# Ipso Nitration of 4-Iodo-*o*-xylene

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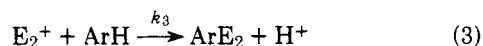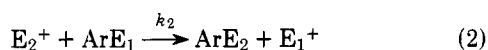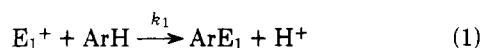
Nitration of 4-iodo-*o*-xylene with mixed acid affords mixtures of 4-nitro-*o*-xylene, 5-iodo-3-nitro-*o*-xylene, and 4-iodo-5-nitro-*o*-xylene. Under certain nitration conditions substantial amounts of 4,5-diiodo-*o*-xylene were also formed. Because of the inefficiency of the nitrodeiodination reaction and the faster rate of nitration of *o*-xylene relative to 4-iodo-*o*-xylene, iodine cannot be used as a catalyst to effectively alter the substitution pattern for nitration of *o*-xylene. Nitration of 4-iodoxy-*o*-xylene was found to give an iodoxynitroxylene.

## Introduction

There is considerable interest in methods of altering isomer distribution in products of electrophilic aromatic substitutions. Recent approaches have included clathration of the aromatic to induce additional steric influence on selectivity[1] and rearrangement of the undesired initial product of electrophilic attack on the aromatic to give the desired one.[2] The nitration of *o*-xylene typifies the problems encountered in attempting to alter product isomer distribution. A wide variety of nitrating agents have been found to give a 4-nitro-*o*-xylene (4-NOX) to 3-nitro-*o*-xylene (3-NOX) product ratio which could not be made to exceed 3:1.[2] Since 4-nitro-*o*-xylene is a useful reagent for further reactions, increasing this ratio without increasing the extent of side reactions would provide a higher yield of a less contaminated material.

As indicated by eq 1 and 2, another method by which selectivity in products of electrophilic substitution may be altered is through the intermediacy of another electrophilic reagent, $E_1^+$, which exhibits a different, more desirable selectivity in substitution of the aromatic. Ipso (self-directed) substitution of $E_1^+$ by the desired electrophile $E_2^+$ as in eq 2 would give the product $ArE_2$ with a more desirable isomer ratio than that obtained by direct attack of $E_2^+$ on ArH (eq 3). If the rates $k_1$ and $k_2$ are fast relative to $k_3$, and if side reactions do not interfere, the system can obviously be effectively catalytic in $E_1^+$.

$$E_1^+ + ArH \xrightarrow{k_1} ArE_1 + H^+ \qquad (1)$$

$$E_2^+ + ArE_1 \xrightarrow{k_2} ArE_2 + E_1^+ \qquad (2)$$

$$E_2^+ + ArH \xrightarrow{k_3} ArE_2 + H^+ \qquad (3)$$

Exactly such a scheme has been achieved by thalliation of *o*-xylene with thallium(III) trifluoroacetate followed by treatment of the thalliated product with nitrogen dioxide.[3] This process produced an 84% yield of 4-NOX together with 4% 3-NOX. This type of scheme would have greater utility if it could be accomplished in a catalytic manner with a nonmetallic electrophilic intermediate. Since iodine is known to be one of the better ipso leaving groups under electrophilic substitution conditions,[4] our attention turned to its utilization.

It has been noted in the literature that iodination of *o*-xylene proceeds in high yield to give 4-iodo-*o*-xylene (4-IOX) and 3-iodo-*o*-xylene (3-IOX) in an 84:16 ratio.[5] A particularly attractive feature of this reaction is that the reported experimental procedure employs iodine in the presence of mixed nitric and sulfuric acids. A number of instances are known where I$^+$ is displaced from aromatics by such a nitrating mixture under somewhat more severe conditions. Iodo aromatics for which such ipso displacements have been reported include 4-iodoanisole,[6,7] 2-iodomesitylene,[8] and 2-iodo-

1,3,5-trineopentylbenzene.[8] Nitrobenzene could not be detected, however, from nitration of iodobenzene with nitric acid in nitromethane,[8] and while iodo appears to be one of the better ipso leaving groups,[9] nitrodeiodination can also be complicated by the liberated I$^+$ (or equivalent species) iodinating either the iodo- or nitro-substituted aromatics.[6-8] Recognizing the potential for such side reactions, we examined the nitration of 4-iodo-*o*-xylene with the view of determining if iodine could be used effectively as a catalyst in directing the selectivity of the nitration of *o*-xylene.

