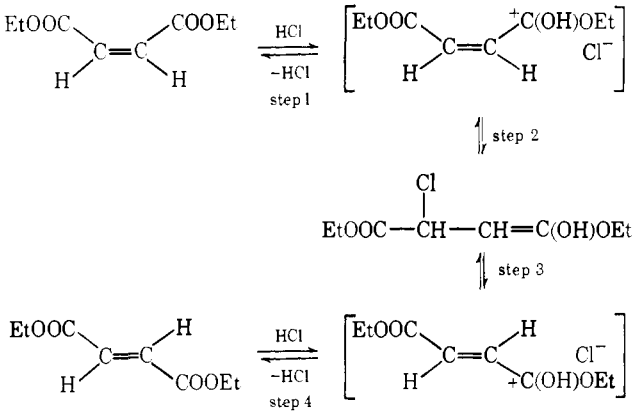
ammonium chloride nor perchloric acid have a marked effect upon the rate.

Discussion

The results obtained in this study allow us to define in some detail both the mechanism for the interconversion DEF and DEM catalyzed by HCl and the mechanism for HCl addition to these olefins. We consider first the mechanism for isomerization of DEM to DEF. The reaction rate is not affected by radical inhibitor which excludes a free-radical mechanism. The rate is effectively first order in DEM and first order in HCl, but is not accelerated by perchloric acid or by chloride salt; this rules out mechanisms involving simple acid catalysis or nucleophilic catalysis by chloride ion. In addition to the above results, the mechanism must accommodate the observed inverse deuterium isotope effect (k_H/k_D = 0.5) and account for the fact that neither DEM nor DEF incorporate deuterium when the isomerization is conducted in DCl–DOAc solution.[25]

Isomerization *via* a 1,4-addition intermediate (Scheme I), a mechanism analogous to that proposed by Nozaki

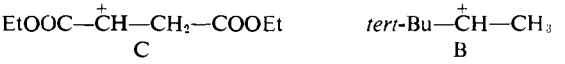
Scheme I



and Ogg[26] for isomerization of maleic acid to fumaric acid in aqueous solution, satisfactorily explains these results. The protonated carbonyl species are written as ion pairs since salts are little dissociated in acetic acid. Direct interconversion of the two ion pairs by rotation about the olefinic bond would require the positive charge to become localized at the olefinic carbon adjacent to a carbonyl group. The observed rate of reaction, compared with that for carbonium ion additions following similar kinetics,[3] is much too fast for this to be a plausible pathway; thus, a 1,4 adduct is postulated as an intermediate. In principle, either step 2 or step 3 (or both) could be rate limiting and an inverse isotope effect upon the observed rate for isomerization is to be expected in either case.[27]

Consider now the results for additon to DEM, DEF, and EC. The rate of all three reactions follows third-order kinetics, first order in olefin and second order in HCl. The lack of effect of inhibitor, light, or free-radical initiator upon the rate of addition to DEF argues against a free-radical mechanism for addition. Additions to DEF and EC were found not to be subject to catalysis by chloride salts so that nucleophilic attack by chloride ion derived from chloride salts is not involved in the slow step. One of the reasons for undertaking this study was to determine whether or not a termolecular 1,2-addition mechanism operates for HCl addition to DEM or DEF; the latter result clearly rules out this type of mechanism. The fact that the kinetic behavior and rate of reaction of DEF and EC are similar indicates that the presence of two carboethoxy groups attached to the olefinic bonds in DEF and DEM has no special bearing upon the mechanism.

It is also clear that a mechanism involving rate-limiting protonation at the olefinic double bond to form a carbonium ion intermediate is not involved. The observed kinetics are not in accord with this mechanism. Moreover, the cation formed from DEF (C) should be much less stable than that formed from *tert*-butylethylene (B) owing to the destabilizing effect of the carboethoxy group and reaction of DEM *via* C should, therefore, be orders of magnitude slower than the re-



action of *tert*-butylethylene. Under comparable conditions addition to DEF occurs at roughly the same rate as addition to *tert*-butylethylene, the latter reaction having been shown to involve the carbonium ion B as an intermediate.[3] Thus, addition to DEF, and by analogous argument to DEM, cannot reasonably involve a carbonium ion intermediate which resembles C.

