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Carbon and Chlorine Kinetic Isotope Effects and Solvent Effects on the Hydrolysis of Chloroformates

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Carbon and chlorine kinetic isotope effects and pseudo-first order rate constants were measured for the hydrolysis of ethyl, benzyl, and isopropyl chloroformate in various mixtures of the binary solvent water-1,4-dioxane. Rate constants decreased as the percentage of 1,4-dioxane increased for all three chloroformates. Carbon-13 kinetic isotope effects (k^{12}/k^{13}) for hydrolysis of these compounds were 1.039–1.042 for ethyl chloroformate (0–75% 1,4-dioxane), 1.034–1.039 for benzyl chloroformate (15–75% 1,4-dioxane), and 1.025–1.037 for isopropyl chloroformate (25–75% 1,4-dioxane). Chlorine-37 kinetic isotope effects (k^{35}/k^{37}) were measured for benzyl and isopropyl chloroformates in 25% 1,4-dioxane (1.0088, benzyl; 1.0080 isopropyl) and 75% 1,4-dioxane (1.0090, benzyl; 1.0102 isopropyl). These data are consistent with an associative mechanism for benzyl and ethyl chloroformates, but hydrolysis of isopropyl chloroformate appears to be dissociative in polar solvents.

Key words: kinetic isotope effect, reaction mechanism, chloroformates

Acyl transfer reactions are often described by three limiting mechanisms: a dissociative mechanism involving an acyl cation intermediate, a concerted mechanism involving a tetrahedral transition state, and an associative mechanism involving a tetrahedral intermediate. The concerted and associative mechanisms are difficult to distinguish, [1] and in few cases is this distinction clear.

The solvolysis of acyl halides covers the entire range of reaction mechanisms [2]. Solvolysis of benzoyl chloride [3] and benzoyl fluoride [4] occurs by a dissociative mechanism in more polar solvent mixtures and an associative (or perhaps concerted) mechanism in less polar solvent mixtures.

Chloroformates are acid chlorides of alkyl carbonic acids. Their hydrolysis results in the formation of a monoalkyl carbonate, which rapidly decomposes to form an alcohol, carbon dioxide, and hydrochloric acid (Eq. 1). Chloroformates solvolyze at rates much slower than other acid chlorides but faster than the analogous alkyl chlorides.

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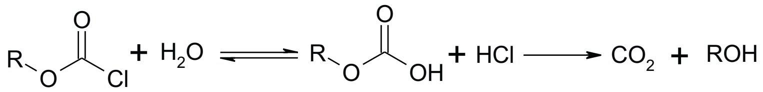
The reduced rates of solvolysis relative to other acid chlorides are due to stabilization of the ground state by π-electron resonance [2a] (Eq. 2).



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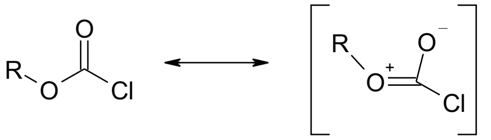
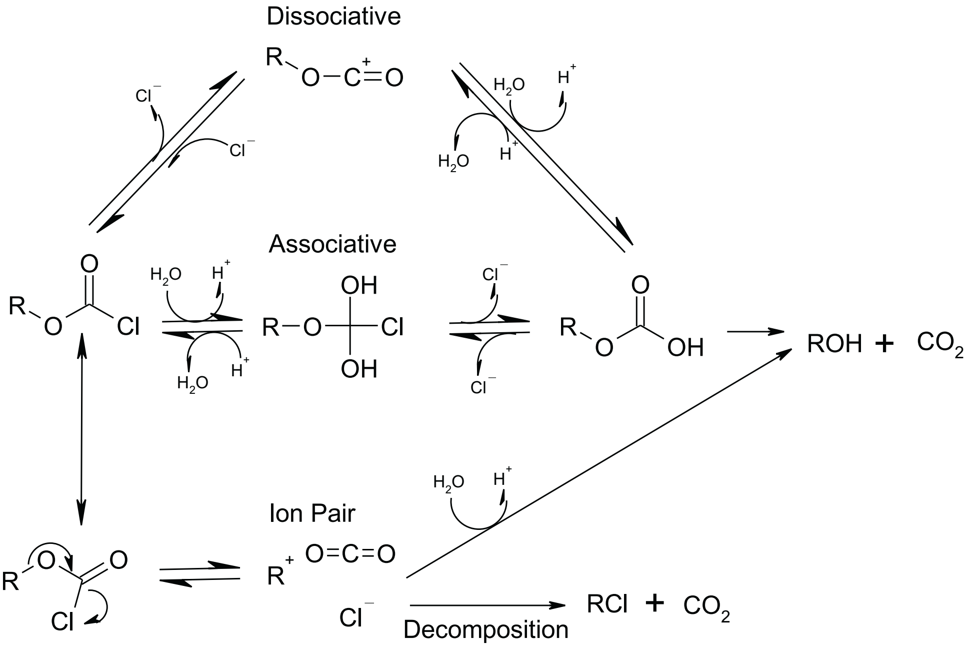