## Results and Discussion

Iodination of *o*-xylene according to the literature procedure[5] afforded a 93% yield of distilled mixed monoiodo isomers which could not be separated by distillation or GLC. Analysis by NMR showed this mixture to contain 80% 4-IOX and 20% 3-IOX. Pure 4-IOX (1) was obtained by fractional crystallization from hexane at −78 °C.[5]

Nitration of 4-IOX was run under several sets of conditions (Table I) and products were analyzed by GLC. The desired 4-NOX (2) was formed in each case in yields ranging from 6 to 13%; however, ordinary nitration (nitrodeprotonation) to give 5-iodo-3-nitro-*o*-xylene (4) and 4-iodo-5-nitro-*o*-xylene[10] (5) was found to be the predominant reaction, and under
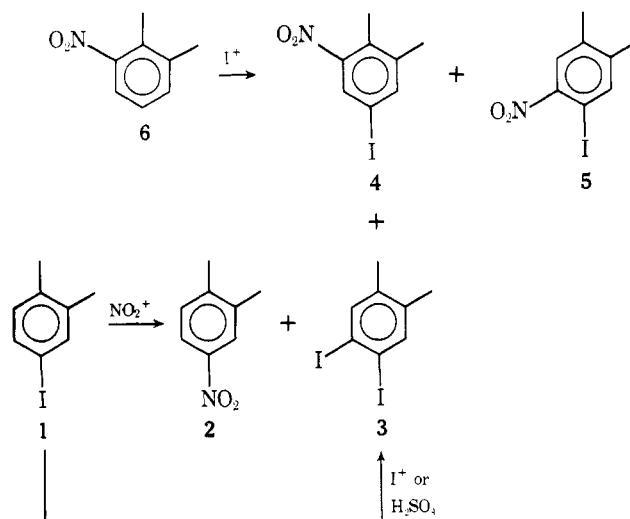


certain conditions (cf. Table I) relatively large amounts of 4,5-diiodo-*o*-xylene (3) were formed as well.

The ipso product 4-NOX was identified by GLC and infrared comparison with an authentic sample. Both 4-iodo-5-nitro-*o*-xylene (5) and 4,5-diiodo-*o*-xylene (3) were isolated from the nitration experiments and were characterized by NMR, mass spectrometry, and infrared analysis. The diiodo compound 3 and 5-iodo-3-nitro-*o*-xylene (4) were independently synthesized by iodination of 4-IOX and 3-NOX, respectively. Attempted iodination of 4-NOX gave no reaction.

## Table I. Nitration of 4-Iodo-*o*-xylene

| Expt. no. | 4-IOX, mol | 70% HNO$_3$, mol | Nitrating agent, mol | H$_2$SO$_4$, mol | H$_2$SO$_4$, % | Solvent, mL | Temp, °C | Time, h | 4-IOX | 4-NOX | 4,5-di-IOX | 5-I-3-NOX | 4-I-5-NOX | ?[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.020 | 0.022 | — | 0.020 | 96 | 5[a] | 50 | 4 | 60% | 8% | 24% | 3% | 3% | — |
| 2 | 0.020 | 0.088 | — | 0.040 | 96 | 5[a] | 60 | 8 | 0 | 13% | 25% | 17% | 42% | — |
| 3 | 0.010 | — | N$_2$O$_4$ 0.040 | 0.023 | 87 | — | 25 | 2 | 8% | 9% | 19% | 21% | 28% | — |
| 4 | 0.0050 | — | NO$_2$BF$_4$ 0.010 | — | — | 5[a] | 25 | 1/2 | 0 | 8% | 6% | 23% | 54% | 9% |
| 5 | 0.010 | 0.020 | NaNO$_2$ 0.001 | 0.022 | 90 | — | 25 | 4 | 3% | 7% | 20% | 23% | 47% | — |
| 6 | 0.010 | 0.050 | NaNO$_2$ 0.002 | — | — | 5[a] | 70 | 22 | 25% | 6% | 41% | 4% | 22% | — |
| 7 | 0.0043 | — | NOBF$_4$ 0.0086 | — | — | 5[b] | 60 | 6 | 0 | 10% | 42% | 16% | 23% | 9% |
| 8 | 0.010 | 0.033 | — | 0.044 | 90 | — | 30 | 1 | 0 | 7% | 0 | 26% | 59% | 7% |
| 9 | 0.010 | 0.033 | — | 0.044 | 90 | — | 25 | 1/2 | 0 | 7% | 0 | 28% | 62% | 3% |
| 10 | 0.010 | 0.100 (90%) | — | — | — | 10[b] | 25 | 2 | 0 | 12% | 0 | 23% | 59% | 6% |