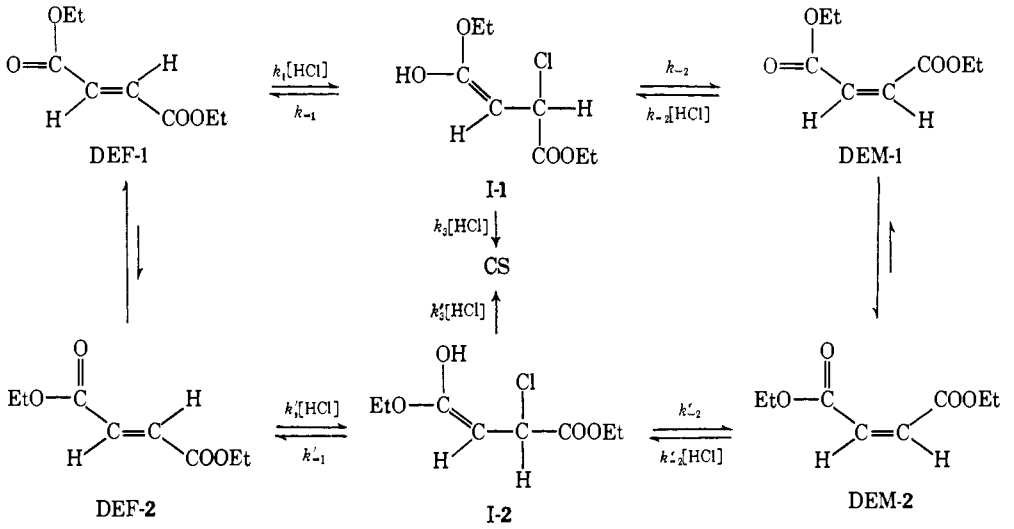
The results for addition to DEM and DEF can be accommodated in terms of a mechanism involving rate-limiting attack by HCl upon the 1,4 adduct of Scheme I. It is important to note at this point that a different product mixture is obtained from DCl addition to DEF than to DEM. This shows that the two reactions do not proceed exclusively *via* the same intermediate since, if they did, both would yield the same product mixture. There are, however, two possible 1,4 adducts from DEF and DEM, corresponding to the two different possible geometries about the double bond, and the different stereochemistry of addition can be explained if DEF

(25) An analogous result has been reported for the isomerization of maleic acid by DCl in D_2O [*cf.* C. Horrex, *Trans. Faraday Soc.*, 33, 570 (1937)].

(26) K. Nozaki and R. Ogg, Jr., *J. Amer. Chem. Soc.*, **63**, 2583 (1941).

(27) HCl is largely un-ionized in acetic acid[21] and the HCl stretching frequency is on the order of 3000 cm^{-1}. A free OH group has a stretching frequency of about 3600 cm^{-1} plus in-plane and out-of-plane bending frequencies of approximately 1400 and 700 cm^{-1}, respectively. A substantial increase in the sum of the hydrogen vibrational frequencies is thus expected to accompany transfer of the proton from chloride to oxygen and this increase can reasonably be of the magnitude required to account for the observed inverse isotope effect.

Scheme II



adds primarily *via* one isomer and DEM *via* the other. A possible mechanism of this type is outlined in Scheme II.

The mechanism of Scheme II accommodates the results for isomerization and for addition providing certain conditions are met. These conditions are best understood in terms of the free-energy diagram shown in Figure 3, it being borne in mind that this diagram has been constructed for 1.0 *M* concentrations in all reactants and that the true diagram for another given set of conditions will be somewhat different.