(2)

The hydrolysis of chloroformates is thought to proceed *via* an associative mechanism in many solvent systems [5] (Scheme 1, middle pathway) although hydrolysis of ethyl chloroformate in 96% aqueous formic acid is thought to proceed by a dissociative mechanism [6] (Scheme 1, upper pathway). Recently, solvolyses of several chloroformates have been analyzed using the Grunwald-Winstein equation [7]. These studies show that phenyl and ethyl chloroformates generally react through an associative mechanism. Solvolysis of ethyl chloroformate in highly ionizing, weakly nucleophilic solvents occurs by a dissociative mechanism. Again, these studies fail to distinguish between a true associative mechanism with a kinetically-significant intermediate and a concerted mechanism with no intermediate.

Scheme 1



Kinetic isotope effects (KIEs) are potentially of value in studying the hydrolysis of chloroformates. The rates of hydrolysis of chloroformates are easily measurable and in a convenient range. The hydrolysis is a simple first-order process when water is the solvent or cosolvent. The carbon dioxide ultimately formed in the reaction contains the carbonyl carbon atom of the substrate and thus provides convenient access to measurement of this isotope effect. The chloride ion produced is easily amenable to isotopic study. The purposes of this study were twofold: 1) to determine isotope effects for the carbonyl carbon and the leaving chloride ion in the hydrolysis of chloroformates; 2) to determine if the reaction mechanism changes when hydrolysis is performed in mixed solvents that are less polar than pure water.

We report here the first heavy atom KIEs for the hydrolysis of chloroformates. Our data show that changes in solvent polarity alter transition state structure for ethyl and benzyl chloroformate but not reaction mechanism. Isopropyl chloroformate appears to change reaction mechanisms as solvent polarity changes.

EXPERIMENTAL

Materials. Anhydrous 1,4-dioxane packaged under nitrogen in sealed bottles was obtained from Aldrich Chemicals. Water was doubly distilled in glass before use. Benzyl chloroformate and isopropyl chloroformate (1.0 M solution in toluene) were purchased from Aldrich. Ethyl chloroformate was purchased from Eastman. All other chemicals were reagent grade or better. All experiments were performed at 30°C.

Kinetic measurements by direct titration. Rates of hydrolysis of chloroformates were measured by titration of the protons released during the reaction using a Radiometer ETS822 titration system with a 2.5 mL burette. Titration data (elapsed time, total volume of titrant added, and pH) were collected and recorded by a personal computer interfaced with the titrator. The titrant (75 mM NaOH) was standardized against potassium hydrogen phthalate primary standard. The pH electrode was calibrated by a two point calibration (pH 4.00 and pH 7.00) using commercially available pH standard buffers. For mixed solvent titrations, the pH standard buffers were diluted with 1,4-dioxane to the same percentage as the reaction solvent. While the interpretation of a pH meter reading in a mixed solvent is problematical, this method was at least self-consistent. This method is unsuitable for reactions that contain greater than 50% 1,4-dioxane (v/v) because the 1,4-dioxane decreases the sensitivity of the pH electrode so that the reaction is severely overtitrated. Kinetic measurements in 75% 1,4-dioxane were performed using the quench titration method (see below).