[a] HOAc. [b] CH$_3$NO$_2$. [c] As determined by GLC. [d] Unidentified; % estimated by GLC.

From the results presented in Table I and the separate iodination experiments, it is clear that nitrodeiodination accounts for only a small amount of the reaction products in the nitration of 4-IOX. Although the origins of the various products are not known with complete certainty, it is likely that **4** is formed entirely by nitrodeprotonation. Since 4-NOX does not iodinate readily, **5** cannot form via 4-NOX. It is most
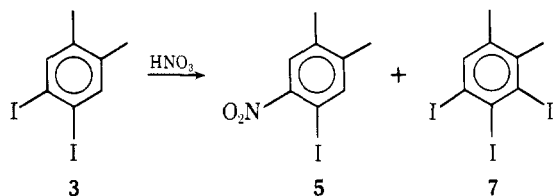


probably formed by nitrodeprotonation of 4-IOX, although to some extent it may also result from nitrodeiodination of **3**. In a separate experiment it was found that nitration of the latter at 65–75 °C for 12 h produced **5** in ca. 75% yield along with some 3,4,5-triiodo-*o*-xylene (**7**).

The origin of **3** is less certain. Although the nitrodeiodination reaction releases an equivalent amount of I$^+$, which is then available to iodinate 4-IOX, the yield of diiodo compound formed was frequently much greater than that of 4-NOX. A possible source of this excess **3** is the Jacobsen reaction of 4-IOX, in which 4-IOX, upon heating with sulfuric acid, produces **3**.[11] The other product of the Jacobsen reaction is presumably a sulfonic acid which would not be detected in our workup or GLC procedures. In a recent study of Friedel–Crafts acylations of iodoaromatics, excesses of diiodoaromatic over ipso substitution product were observed.[12] Whatever the origin of **3**, its formation could be suppressed by modification of the experimental conditions (Table I, experiments 8 and 9). Thus, in reactions of 4-IOX with excess mixed acid at 25 °C for short periods of time, no **3** was detected, and the product distribution was 7% 4-NOX, 28% **4**, 62% **5**, and 3% unidentified (probably dinitrated) material.

Several variations of the nitration procedure were attempted in an effort to increase the yield of 4-NOX (cf. Table I). These included use of N$_2$O$_4$, NO$_2$BF$_4$, and NOBF$_4$ as nitrating agents, addition of NaNO$_2$ to the nitric acid, and the use of nitromethane as a solvent. None of these conditions provided more than a 12% yield of 4-NOX. We had originally hoped that reaction of 4-IOX with NO$^+$ followed by oxidation would increase the amount of ipso substitution, based on the work of Butler and Sanderson,[7] who reported that nitro-

deiodination of 4-iodoanisole proceeded via nitrosation rather than nitration. More recently, Olsson[13] reported that added NaNO$_2$ did not increase the amount of nitrodeiodination of 2-iodo-1,3,5-trineopentylbenzene relative to nitrodeprotonation. As seen in Table I, however, neither NOBF$_4$ nor nitric acid containing added NaNO$_2$ was effective in increasing the 4-NOX yields. Thus, the data indicate that NO$^+$ and NO$_2^+$ produce comparable proportions of nitrodeiodination product from 4-IOX.

