kinetic analysis ($K = 11 \times 10^3$ L/mol) compares favorably with the constant $K = (12 \pm 1) \times 10^3$ L/mol, which we obtained by NMR titration under the same conditions. Since acetylcholine hydrolyzes too fast at the minimum pH necessary to keep the host H in solution, we measured the product choline instead, which is justified for the reasons given above. Figure 2 shows the result of a numerical curve fit[7] yielding a K value which is lower than the previously reported[3] because of different temperature and salt concentrations.

Experimental and Computational Details

Preparation and spectroscopic properties of H have been described elsewhere;[8] all other compounds were commercially available.

^{1}H NMR shift titrations were carried out with a Bruker AM 400 system at 400 MHz and were evaluated with a numerical least-squares simulation program.[7] The complexation induced shift (CIS, corresponding to 100% complexation, in ppm) and the association constants K (L/mol) obtained from the analysis of the different choline chloride proton signals were as follows: with CH_3, CIS = 2.09, K = 12 450; with N–CH_2, CIS = 1.14, K = 13 100; with O–CH_2, CIS = 0.52, K = 10 500 (initial concentrations: choline, 2.00×10^{-4} M; H, $(0–1.33) \times 10^{-3}$ M; D_2O at 60.0 ± 1 °C).

Kinetics of choline acetate hydrolysis were followed by continuous titration of the liberated acetic acid with a Metrohm pH-stat apparatus (E 373, E412, E 300), which was connected to a microcomputer-based automatic data aquisition system.[9] At pH 10.00, 60.0 ± 0.2 °C, initial concentration of 1 at 2.00×10^{-3} M, and ionic strength of 0.10 M, the following rate constants ($k \times 10^3$, in s^{-1}) were obtained at different H concentrations (10^{-3} M): [H] = 0.00:4.1 ± 0.2; 0.50:3.2 ± 0.3; 1.00:2.4 ± 0.1; 2.00:1.2 ± 0.1; 5.00:0.6 ± 0.1; 7.00:0.5 ± 0.1.

All linearizations were based on first order and showed correlation coefficients of $r \geq 0.99$.

Hydrolysis kinetics of *p*-nitrophenyl acetate (PNPA) were followed by extinction measurements at λ = 420 nm, where interference with H absorption was small enough (H showed increasing absorption at shorter wavelengths due to oxidation products); the instrument used was a Kontron UV-spectrometer Uvikon 725. At 25 ± 0.2 °C in water/methanol/dioxane [71/24/5% (v/v)], pH 10.00, 0.1 M H_3BO_3/NaOH, and an initial PNPA concentration of 5.0×10^{-4} M, we obtained at different H (10^{-3} M) concentrations the following pseudo-first-order rate constants ($k \times 10^2$ [s^{-1}]): [H] = 0.00:0.20 ± 0.02; 4.0:1.3 ± 0.1; 6.0:1.7 ± 0.1; 8.0:2.0 ± 0.2; 10.0:2.4 ± 0.2. The k values showed a linear increase with [H]; on the basis of the corresponding correlation $k = k_{OH^-} + k_2[H]$, where k_{OH^-} is the rate constant in absence of H, a bimolecular rate constant of $k_2 = 2.2 \pm 0.1$ L/(mol s) is obtained from the slope, which is close to the corresponding reported value for the reaction with phenolate alone (k = 1.8 L/(mol s).[10]

The rate equations can be derived as follows. For S = 1, P = 2, R = H, $[S_0]$ = initial [1], and $K = K'$, we obtain with

$$[S_0] = [S] + [P] + [RS] + [RP] = [S] + [RS] + [A] \quad (1)$$

the following:

$$[RS] + [RP] = \frac{[S_0][R]K}{1 + [R]K} \quad (2)$$

$$[S] + [P] = \frac{[S_0]}{1 + [R]K} \quad (3)$$

$$[S_0] = ([S] + [P])(1 + [R]K) \quad (4)$$

With eq 4 and eq 2, we obtain:

$$K = \frac{[RS] + [RP]}{[R]([S] + [P])} \quad (5)$$

The differential equation for the formation of acetic acid,

$$dA/dt = [S]k_1 + [RS]k_2 \quad (6)$$

can be written as (by using eq 1 and 2)

$$dA/dt = \frac{k_1 + k_2K[R]}{K[R] + 1}([S_0] - [A]) \quad (7)$$

and integrated to

$$k_{exp} = \frac{[R]K}{[R]K + 1}k_2 + \frac{1}{[R]K + 1}k_1 \quad (8)$$

or (with eq 5)

$$k_{exp} = \frac{[RS] + [RP]}{[S_0]}k_2 + \frac{[S] + [P]}{[S_0]}k_1 \quad (9)$$

and

$$[RS] + [RP] = \frac{k_1 - k_{exp}}{k_1 - k_2}[S_0] \quad (10)$$

Furthermore, we can write

$$K = \frac{[RS] + [RP]}{([S_0] - [RS] - [RP])([R_0] - [RS] - [RP])} \quad (11)$$

or

$$[RS] + [RP] = \frac{[R_0] + [S_0] + K}{2} - \left[\frac{([R_0] + [S_0] + K^2}{4} - [R_0][S_0]\right]^{1/2} \quad (12)$$