For each reaction, 25 mL of solvent was placed in a titration beaker equipped with a water jacket connected to a circulating water bath. The titrator was used in pH stat mode, which maintains the solution at a constant pH. The solvent pH was adjusted to 7.00 before adding chloroformate and maintained at pH 7.00 throughout the reaction by addition of titrant. The reaction was initiated by addition of 10 μmol of chloroformate in a small volume of 1,4-dioxane (0.4 mM final concentration of chloroformate). A typical reaction consumed less than 250 μL of titrant over the entire time course of the reaction. Reactions were allowed to proceed for at least 10 half lives. Apparent first order rate constants were determined graphically by plotting ln (vol. $\text{titrant}_{\text{final}}$ - vol. $\text{titrant}_{\text{time=t}}$) *versus* time.

Kinetic measurements by quench titration. The quench titration method is adapted from Kivinen [5b]. Aliquots of the reaction were withdrawn and quenched with morpholine at various times. The quenching agent of choice is a secondary amine because chloroformates react rapidly and stoichiometrically with amines.

Solvent (148 mL) was added to a 250 mL round bottom flask that contained a magnetic stirbar. The reaction was started by addition of 300 μmol of neat chloroformate diluted to 2 mL total volume in

1,4-dioxane to the reaction flask (2 mM final concentration of chloroformate). Immediately after the chloroformate was added, a 2 mL aliquot was withdrawn and added to 10 mL of 12 mM aqueous morpholine solution (a threefold excess of morpholine over chloroformate) in a 25 mL Erlenmeyer flask. The flask was stoppered and shaken. This initial time point served as the time zero reference point. At appropriate times additional aliquots were removed from the reaction and quenched as described above. A final time point was taken after more than ten half-lives of the reaction. The amount of unprotonated morpholine remaining in each quench solution was determined by titrating 3 mL aliquots of the quench solutions with a standard HCl solution. The amount of chloroformate remaining at a given time point was determined by using the following equation:

$$\frac{[\mathrm{VolumeHCl}_{\mathrm{time}=\infty} - \mathrm{VolumeHCl}_{\mathrm{time}=0}]}{[\mathrm{VolumeHCl}_{\mathrm{time}=\infty} - \mathrm{VolumeHCl}_{\mathrm{time}=t}]} = \frac{[\mathrm{chloroformate}]_{\mathrm{time}=0}}{[\mathrm{chloroformate}]_{\mathrm{time}=t}} \qquad (3)$$

This equation takes into account that unreacted chloroformate consumes two equivalents of morpholine and hydrolyzed chloroformate consumes only one equivalent of morpholine.

Kinetic Isotope Effect Measurements. Isotope effects were determined by the competitive method using materials of natural isotopic abundance. Since the reaction product, either CO_2 or chloride ion, was analyzed for isotopic changes, samples were taken at low conversion (10%) and complete conversion of the reactant to product [16].

Determination of KIEs on the Carbonyl Carbon of Chloroformates. All water used in isotope effect procedures was purged of CO_2 by sparging with CO_2-free N_2 for at least 1 hour. All 1,4-dioxane used in these procedures was directly delivered from the sealed bottle to the sealed CO_2-free reaction flasks via syringe or transferred using positive pressure of CO_2-free N_2 from sealed graduated cylinders via double tip needles. Control experiments showed that the 1,4-dioxane-water mixtures contained no measurable CO_2 in the absence of chloroformate. All samples were acidified and the CO_2 was purified by vacuum cryodistillation before measuring carbon isotope ratios on a Finnigan Delta S isotope ratio mass spectrometer.