Competitive mixed acid nitration of an equimolar mixture of *o*-xylene and 4-IOX was studied in an effort to determine which was the more reactive substrate. At the end of the reaction no *o*-xylene could be detected but 44% of the original 4-IOX remained unreacted. Clearly, the relative rates are in the wrong order for iodine catalysis of nitration as discussed in the Introduction. Thus, even if the 4-IOX → 4-NOX conversion could be made more efficient, the directive effects of a catalytic amount of iodine would be minimal because most of the reaction would proceed by direct nitration of *o*-xylene.

As a final empirical test of the iodine catalysis scheme, the mixed acid nitration of *o*-xylene was carried out in the presence of 5 mol % added iodine and the GLC analysis was compared with that of a similar reaction run without added I$_2$. In the presence of I$_2$ an 88% combined yield of mononitro isomers was obtained with a 4-NOX/3-NOX ratio of 46:54. In addition about 4% of 4-IOX was detected. In the absence of I$_2$ an 89% combined yield of 4-NOX and 3-NOX was obtained and the isomer ratio was 44:56. Thus, no significant effect on isomer distribution was observed.

The possibility of converting 4-IOX to a derivative which might undergo electrophilic ipso substitution more readily than 4-IOX itself was also examined. Since oxidation of 4-IOX to a polyvalent iodine compound would be expected to weaken the C–I bond,[14] and may thus increase susceptibility to ipso substitution, 4-IOX was oxidized with peracetic acid to give 4-iodoxy-*o*-xylene (**8**). This new compound was reacted with excess mixed acid (Caution: see Experimental Section) to give
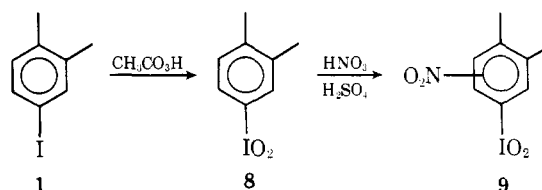
a compound the elemental analysis and IR of which indicated a nitrodeprotonation product **9** in 53% yield, along with a small amount of 4-I-5-NOX. No 4-NOX was found. We have been unable to locate any reference to electrophilic substitution of iodoxy-substituted aromatics in the literature.

The position of the nitro group in the insoluble, explosive, new compound **9** could only be inferred from its infrared spectrum. Compound **8** shows bands at 882 cm$^{-1}$ (lone H out-of-plane vibration) and 808 cm$^{-1}$ (2 adjacent H out-of-plane vibrations), while **9** displays a band corresponding to the former (876 cm$^{-1}$) but no band corresponding to the latter. The absence of adjacent hydrogens excludes 4-iodoxy-3-nitro-o-xylene as the correct structure. Of the two remaining possibilities, we favor assigning 5-iodoxy-3-nitro-o-xylene to compound **9** on mechanistic grounds since its Hammett $\sigma$ parameters suggest that the iodoxy substituent is meta directing[15,16] and also the 3-position is the less hindered one.

In another experiment 4-IOX was treated with peracetic acid under conditions for making iodosodiacetates.[17] Treatment of the crude product with excess mixed acid gave a complex mixture of products but 4-NOX could not be detected by GLC.

## Experimental Section

**General.** The NMR spectra were run in CDCl$_3$ on a Varian HA-100 spectrometer. GLC analyses were performed on a Hewlett-Packard Model 5750 instrument equipped with a flame ionization detector. The column was a 10 ft × 1/8 in. SS 20% QF-1 on 90/110 mesh Anakrom ABS and the temperature was programmed from 150 to 225 °C at 30 °C/min followed by 10 min at 225 °C. The following retention times (in minutes) were observed under these conditions: 4-IOX (2.8), 4-NOX (4.6), 4,5-di-IOX (5.5), 5-I-3-NOX (6.6), and 4-I-5-NOX (8.7). Quantitation was made from peak areas calibrated with known quantities of the compounds.