DEF can exist in the two conformations shown in Scheme II and it seems probable that the most stable is DEF-**1** in which the carbonyl and olefinic double bonds are in the more stable trans orientation. If the difference in stability between DEF-**1** and DEF-**2** is reflected in the rates for formation of **I-1** and **I-2**, then $k_1 > k_1'$ and point 1 in Figure 3 will be lower than point 1′. Similarly, it can be argued that DEM-**1** is less stable than DEM-**2** owing to unfavorable steric repulsion between the ethoxy and carboethoxy groups in DEM-**1** and that point 2′ in Figure 3 must lie below point 2 ($k_2' > k_2$).[28] Now the observed third-order rate law for addition requires that point 1 lie below 3 and point 2′ below 3′. The observed rate constants for addition fix the position of 3 and 3′ and the fact that isomerization of and addition to DEM compete requires that either point 2 or point 1′ (or both) be at a comparable free energy to point 3′.

With these restrictions on the mechanism of Scheme II the course of the various reactions can now be understood. Reaction of DEF is seen to involve competing addition *via* the transition state at point 3 and isomerization to DEM *via* points 1′ or 2 until the steady state in DEM is reached, after which addition *via* 3 and 3′ compete, with the former being the favored path. Thus, most of the HCl adduct from DEF arises from ketonization of **I-1**. For reaction of DEM, addition occurs *via* **I-2** over the transition state at point 3′ while isomerization to DEF occurs *via* 2 or 1′. So long as the concentration of DEF does not markedly exceed that of DEM, no significant amount of addition occurs *via* **I-1** and the observed adduct from DEM derives very predominantly from ketonization of **I-2**. It is not expected that the ketonization of either **I-1** or of **I-2** should be a stereospecific process which is in accord with the fact that neither DEF nor DEM add DCl with high stereospecificity. On the other hand, **I-1** and **I-2** are reasonably expected to ketonize with somewhat different preferences for formation of EE which accounts for the fact that different amounts of EE are formed from DEM and DEF.

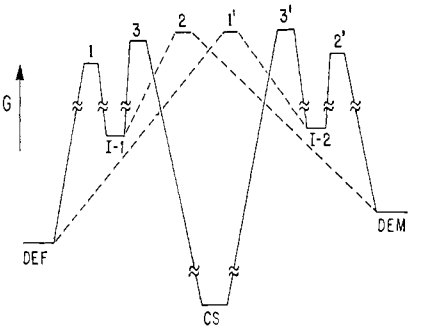


Figure 3. Free-energy diagram for the mechanism of Scheme II. See text for explanation.

The very large negative entropies of activation (~−50 eu) found for HCl addition to DEF and to DEM require that the transition states for these additions be much more highly ordered than the ground states which is in complete accord with the proposed mechanism. Moreover, conversion of DEM to a 1,4 adduct should alleviate much of the unfavorable steric interaction present in the starting *cis*-olefin and the transition state for addition should also be free from excessive steric crowding. The fact that $k_M \approx 80 \times k_F$ is in accord with this prediction and it can be noted that this difference in reactivity is reflected in the activation enthalpies for addition rather than in the activation entropies.

One feature of the results does seem somewhat puzzling. Perchloric acid is a stronger acid than HCl in acetic acid and should presumably catalyze the ketonization of the 1,4 adduct, but no pronounced catalysis by perchloric acid was observed. Even if we assume

(28) It should be emphasized that the specific assignment of **I-1** and **I-2** is based on indirect arguments and that the results themselves provide no direct information as to which isomer is preferentially formed from DEM.