Complete conversion samples contained 20 mL of solvent. The reaction was initiated by addition of 50 µmol chloroformate in a small volume of 1,4-dioxane. The complete conversion samples were allowed to react for more than ten half lives. The low conversion (10%) samples contained 200 mL of solvent. The reaction was initiated by the addition of 500 µmol chloroformate in a small volume of 1,4-dioxane. The reaction was quenched at the appropriate time by addition of 150 µL of neat morpholine. Isotope effects were calculated as previously described [17]. Because the solubility of benzyl and isopropyl chloroformates is limited in pure water, the KIEs for the high polarity solvents were performed in 15% 1,4-dioxane and 25% 1,4-dioxane respectively.

Determination of KIEs on the Chlorine of Chloroformates. Chloride ion released from the hydrolysis reactions was isolated from all reactions as silver chloride. For reactions in 75% 1,4-dioxane, 300 mL of solvent was used and chloroformate was added to give 1 mmole of chloride ion. For reactions in 25% 1,4-dioxane, 225 µmoles of isopropyl chloroformate was used for both 10% and complete reactions due to the limited solubility of this compound. For the benzyl chloroformate reactions in this solvent mixture, 1.75 mmoles of benzyl chloroformate was added. The reactions were stopped by extracting the reaction mixture with 600 mL cold (0°C or –20°C) toluene to remove the 1,4-dioxane and unreacted chloroformate. The aqueous layer was recovered and extracted again with 200 mL cold toluene. The aqueous layer was retained and adjusted to 0.4 M KNO_3 by addition of solid KNO_3. The chloride ion was precipitated as AgCl by addition of excess $AgNO_3$. The precipitates were collected by vacuum filtration into a 30 mL Gooch crucible (fine porosity) that had previously been dried to constant mass in a 110°C oven. Silver chloride was recovered from the crucibles and analyzed for isotopic ratios.

The isotope ratios of the chloride ions from the silver chloride were measured using a hybrid FAB (Fast Atom Bombardment) isotope ratio mass spectrometer, MI 1201E (PO Electron, Ukraine) [18]. The FAB ion source, which was equipped with a special focusing unit, ensures high intensity of ions and stability of ion current for 0.5–1 hr in the negative ion mode. Samples of silver chloride were placed on a silver tip of the direct insertion probe by heating the tip and melting the samples onto it. Xenon atoms of 6 keV were used for ionization by impacting the probe at an incidence angle of 45°. Negative ions formed in this way were accelerated to a potential of 5 kV and detected in a Faraday cup collector system. The mean values of I(37)/I(35) isotopic ratios were obtained from up to 50 separate determinations, each being an average of 10 measurements.

RESULTS AND DISCUSSION

Rate constants were measured for the hydrolysis of ethyl, benzyl, and isopropyl chloroformates in various mixtures of 1,4-dioxane and water. Five to twelve replications of each experimental condition were performed to ensure reproducibility. The first order rate constants decreased as the fraction of 1,4-dioxane in the solvent mixture increased (Table 1). This trend is expected because the transition state is more polar than the ground state [8]. The amount of the decrease in rate constant varies with the substituent on the chloroformate: 24 fold for ethyl, 30 fold for benzyl and 222 fold for isopropyl chloroformate. Our rate constants for the hydrolysis of ethyl chloroformate in pure water at 30°C are in good agreement with previous values [2a,5a,5c] (measured at 25°C or 30°C).

Table 1. Apparent first order rate constants of hydrolysis of chloroformates in various mixtures of water and 1,4-dioxane at 30°C.

Solvent	Ethyl Chloroformate			Benzyl Chloroformate			Isopropyl Chloroformate		
% 1,4-dioxane	k[a]	SD	n	k[a]	SD	n	k[a]	SD	n
0%	70.54	1.36	6	159.0	11.7	7	425.4	19.2	11
25%	56.54	2.30	6	105.4	5.8	6	221.8	25.2	12
50%	20.36	3.98	6	47.26	3.00	5	63.54	14.02	11
75%	2.90	0.40	6	5.35	0.86	5	1.92	0.21	6

[a] Rate constants are expressed in units of sec^{-1} x 10^5.