**4-Iodo-o-xylene (1).** To 500 mL of acetic acid was added slowly with stirring 140 mL of concentrated H$_2$SO$_4$ (2.60 mol) followed by 376 g (3.54 mol) of o-xylene and 210 g of finely divided iodine. The stirred mixture was heated to 50 °C, the heating bath was removed, and 140 mL of 70% HNO$_3$ (2.24 mol) was added dropwise at a rate to keep the temperature below 55 °C. After most of the iodine had reacted, an additional 210 g was added (total 420 g, 3.32 g-atoms) and addition of HNO$_3$ was completed. Stirring at 50 °C was continued for 40 min and the mixture was then cooled and poured over crushed ice. The organic layer was separated and the aqueous layer was extracted twice with methylene chloride. The combined organic material was washed twice with dilute NaOH and once with water, dried, and evaporated. Distillation of the resulting oil gave 719 g (93%) of iodo-o-xylenes, bp 96–102 °C (7 mm), which was determined to consist of 80% 4-iodo-o-xylene and 20% 3-iodo-o-xylene by NMR analysis.

Pure 4-iodo-o-xylene (1) was obtained by three crystallizations from hexane at −78 °C, decanting the mother liquor from the filter cake after each crystallization, and evaporating in vacuo to remove the residual hexane after the last crystallization. This procedure gave 440 g (57%) of pure 4-iodo-o-xylene, the $^1$H NMR of which showed a singlet methyl at $\delta$ 2.14, containing no detectable amount of the 3-isomer (doublet methyl centered at $\delta$ 2.33).

**Nitration of 4-Iodo-o-xylene in Mixed Acid. Isolation of 4-Iodo-5-nitro-o-xylene (5).** Mixed acid was prepared from 0.3 mL of water, 2.4 mL of 96% H$_2$SO$_4$ (0.044 mol) and 2.1 mL of 70% HNO$_3$ (0.033 mol). The acid solution was added dropwise with stirring to 2.3 g (0.010 mol) of 4-iodo-o-xylene cooled in an ice bath to keep the reaction temperature ≤25 °C. After stirring for 20 min at 25 °C the mixture was poured into ice water and extracted with methylene chloride. The extracts were washed with dilute NaOH and water, dried, and evaporated to give 2.5 g of orange oil. GLC analysis of the oil showed 7% 4-NOX, 28% 5-I-3-NOX, 62% 4-I-5-NOX, and 3% of an unknown product. The oil was partially crystallized from ethanol to give 0.55 g of **5**, mp 62–66 °C. Successive recrystallization from ethanol and petroleum ether afforded yellow flakes, mp 65.5–67.5 °C.

Anal. Calcd for C$_8$H$_8$NO$_2$I: C, 34.61; H, 2.91; N, 5.06; mol wt, 277. Found: C, 34.47; H, 2.88; N, 4.86; m/e 277. $^1$H NMR $\delta$ 7.78 (s, ArH), 7.68 (s, ArH), 2.26 (s, CH$_3$).

**5-Iodo-3-nitro-o-xylene from Iodination of 3-Nitro-o-xylene.** A mixture of 1.8 mL of 96% H$_2$SO$_4$ (0.032 mol), 6.0 g of 3-nitro-o-xylene (0.040 mol), 5.1 g of iodine (0.020 mol) and 1.8 mL of 70% HNO$_3$

(0.028 mol) in 10 mL of acetic acid was stirred at 80–85 °C for 24 h. The reaction mixture was poured into ice water containing sodium thiosulfate and extracted three times with methylene chloride. The combined extracts were washed with dilute NaOH and water, then dried and evaporated. GLC analysis of this oil showed about 70% unreacted starting material and about 30% product. Chromatography over grade I neutral alumina gave a small amount of crystalline product, mp 56–60 °C, from petroleum ether, identified as **4** by analysis and NMR.

Anal. Calcd for C$_8$H$_8$NO$_2$I: C, 34.61; H, 2.91; N, 5.06. Found: C, 34.57; H, 2.88; N, 5.08. $^1$H NMR $\delta$ 7.90 (s, ArH), 7.69 (s, ArH), 2.31 (s, CH$_3$).