With a numerical least-squares curve-fitting program based on a SIMPLEX minimization[9c] the unknowns k_2 and K were varied until a fit between the right side of eq 10 and 12 was obtained (see Figure 1).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft, Bonn, and the Fonds der Chemischen Industrie, Frankfurt, West Germany.

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Substituent Effects on the Pyrolysis of α-Chloro-*o*-xylenes

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Pyrolysis of α-chloro-*o*-xylene in the gas phase provides an excellent preparative route to benzocyclobutene[1] and has been used in several elegant syntheses.[2] It is generally believed that α-chloro-*o*-xylene undergoes intramolecular 1,4 elimination of HCl to give *o*-quinodimethane as the

(1) (a) Although the name recommended ty IUPAC is 1,2-dihydrobenzocyclobutene, we will use benzocyclobutene in the paper, in keeping with common usage. (b) Maccoll, A.; London, A. G.; Wong, S. K. *J. Am. Chem. Soc* **1969**, *91*, 7577–7580. (c) For a review article: Schiess, P.; Rutschman, S. *Chimia* **1985**, *39*, 213–224.

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Table I. Comparative Reactivities of α-Chloro-o-xylene and Substituted α-Chloro-o-xylene

pairs of compds[a]	reactn temp, °C	reactn conversn, %	product select., %	rel react.,[7] $\kappa x/\kappa H$
1	700	54	45	1.4
3		42	54	
2	700	49	56	1.2
3		43	53	
4	710	30	63	0.64
3		43	58	
4	735	42	55	0.64
3		57	50	

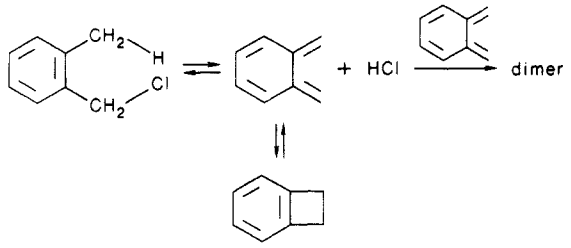
[a] All runs were duplicated. Reaction pressure was 0.1–0.5 Torr.

Table II. Reactivity of α-Chloro-o-xylenes with Substituents Para or Meta to the Chloromethylene Group

compd	reactn temp, °C	conversn, %	rel react.
2	690	69	1
5		83	1.5
4	750	58	1
6		49	0.76

[a] Reaction pressure was 1–3 Torr.

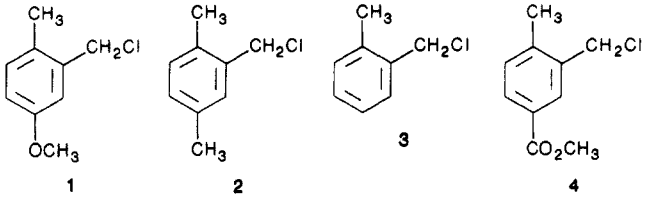
intermediate that can then cyclize to give benzocyclobutene or dimerize.[1,3]



Certain substituted benzocyclobutenes can also be prepared by pyrolyzing substituted α-chloro-o-xylenes.[2b,4] The substituent effect of the reaction, however, has never been systematically investigated.[5] This report studies the reactivity of several substituted α-chloro-o-xylenes when they are pyrolyzed under reduced pressure in a flow system.

Results and Discussion

The reactivities of 2-methyl-5-methoxybenzyl chloride (1), 2,5-dimethylbenzyl chloride (2), α-chloro-o-xylene (3), and 2-methyl-5-carbomethoxybenzyl chloride (4) were compared.

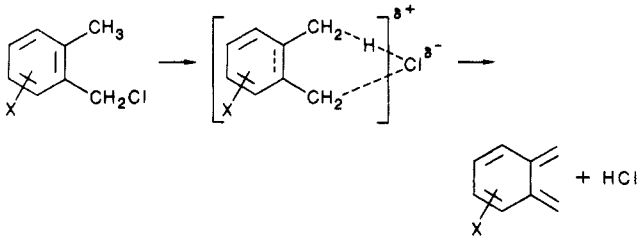


An equal molar mixture of α-chloro-o-xylene and substituted α-chloro-o-xylene was passed through the reaction zone. Unreacted starting materials were determined by GLC.[6] The reaction conversion was defined as the amount of α-chloro-o-xylene passed through the reactor minus the recovered starting material.