that perchloric acid has a negative "salt" effect upon the rate equal to that of lithium perchlorate, the data of Table II require that perchloric acid be less than half as effective as HCl in the ketonization of the 1,4 adduct. The only plausible explanation we can give for this observation is that ketonization by HCl is in some fashion assisted by the chloride ion derived from HCl but not by the perchlorate ion derived from $HClO_4$. Hydrogen chloride is largely un-ionized in acetic acid which implies that chloride ion is more basic than acetic acid in the latter as solvent.[21] Perchloric acid, however, is largely ionized in acetic acid which shows that the perchlorate ion is an effectively weaker base than acetic acid. If the chloride ion associated with the proton assists proton removal from the hydroxyl group then HCl could reasonably be more effective than $HClO_4$ in catalyzing the ketonization process. Moreover, to the extent that chloride ion binds to the proton of the hydroxyl group, charge separation in the transition state for addition will be reduced. The transition state could then logically be no more polar than the ground state explaining why salts and nonpolar diluents have little effect upon the reaction rate.

Although a detailed understanding of isotope effects in HCl–HOAc solutions is lacking, the observed absence of a deuterium isotope effect upon k_F appears consistent with the mechanism of Scheme II. We pointed out above that the formation of the 1,4 adducts **1-1** and **1-2** is subject to an inverse isotope effect. The ketonization rate of **1-1** and **1-2** should be subject to a primary isotope effect. These two opposing effects might reasonably be expected to cancel each other resulting in no observed isotope effect on the rate of addition. Only a small primary isotope effect ($k_H/k_D \cong 1.3$) was observed for rate-limiting proton transfer to olefins in our earlier studies[3,4] and a value of this magnitude is too small to produce the required cancellation. However, the present case is not analogous in that the proton transfer reaction involved in ketonization is much faster than the reactions studied previously.[29] Moreover, if OH bond breaking is involved in the rate-limiting ketonization step (as argued above) then a larger primary isotope effect ($k_H/k_D \sim 2$) is reasonable for this step.

The foregoing results and conclusions provide substantial support for the view that hydrogen halide addition to α,β-unsaturated carbonyl compounds occurs *via* a 1,4-addition mechanism. It is, in fact, difficult to envision a reasonable alternative to the mechanism of Scheme II which would be consistent with the observed results.

A significant feature of the present results is that while the reactions of DEM and DEF are found to involve stereoselective anti addition they are not completely stereospecific processes. A recent study of the HCl-catalyzed addition of Cl_2 to *trans*-cinnamaldehyde in acetic acid has shown that this reaction involves attack by Cl_2 at the α-carbon of a reversibly formed 1,4 adduct in a fashion analogous to that proposed here for HCl addition.[32] The reaction yielded 18% of the syn adduct and 82% of the anti adduct which further demonstrates that electrophilic attack on the 1,4 adduct is a stereoselective but not necessarily stereospecific process. The exact reasons why stereoselective ketonization favoring formation of the anti adduct occurs in the additions to acyclic α,β-unsaturated carbonyl compounds are not clear, but a combination of conformational and steric factors is probably involved. Reasonable arguments for stereoselective ketonization resulting in anti addition to cyclohexene-1-carboxylic acid and related compounds have been presented by Vaughan and Caple.[10]

There is one significant difference between the mechanism proposed in this paper and that given by Vaughan and Caple[10] for HBr addition to cyclohexene-1-carboxylic acid. In the present work, ketonization is postulated as the slow step while in the earlier study formation of the 1,4 adduct is proposed to be rate determining based on limited kinetic studies. It is, of course, possible that the slow step changes with a change in the olefin structure, the hydrogen halide, or the reaction conditions, but the available kinetic data do not justify serious consideration of this question at the present time.

Given that addition to α,β-unsaturated carbonyl compounds *via* an intermediate 1,4 adduct is a favorable process for nonenzymatic reactions, it might be tempting to speculate that the enzyme-catalyzed reactions follow a similar course. However, recent results of secondary kinetic isotope effect studies[33] and isotopic exchange experiments[34] on the fumarase-catalyzed interconversion of L-malate and fumarate appear incompatible with this type of mechanism. These and other results have been interpreted[33,34] in terms of reaction *via* an intermediate resembling a carbonium ion. Since the formation of a carbonium ion adjacent to a carbonyl group is an energetically unfavorable process, it is quite unexpected that a carbonium ion mechanism should be involved in the enzyme-catalyzed addition.