**4,5-Diiodo-o-xylene (3).** A mixture of 4.65 g (0.020 mol) of 4-iodo-o-xylene, 2.55 g (0.010 mol) of iodine and 1.6 mL (0.030 mol) of 96% H$_2$SO$_4$ in 5 mL of acetic acid was heated with stirring to 50 °C and 0.9 mL (0.014 mol) of 70% HNO$_3$ was added dropwise. Stirring was continued at 50–55 °C for 3 h and the mixture was poured into ice water and worked up as in the above example to give 5.9 g (82%) of crude **3**, mp 70–85 °C. Three recrystallizations from ethanol gave faintly yellow prisms: mp 91–93 °C (lit.[18] mp 93–94 °C); $^1$H NMR $\delta$ 7.59 (s, ArH), 2.13 (s, CH$_3$).

**Nitration of 4,5-Diiodo-o-xylene.** A stirred suspension of 1.8 g of 4,5-diiodo-o-xylene (0.0050 mol) in 10 mL of acetic acid was heated to 50 °C and a solution of 1.0 g of 96% H$_2$SO$_4$ and 1.5 g of 70% HNO$_3$ was added. The reaction mixture was stirred at 65 °C for 6 h and then another 0.25 g of H$_2$SO$_4$ (total 0.0125 mol) and 0.4 g of HNO$_3$ (total 0.030 mol) were added and stirring was continued at 75 °C for another 6 h. The cooled reaction mixture was poured into ice water and extracted with methylene chloride. The extracts were washed with dilute NaOH and water, dried, and evaporated to give a yellow solid. GLC analysis showed this to be approximately 75% **5**, 5% unreacted **3**, and 20% of a new product. Fractional crystallization from ethanol gave a few milligrams of pale yellow crystals, mp 111–113 °C, identified as 3,4,5-triiodo-o-xylene (**7**) by analysis, IR, and NMR.

Anal. Calcd for C$_8$H$_7$I$_3$: C, 19.86; H, 1.46. Found: C, 19.61; H, 1.46. $^1$H NMR $\delta$ 7.73 (s, ArH), 2.55 (s, CH$_3$), 2.24 (s, CH$_3$).

**4-Iodoxy-o-xylene (8).** The general procedure of Sharefkin and Saltzman[17] was used. To 23.2 g (0.100 mol) of 4-iodo-o-xylene stirred at 35 °C was added dropwise 65 mL of 40% aqueous peracetic acid (0.500 mol). After addition was complete, 80 mL of water was added and the bath temperature was raised to 100 °C. Considerable frothing occurred during heating. The mixture was stirred at 100 °C for 45 min and then cooled and filtered. The white solid was washed with water and dried in a vacuum desiccator to give 22.1 g (84%) of **8**, mp 207 °C (explodes), impact sensitivity = 20 cm.

**Nitration of 4-Iodoxy-o-xylene.** Ten milliliters of mixed acid of composition 35% HNO$_3$, 63% H$_2$SO$_4$, and 2% H$_2$O (from combining the proper quantities of 90% HNO$_3$, 96% H$_2$SO$_4$, and fuming H$_2$SO$_4$, 20–23% SO$_3$) was stirred in an ice bath while 0.5 g of finely divided solid 4-iodoxy-o-xylene (**8**) was added in small portions. (When a small lump was added a sudden violent reaction occurred.) After the addition, the yellow solution was poured over ice and the white solid which formed was filtered and washed with acetone to give 0.31 g (53%) of **9**, mp 204 °C (explodes).

Anal. Calcd for C$_8$H$_8$NO$_4$I: C, 31.08; H, 2.61; N, 4.53; I, 41.06. Found: C, 31.32; H, 2.23; N, 4.75; I, 40.81. Insolubility precluded NMR analysis and prevented establishment of the isomeric structure of this product.

## References and Notes

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(15) Although very limited data are available, iodoxy appears to be a typical electron withdrawing group with Hammett $\sigma$ parameters ($\sigma_m = 0.70$, $\sigma_p = 0.76$) very similar to those of the nitro group ($\sigma_m = 0.71$, $\sigma_p = 0.78$).[16]
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# Rates and Products of the Reaction of a β,β-Dichlorobenzylic Alcohol and Its Derivatives in CF3CO2H–H2SO4. A 1,2-Chlorine Shift Giving an α-Chloro Ketone

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The p-toluenesulfonate and p-bromobenzenesulfonate of 1-(o-chlorophenyl)-2,2-dichloro-1-propanol (1) reacted at a conveniently measurable rate in 25 mL of CF3CO2H containing 1.127 g of 96% H2SO4. 1-(o-Chlorophenyl)-1-chloro-2-propanone and the trifluoroacetate of 1 were formed. The ketone, previously obtained from reaction of 1 in H2SO4, appears to be formed via a chloronium ion intermediate. The absence of rate effects of substituents in the leaving group is connected with acid catalysis.