The relative reactivities of the substituted α-chloro-o-xylenes and α-chloro-o-xylene ($\kappa x/\kappa H$)[7] are shown in Table I. A Hammett plot of ln ($\kappa x/\kappa H$) vs. σ_p produced a ρ value of −0.46 as calculated by the least-squares method (γ 0.99). A small negative ρ value indicates that a small positive charge is involved in the transition state.

The reaction rates of 2,4-dimethylbenzyl chloride (5) and 2,5-dimethylbenzyl chloride (2) were studied by pyrolyzing a mixture of the two isomers. The results in Table II show that an electron-donating moiety para to the chloremethylene group enhances the reactivity more than its meta isomer. To react a mixture of 2-methyl-4-carbomethoxybenzyl chloride (6) and 2-methyl-5-carbomethoxybenzyl chloride (4) shows that an electron-withdrawing substituent retards the reaction more when it is para to the chloromethylene group.

The different reactivities of the isomers and the Hammett plot are consistent with the postulation that the chloride ion leaves slightly ahead of the proton in the 1,4 elimination of HCl. The small positive charge developed is stabilized by electron-donating groups. Although the formation of o-quinodimethane from the pyrolysis of α-chloro-o-xylene may not be synchronous,[8] the small ρ value indicates very little charge is developed in the transition state.



Experimental Section

Melting points are uncorrected. GLC analyses were performed on an HP5840A chromatograph equipped with a 30-m J&W fused silica capillary column. Proton NMR spectra were obtained with a Varian EM360 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard (δ 0). An HP5992 mass spectrometer equipped with a 60-m J&W fused silica capillary column was used for GC/MS. IR spectra were recorded with a Perkin-Elmer 683 spectrophotometer. Microanalyses were performed by a CHN 240B Perkin-Elmer analyzer.

Materials. α-Chloro-o-xylene, 2,5-dimethylbenzyl chloride, and 2,4-dimethylbenzyl alcohol were purchased from Aldrich Chemical Co. Reaction of 2,4-dimethylbenzyl alcohol with thionyl chloride produced 2,4-dimethylbenzyl chloride. 2-Methyl-5-carbomethoxybenzyl chloride was prepared by the chloromethylation of methyl 4-methylbenzoate according to a literature procedure.[9] 2-Bromo-4-methoxytoluene was synthesized via an

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(5) Schiess and co-workers showed methyl and methoxy groups lowered the reaction temperatures for 50% conversion of α-chloro-o-xylenes.[2b,4d]

(6) Besides unreacted starting materials and benzocyclobutenes, o-quinodimethane dimer, substituted o-quinodimethane dimer, and mixed dimers of the two were also detected by GC/MS. The material balance was 85–90%.

(7) For a first-order reaction, $\ln [1/(1 - C_A)] = \kappa_A t$, where κ_A and C_A are, respectively, the rate of reaction and conversion of reactant A. The relative reactivities of the substituted α-chloro-o-xylenes and α-chloro-o-exylene ($\kappa x/\kappa H$) were determined by $\kappa x/\kappa H = \ln [1/(1 - C_x)]/\ln [1/(1 - CH)]$, where C_x is the conversion of substituted α-chloro-o-xylene and C_H is the conversion of α-chloro-o-xylene.

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unpublished scheme.[10] Treatment of the Grignard reagent of 2-bromo-4-methoxytoluene with formaldehyde provided 2-methyl-5-methoxybenzyl alcohol which was converted to 2-methyl-5-methoxybenzyl chloride with thionyl chloride.

2-Methyl-5-methoxybenzyl chloride: IR (neat) 2720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.6–7.2 (m, 3 H), 4.52 (s, 2 H), 3.78 (s, 3 H), 2.35 (s, 3 H); MS, *m/e* 175 (M + 2, 15%), 170 (M, 49%), 135 (100%), 91 (26%). Anal. Calcd for $C_9H_{11}ClO$: C, 63.33; H, 6.45. Found: C, 63.27; H, 6.50.

Apparatus. The experimental setup was a modification of that described in the literature.[11] A 30-cm portion of a quartz tube with a 2-cm outside diameter packed with pieces of quartz chips was mounted vertically in a Hoskins FD303A electric furnace. The reaction temperature was measured by a thermocouple inside a thermowell that extended into the middle of the heated zone. A 12-cm portion above the furnace served as the preheating zone, the temperature in the middle of which was 250–300 °C. An addition funnel was attached to the upper end of the quartz tube, and the lower end was joined to two cold traps in series which in turn was connected to a vaccum pump.