KIEs on the carbonyl carbon were measured for all of the chloroformates in the same solvent mixtures (Table 2). Four to eight isotope effect determinations were made for each condition to maintain high precision. The KIEs for ethyl and benzyl chloroformates increase slightly as the solvent polarity is decreased. The KIEs for isopropyl chloroformate are more affected by solvent polarity, showing a 1.1% increase as the solvent polarity is decreased.

Table 2. KIEs on the carbonyl carbon of chloroformates on hydrolysis of chloroformates in various mixtures of water and 1,4-dioxane at 30°C.

Solvent	Ethyl Chloroformate			Benzyl Chloroformate			Isopropyl Chloroformate		
% 1,4-dioxane	$^{12}k/^{13}k$	SD	n	$^{12}k/^{13}k$	SD	n	$^{12}k/^{13}k$	SD	n
0%	1.0389	0.0007	7	nd			nd		
15%	nd			1.0338	0.0009	8	nd		
25%	nd			nd			1.0251	0.0014	8
50%	1.0412	0.0011	7	1.0350	0.0015	8	1.0266	0.0014	8
75%	1.0420	0.0005	4	1.0389	0.0005	7	1.0369	0.0008	8

KIEs on the leaving chlorine atom were measured for benzyl and isopropyl chloroformate in 25% and 75% 1,4-dioxane (Table 3). Good precision was achieved by measuring samples from three to four reactions for each condition. In both cosolvent systems the chlorine isotope effects on hydrolysis of benzyl chloroformate were the same within experimental error. The chlorine KIE for isopropyl chloroformate increases by 0.22% as the solvent polarity is decreased.

Table 3. KIEs on the chlorine of chloroformates on hydrolysis of chloroformates in various mixtures of water and 1,4-dioxane at 30°C.

Solvent	Benzyl Chloroformate			Isopropyl Chloroformate		
% 1,4-dioxane	$^{35}k/^{37}k$	SD	n	$^{35}k/^{37}k$	SD	n
25%	1.0088	0.0003	3	1.0080	0.0004	3
75%	1.0090	0.0008	3	1.0102	0.0008	4

A large body of kinetic evidence suggests that hydrolysis of most chloroformates in aqueous solvents proceeds through an associative or concerted mechanism [2a,9]. Comparison of relative rates of hydrolysis of chloroformates in aqueous acetone [6] (methyl > ethyl) or water [5c] (phenyl>methyl>propyl~ethyl) give rate orders that are consistent with an associative mechanism. Hydrolysis of ethyl chloroformate is catalyzed by hydroxide ion, and rates of nucleophilic substitution of ethyl chloroformate increase when the reactant is a better nucleophile [10]. Hydrolysis of ethyl or phenyl chloroformate in a series of solvent mixtures of decreasing polarity resulted in a small depression of apparent rate constants [5b,6,11]. Entropies of activation for solvolysis of phenyl, methyl, ethyl, and propyl chloroformates in pure water were found to be between –20 and –17 cal mol^{-1} K^{-1}, consistent with an associative mechanism [5c]. Solvent isotope effects for phenyl, methyl, and ethyl chloroformate hydrolysis range from ^{H_2O}k / $^{D_2O}k = 1.78$ to 1.96. These effects are consistent with substantial solvent reorganization in the transition state. Application of the extended Grunwald-Winstein equation to the solvolyses of phenyl and ethyl chloroformates show that both chloroformates react by associative mechanisms under most conditions [2c,7a].

Effect of Solvent on Rate and Mechanism of Chloroformate Hydrolysis. Decreasing the water content of the solvent decreases the rates of hydrolysis for all of the chloroformates (Table 1). The trends are similar for ethyl, benzyl, and phenyl chloroformates (Figure 1). This evidence suggests that, like phenyl chloroformate, ethyl and benzyl chloroformates react through an associative mechanism.

In contrast, kinetic data suggest that isopropyl chloroformate reacts through a dissociative mechanism. Rates of solvolysis of isopropyl chloroformate are essentially the same in 65% aqueous acetone (v/v) and in formic acid containing 1% water, suggesting there is little effect of solvent nucleophilicity on the reaction [6]. In comparison, the rates of ethyl and methyl chloroformates are reduced in formic acid with 1% water by 14 and 2300 fold, respectively.