Recently it was found[1] that the chlorine-containing alcohol 1 was converted exclusively to the α-chloro ketone 2 upon reaction with concentrated (96%) sulfuric acid. The formation



$$(1)$$
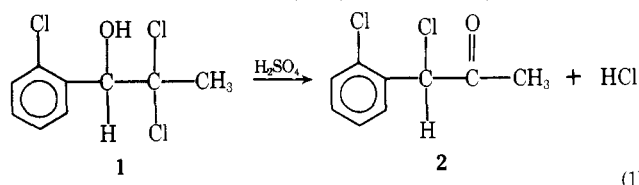
of 2, the apparent product of a 1,2-chlorine shift, was so facile that 1 formed no condensation product with chlorobenzene in the presence of H2SO4. Various alcohols related to 1 do undergo such condensation (e.g., that of eq 2) to give the



$$(2)$$
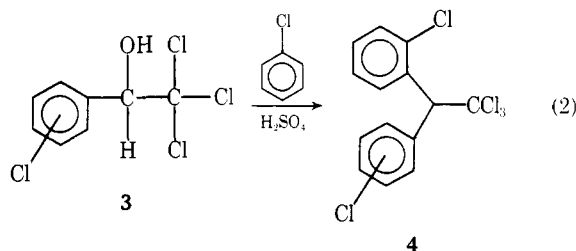
pesticide DDT or related compounds.[2] Accordingly, we were prompted to further define the mechanism of the reaction of eq 1 and related processes. At the outset of our study, two main types of mechanism were considered. In one, mentioned previously,[1] the reaction of eq 1 is initiated by breaking the C–O bond, possibly with simultaneous chlorine participation to give a chloronium ion intermediate 5. Another mechanism
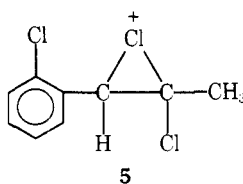


involves breaking of a C–Cl bond, presumably facilitated by electrophilic acid catalysis, with possible simultaneous hydroxyl participation to form a chloro epoxide intermediate, 6. McDonald and co-workers have shown that chloro epoxides
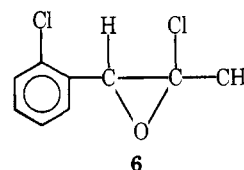


may rearrange with chlorine shift, to chloro ketones, probably via ketocarbonium ion intermediates.[3] The example[3a] of eq 3 is particularly relevant (cf. eq 1). The McDonald reaction typically occurs in neat liquid. Lewis acid catalysis may occur, but protonic acids tend to favor alternative reaction paths.[3b] Although the reaction of this paper occurs in protonic solvents, it appears that the McDonald mechanism should not be ruled out of consideration. A third type of mechanism for formation



$$(3)$$
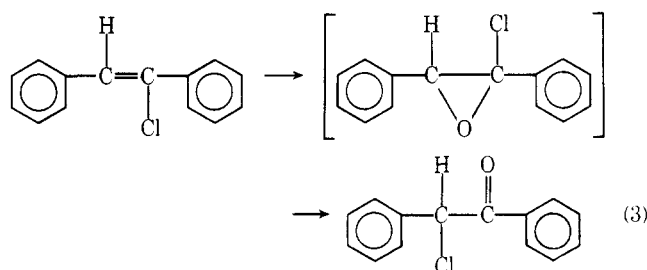
of 2 involves the intermediacy of chloride 7a, formed in an intermolecular reaction from HCl evolved into the sulfuric acid solvent via side reactions or, after reaction has begun, via eq 1. Although reaction via 7 would involve no chlorine shift, hydrolysis of geminal halides is known to yield ketones. Furthermore, the reported isolation of 7b from an experiment in H2SO4[1] suggested that the sequence involving 7 must be considered!