General Procedures. The furnace was heated to the desired temperature, and vacuum was applied, at which time the starting materials in the addition funnel were added. The rate of addition was determined by dividing the amount of the added materials by the elapsed time and was about 0.2 g/min. Products and unreacted starting materials were collected in the cold traps. The amounts of unreacted starting materials and products were determined by GLC with internal standards. Their structures were confirmed by GC/MS.

Acknowledgment. I am indebted to Dr. Chi-I Kao and Dr. George Quarderer for helpful discussions and criticisms.

Registry No. 1, 90416-25-4; 2, 824-45-3; 3, 552-45-4; 4, 34815-23-1; HCHO, 50-00-0; 2-bromo-4-methoxytoluene, 36942-56-0; 2-methyl-5-methoxybenzyl chloride, 73502-04-2.

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Direct Observation of a Diiodo Derivative and Phosphonium Intermediates in Iodolactonization by Fast Atom Bombardment Mass Spectrometry

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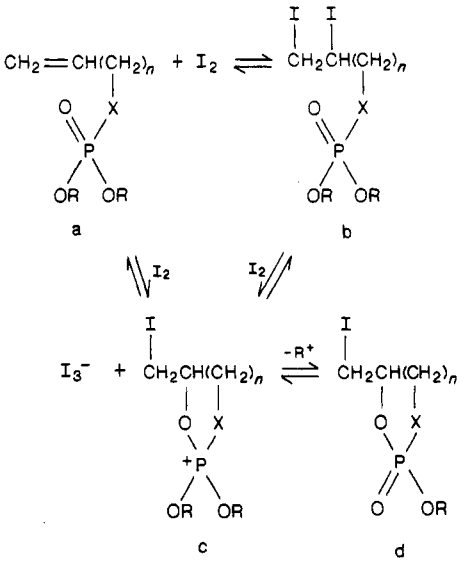
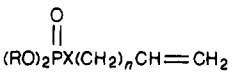
It has been recognized, since Bougault[1] first reported the conversion of β,γ- or γ,δ-unsaturated acids into iodo lactones, that γ,δ-unsaturated acids frequently react with iodine to form iodo lactones instead of the simple addition products. This iodolactonization reaction has shown great value in organic synthesis in different aspects,[2] especially for stereocontrolling purposes[3] and structural determination. Arnold et al.[4] proposed a general mechanism for the reaction of halogen and γ,δ-unsaturated acids and esters. Later on, based on a kinetic study, Amaral and Melo[5] presented a more detailed mechanism, in which the fast formation of an iodine–double bond complex intermediate was supposed. This explains the fact that in chloroform, 1 mol of unsaturated acid reacts with 2 mol of iodine. Zhao and co-workers[6] traced the iodine-induced cyclization reaction of δ,ϵ-unsaturated phosphonate by ^{31}P NMR, and found that two intermediates resulted: the diiodo derivative and the cyclic phosphonium ion. However, these labile short-lived intermediates do not allow any separation and purification, and they are not amenable to full characterization.

Scheme I



Fast atom bombardment mass spectrometry (FAB MS), which was introduced by Barber et al.[7] in 1981, has shown promise in the direct characterization of liquid-phase systems. In FAB MS, the sample is dissolved in a liquid matrix (usually glycerol) and then bombarded by a beam of energetic particles (such as Ar^0 and Xe^0 of 5–10 keV). With this technique, Saito and Kato[8] detected short-lived glutathione-conjugate intermediates in a rapid conjugation reaction of carcinogenic–mutagenic arylnitroso compounds with glutathione, which was performed within a mass spectrometer. Daves et al.[9] directly observed the transmetalation intermediates, which is central to palladium-mediated reaction of organomercurials, in reaction mixtures.

During the verification of iodolactonization products of unsaturated phosphoamidate I, phosphonates II and III, and phosphate IV by FAB MS, we observed the diiodo derivative and monoiodo phosphonium intermediates in the mass spectra of the reaction mixtures, which is the direct evidence for the mechanism of iodine-induced cyclization of unsaturated organophosphorus compounds.



	X	n	R
I	NH	1	Et
II	CH_2	1	Et
III	CH_2	2	n-Pr
IV	O	2	Et

Results and Discussion

The iodine-induced cyclization of unsaturated organophosphorus compounds I–IV is described in Scheme I based on the mechanism proposed by Zhao et al.[6] The overall process involves two intermediates: iodine addition

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