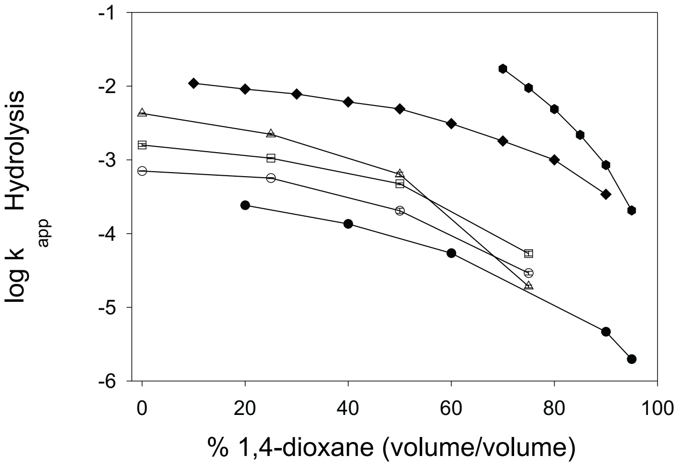


Figure 1. Effects of water concentration on the rate constants of hydrolysis of various chloroformates. Symbols for the chloroformates: benzyl chloroformate (squares); ethyl chloroformate (circles); isopropyl chloroformate (triangles); phenyl chloroformate (diamonds) and adamantyl chloroformate (hexagons). Open symbols represent data measured by us at 30°C. Closed symbols represent data measured by others. The data for the rates of hydrolysis of phenyl chloroformate at 25°C was taken from Butler *et al.* [11]. The data for hydrolysis of ethyl chloroformate in higher concentrations of 1,4-dioxane at 25°C was taken from Kevill and D'Souza [2c]. The data for the hydrolysis of adamantyl chloroformate at 25°C was taken from Kevill, Kyong, and Weitl [15].

Solvents with high concentrations of formic acid are believed to suppress associative reaction mechanisms because of reduced solvent nucleophilicity. These rate changes are consistent with a change from an associative to a dissociative mechanism for ethyl and methyl chloroformates. The lack of change of rate in these solvents for isopropyl chloroformate suggests that its hydrolysis mechanism is dissociative. The solvent isotope effect for the hydrolysis of isopropyl chloroformate is smaller than other chloroformates (see above), ${}^{H_2O}k / {}^{D_2O}k = 1.25$, consistent with less solvent reorganization in the transition state, which is characteristic of a dissociative mechanism. Our data show a larger decrease in rate constant of hydrolysis of isopropyl chloroformate with decreasing water content of the solvent than the other chloroformates measured (222 fold). This result may be suggestive of either a shift to an earlier transition state caused by increased solvent polarity or a mechanistic change in the reaction. The entropy of activation for the solvolysis of isopropyl chloroformate in pure water is +10 cal mol^{-1} K^{-1}, which is consistent with a dissociative mechanism [5c].

Carbon Isotope Effects. Kinetic isotope effects reflect the transition state structure and/or the relative rates of the rate determining steps in a multistep reaction. Increasing bonding to carbon in the transition state is expected to result in a decrease in KIE on carbon. Carbonyl carbon isotope effects on the solvolysis of esters and alkyl halides vary widely ($^{12}k/^{13}k = 0.9991–1.0891$; see Table 16 in Shiner & Wilgis [12], [$^{12}k/^{14}k$ converted to $^{12}k/^{13}k$]). Typically, values for KIEs of carbonyl carbons are small for dissociative reactions, $^{12}k/^{13}k = 1.00–1.03$, and larger for associative and concerted type reactions, $^{12}k/^{13}k = 1.03–1.08$. Large changes in KIEs may indicate a change in mechanism of reaction or a change in rate determining steps for a multistep reaction.