Experimental Section

An Aerograph Model 200 gas chromatograph equipped with thermal conductivity detectors was used for analytical and small scale preparative separations and an Aerograph Autoprep Model 700 instrument employed for large scale preparative glpc. An 8 ft × 1/4 in. column packed with 20% DEGS on Chromosorb P (regular) was employed for all separations. Nmr spectra were measured on a Varian HR-60 spectrometer equipped with a Nuclear Magnetic Resonance Specialties Model SD-60 heteronuclear spin decoupler, and were calibrated by the side-band technique.

Materials. Diethyl fumarate was obtained from J. T. Baker (99.9% by glpc) on Aldrich (99.5% by glpc). Diethyl maleate was obtained from J. T. Baker and purified by preparative glpc (99.8% pure). Ethyl crotonate, acetic anhydride, pentane, chromatoquality cyclohexane, formic acid, spectroquality dimethylformamide, tetramethylammonium chloride (dried prior to use) were all obtained from Matheson Coleman and Bell. Other sources were: acetyl chloride and lithium chloride (Baker, Analyzed Reagent); perchloric acid, analytical reagent (Mallinckrodt); lithium perchlorate (G. Fredrick Smith Chemical Co.); a deuterium oxide, 99.8% (Diaprep, Inc.).

Addition of HCl to Diethyl Fumarate (DEF) and Diethyl Maleate (DEM). Stock solutions of HCl in HOAc were prepared as de-

(29) In this regard, it is worth noting that the isotope effect for the hydration of isobutylene, ($k_{H_3O^+}/k_{D_3O^+} = 1.45$),[30] is significantly smaller than that ($k_{H_3O^+}/k_{D_3O^+} = 3.0$) for the protonation of the more reactive cyanoketene dimethylacetal[31] in aqueous solution.

(30) V. Gold and M. A. Kessick, *J. Chem. Soc.*, 6718 (1965).

(31) V. Gold and D. C. A. Waterman, *Chem. Commun.*, 40 (1967).

(32) M. C. Cabaleiro, C. J. Cooksey, M. D. Johnson, B. E. Swedlund, and J. G. Williams, *J. Chem. Soc. B*, 1026 (1968).

(33) D. E. Schmidt, Jr., W. G. Nigh, C. Tanzer, and J. H. Richards, *J. Amer. Chem. Soc.*, 91, 5849 (1969).

(34) J. N. Hansen, E. L. Dinovo, and P. D. Boyer, *J. Biol. Chem.*, 244, 6270 (1969).

scribed previously.[3] Stock solutions of $HClO_4$ in HOAc were prepared by mixing 60% $HClO_4$, HOAc, and acetic anhydride in the required ratio; the resulting solutions were standardized by potentiometric titration *vs.* lithium acetate in acetic acid. Solutions of DCl in DOAc were prepared by reaction of the necessary amounts of acetyl chloride, acetic anhydride, and deuterium oxide yielding solutions of $\geq 99.5\%$ isotopic purity (by nmr) and containing $<0.5\%$ acetic anhydride (by glpc). The water content (<0.02 *M*) of all solutions was checked by Karl–Fischer titration.

Reaction solutions were prepared by adding the required amounts of stock solution, DEF or DEM, and other reagents in a volumetric flask and diluting to the mark with acetic acid. After rapid mixing, the solutions were placed in a constant temperature bath (25° runs) or sealed in ampoules and then placed in a constant temperature bath (runs at >25°). Samples from 0.5 to 3 ml were taken at intervals and worked up. A typical procedure involved addition of a 3-ml sample to 5 ml of 10% sodium chloride and 1 ml of pentane in a separatory funnel and shaking. The organic layer was separated, washed with 5 ml of saturated sodium bicarbonate, and dried over anhydrous sodium sulfate. The pentane solution was analyzed by glpc on column A (180°, 50 ml of He/min) Retention times (minutes) were: DEF, 6.2; DEM, 8.8; CS, 11.1. Mole ratios were taken equal to peak area ratios; the work-up and glpc procedures were independently checked with standard samples and found to reproduce known values to ±2%.