The carbon KIE on the carbonyl carbon of ethyl chloroformate for hydrolysis in 75% 1,4-dioxane is 1.0420, consistent with a symmetrical transition state with large changes in bonding to the carbon atom. The carbon KIE on the carbonyl carbon for the alkaline hydrolysis of methyl benzoate is similar in magnitude [13] (1.043). Ester hydrolyses have been generally characterized as reactions with associative mechanisms, and ethyl chloroformate appears to hydrolyze in 75% 1,4-dioxane by an associative mechanism.

The ethyl chloroformate KIE changes from 1.0420 to 1.0389 as solvent is changed from 75% 1,4-dioxane to 25% 1,4-dioxane. These changes likely show a transition state that becomes more reactant-like in the more polar solvent. The changes in the carbon KIE are small, and it seems likely that changing water content of the solvent causes modest variation in transition state structure without causing a change in reaction mechanism for ethyl chloroformate.

Benzyl chloroformate behaves similarly to ethyl chloroformate, but the magnitudes of the KIE changes are somewhat larger. The carbon KIE on hydrolysis of benzyl chloroformate in 25% 1,4-dioxane is 1.0338. This effect is similar in magnitude to the acyl carbon KIE for the alkaline hydrolysis of methyl formate [14] (1.034). The mechanism for benzyl chloroformate is similar to that of ethyl chloroformate but the transition states appear to be earlier than ethyl chloroformate. Earlier transition states for benzyl chloroformate are also supported by the kinetics of hydrolysis. Benzyl chloroformate reacts faster than ethyl chloroformate under the same solvent conditions. Benzyl chloroformate KIEs on the carbonyl carbon change more with water content of the solvent than do ethyl chloroformate KIEs (5.1‰ for benzyl *versus* 3.1‰ for ethyl). In non-polar solvents the mechanism of benzyl chloroformate is most likely an associative one.

Isopropyl chloroformate carbon KIEs are much more affected by solvent polarity. The KIE on the acyl carbon for the hydrolysis for isopropyl chloroformate in 75% 1,4-dioxane is similar to the other chloroformates (1.0369). The isotope effect on carbon for the hydrolysis of isopropyl chloroformate in 25% 1,4-dioxane is much smaller than ethyl or benzyl chloroformates (1.0251). This variation in KIEs (Table 2) suggests a change in reaction mechanism from a dissociative to an associative mechanism. The change in KIEs might also be accounted for by a shift to an earlier transition state with increased solvent polarity within a dissociative mechanism.

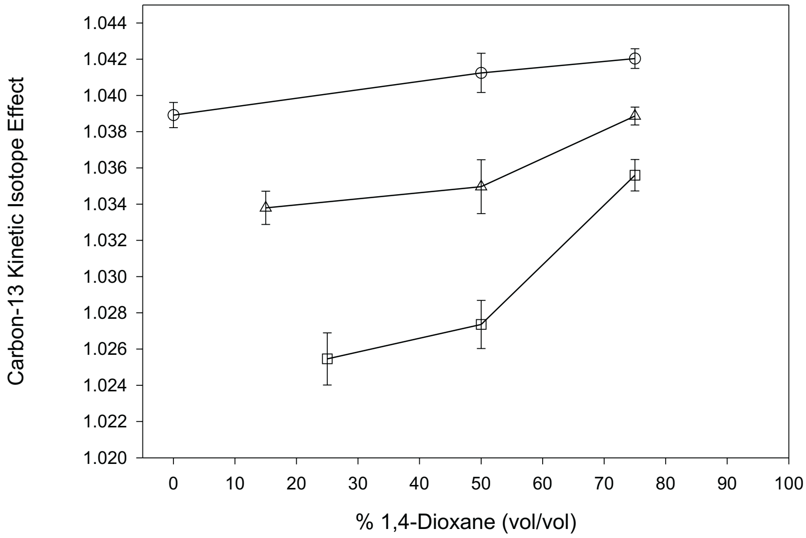


Figure 2. Effects of water content on the KIEs on hydrolysis of various chloroformates. Symbols for the chloroformates: isopropyl chloroformate (open squares); ethyl chloroformate (open circles); benzyl chloroformate (open triangles).

Chlorine KIEs. Leaving group chlorine KIEs would seem ideal for determining reaction mechanisms. In theory, the leaving chlorine isotope effect should be proportional to the amount of bond breaking in the transition state, with larger effects indicating later transition states. In practice, leaving group chlorine KIEs do not always present a clear picture of the transition state structure due to effects of solvation.

The chlorine KIE on the hydrolysis of benzyl chloroformate in 75% 1,4-dioxane is large (1.0090). This suggests a transition state with the chlorine–carbon bond mostly broken, *i.e.* a more product-like transition state. The chlorine isotope effect for benzyl chloroformate does not change when the water content of the solvent is increased. This suggests a constant mechanism of hydrolysis for benzyl chloroformate in the various solvent systems.

For the hydrolysis of isopropyl chloroformate in 75% 1,4-dioxane, the chlorine isotope effect was very large (1.0102). This does not support an associative mechanism. In 25% 1,4-dioxane, however, the chlorine isotope effect decreases to a value smaller than seen for benzyl chloroformate in the same solvent. It would be expected that a dissociative mechanism would have a larger chloride KIE than an associative mechanism.

Mechanism. In order to make sense of these data we consider three reaction mechanisms as shown in Scheme 1. The dissociative pathway generates a carboxylium ion, which reacts with water to generate a monoalkyl carbonate. The associative pathway has a tetrahedral intermediate (or transition state) that breaks down to form the monoalkyl carbonate. The decomposition pathway does not generate a monoalkyl carbonate. Rather, the chloroformate breaks down into the alkyl cation, carbon dioxide, and chloride ion in a concerted step. The alkyl cation may then either recombine to form an alkyl chloride or react with substrate to form the hydrolysis products.

Both the KIEs and the kinetic results suggest that ethyl and benzyl chloroformate use the associative (or concerted) mechanism for hydrolysis. The chlorine isotope effects for benzyl chloroformate support a transition state with a carbon chlorine bond that is mostly broken in all solvent conditions. The carbon isotope effects for both ethyl and benzyl chloroformates together with the data from the chlorine isotope effects from benzyl chloroformate suggest that the transition state is more reactant-like in general. When the solvent is made less nucleophilic the transition state becomes more symmetrical.

The data above support a dissociative mechanism for the hydrolysis of isopropyl chloroformate in pure water. Decreasing solvent polarity would be expected to have a greater effect on reaction rate for a dissociative mechanism as compared to either an associative or concerted mechanism. In fact, this is exactly what we observed (Table 1). The KIEs on hydrolysis of isopropyl chloroformate also support a dissociative mechanism.

For isopropyl chloroformate, rate determinations and carbon KIEs showed large changes between reactions in 50% 1,4-dioxane and 75% 1,4-dioxane (Tables 1 and 2). Chlorine KIEs were not determined in 50% 1,4-dioxane. We expect that they would be of similar magnitude to the values in 25% 1,4-dioxane, as the KIEs on carbon and rate constants are similar between the two conditions. The increase between KIEs on chlorine in 25% 1,4-dioxane and 75% 1,4-dioxane is also large (Table 3). These large changes in KIEs and rates suggest a change in reaction mechanism. It appears unlikely that solvation or internal return can be used to explain the changes in the observed chloride KIE for isopropyl chloroformate. Instead, the mechanism appears to change from dissociative to associative.

It has been postulated that the entropy of activation may be evidence for decomposition as part of the reaction mechanism [5c]. Decomposition has been observed during the solvolysis of adamantyl chloroformate in various solvents and cosolvent mixtures [15]. This study observed that the percentage of the chloroformate reacting through the decomposition pathway increased as solvent ionizing power decreased.

For isopropyl chloroformate, more that one mechanism may be operational. When the solvent has a high enough water content (25% and 50% 1,4-dioxane) the mechanism is dissociative. The chlorine KIE suggests less chlorine–carbon bond breakage in the transition state than the other chloroformates. The carbon KIE under the same condition is small, consistent with a dissociative mechanism. However, the decomposition mechanism is not consistent with the experimental data, because of the stability of the alkyl chloride under the reaction conditions.

Acknowledgment

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