Initial rates were calculated from the fraction of CS formed at less than 10% DEM conversion for addition to DEM and at less than 10% HCl conversion for addition to DEF. In some runs, the DEF used contained 0.5% of an unidentified impurity with retention time identical with CS and, in these cases, the results were corrected by subtracting this amount from the observed CS percentage. In most runs with DEF, DEM was not measured, but for three runs the ratio of DEM to DEF was determined in order to evaluate k_1. In the presence of 1.0 *M* water, a peak with retention time identical with ethyl acetate was observed and fumaric acid precipitated from the reaction mixture.

Isomerization of Diethyl Maleate (DEM). Attempts were made to simultaneously study the isomerization of and addition to DEM using the procedure and glpc techniques described above but control experiments established that DEM partially isomerized to DEF under the conditions of the work-up procedure. This procedure was used, however, in the potassium thiocyanate catalyzed isomerization since the purpose of this experiment was to establish the equilibrium ratio for isomerization. The rate of isomerization was followed by integration of the olefinic proton nmr signals of DEF and DEM. Reaction solutions were prepared in 1- or 5-ml volumetric flasks and a sample placed in an nmr tube immersed in a constant temperature bath. The sample tube was removed periodically (5–90% conversion) and the spectrum of the olefinic region integrated (average deviation ±1%).

Stereochemistry. The addition of DCl to DEM and DEF was carried out essentially as described above for the kinetic studies. In a preparative run with DEM, DEM, DEF, and CS were recovered from the product by preparative glpc. The nmr spectra of these samples showed 1.00 ± 0.05 equiv of deuterium at C-3 in CS and <2% deuterium incorporation in recovered DEM and DEF. In a similar run with DEF, recovered CS contained 1.00 ± 0.05 equiv of deuterium and DEF contained <2% deuterium. Purified samples of the DCl adducts (100 mg) were vigorously shaken with 0.6 ml at 2.3 *M* DCl in D_2O (prepared from benzoyl chloride and D_2O) for 5 days after which time the solutions were homogeneous. The solutions were then titrated to pH 7.5 with 2.7 *M* NaOD in D_2O. The resulting solutions of the dianion of 2-chloro-3-deuteriosuccinic acid were analyzed directly by nmr.

In quantitative runs, smaller samples were taken and worked up with benzene in place of pentane. The benzene solutions were concentrated to ~1 ml after drying and then analyzed by nmr with deuterium decoupling.

Addition of HCl to Ethyl Crotonate (EC). In a preparative run, 3 ml of EC and 25 ml of 1.24 *M* HCl in HOAc were sealed in an ampoule and the ampoule placed in a 50° bath for 5 days. The reaction mixture was worked up in the usual fashion and the organic fraction distilled. A fraction (bp 167–169°) was collected and found by glpc to contain 97% β-chlorobutyric acid (CB) and 3% EC. The nmr spectrum of this sample was consistent with the assigned structure. Kinetic studies were carried out in a fashion identical with that for addition to DEM and DEF. For glpc analysis (180°, 50 ml of He/min) retention times (minutes) were: EC, 3.9; CB, 9.0. The glpc procedure was calibrated with standard samples.

Acknowledgments. We are grateful to the National Science Foundation (Grant No. GP-8308) and the Public Health Service (Grant No. GM-16796) for support of this research. A grant (GP-2137) from the National Science Foundation assisted the purchase of the nmr equipment used in these studies. We thank Professor Charles L. Perrin for helpful comments.