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Substituted 3-phenylpropenoates and related analogs: electron ionization mass spectral fragmentation and density functional theory calculations

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Analysis of ethyl 3-(2-chlorophenyl)propenoate by electron ionization mass spectrometry showed the distinct loss of an *ortho* chlorine. To characterize the structural requisites for the observed mass fragmentation, a series of 30 halogen-substituted 3-phenylpropenoate-related structures were examined. All ester-containing alkene derivatives exhibited loss of the distinctive chlorine from the 2-position of the phenyl ring. Analogous derivatives with the halogen (chlorine or bromine) in the *para* position did not evidence selective halogen loss. Results demonstrated that substituted 3-phenylpropenoates and their analogs fragment via the formation of a previously reported benzopyrylium intermediate. To understand the correlation between the intramolecular radical substitution and the abundance and selectivity of the chlorine (or other halogen) displacement, density functional theory calculations were performed to determine the charge on the principal cation involved in the chlorine loss (in the *ortho*, *meta*, and *para* positions), the charge for the neutral radical (noncation), the excess alpha-electron density on the relevant atom and the energy to form the cation from the neutral atom (ionization energy). Results showed that the selectivity and extent of halogen displacement correlated highly to the electrophilicity of the radical cation as well as the neutral radical. These data further support the proposed fragmentation mechanism involving intramolecular radical elimination. Copyright © 2008 John Wiley & Sons, Ltd.

KEYWORDS: 3-phenylpropenoate; substituted cinnamic esters; benzopyrylium cation; density functional theory calculations; electron ionization mass spectrometry

INTRODUCTION

Our laboratory reported the synthesis of haptens for the detection of polyhalogenated dibenzodioxins by enzyme-linked immunosorbent assay (ELISA).[1] This ELISA has been successfully used in the analysis of these contaminants in a variety of environmental matrices.[2–6] In the process of designing the ELISA, a series of dioxin analogs containing a rigid propenoic acid side chain were synthesized for coupling the hapten to immunizing proteins. During the electron ionization (EI) mass spectral (MS) characterization of these haptens and the synthetic intermediates used to prepare the haptens, an interesting fragmentation was observed for molecules structurally related to ethyl 3-(2-chlorophenyl)propenoate. Examination revealed that a significant loss of chlorine occurred from the molecular ion (m/z 384) of ethyl *trans*-3-(3,7,8-trichlorodibenzo-*p*-dioxin-2-yl)propenoate, giving a fragment of m/z 349. A literature search showed that this type of fragmentation pattern had been previously reported for α,β-unsaturated esters of propenoic acids and nitriles,[7] cinnamic acids[8] and α-phenylcinnamic acids.[9] The fragmentation occurred via a substituted benzopyrylium intermediate, whose relative abundance depended upon the position of halogen substitution on the phenyl ring. In particular, Williams *et al*. reported that the *ortho*-isomer of chlorine-substituted diethyl benzalmalonate exhibited a relatively abundant ($[M]^{\bullet+} - Cl$) because of chlorine loss, whereas the *meta*- and *para*-isomers did not.[7] These data strongly suggested that the *ortho*-isomer underwent a facile chlorine radical elimination via cyclization similar to that reported by Ronayne *et al*.[10] In addition, Schaldach and Grützmacher reported that *m*- and *p*-chlorocinnamic acids were capable of undergoing the same chlorine elimination process as the *ortho* analog.[8]

Therefore, to further investigate this mass spectral fragmentation process, a series of ethyl and methyl *trans*-3-(3,7,8-trichlorodibenzo-*p*-dioxin-2-yl)propenoate-related analogs were prepared and subjected to EI-MS analysis. We analyzed three dibenzodioxin structures related to ethyl *trans*-3-(3,7,8-trichlorodibenzo-*p*-dioxin-2-yl)propenoate and 26 3-(substituted phenyl)propenoate-related compounds. This

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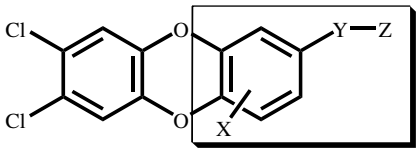

Figure 1. The structure inside the box shows the general composition of the ethyl *trans*-3-(3,7,8-trichlorodibenzo-*p*-dioxin-2-yl)propenoate analogs examined in this study. X = a series of substituted halogens or hydrogens. Y = a range of 1 or 2 carbon alkane, alkene, and alkyne derivatives. Z = ethyl ester, primary alcohol, methyl ketone, or nitrile.

series of 3-phenylpropenoate-related structures shown in Fig. 1 was rationally designed to explore the steric and electronic effects on this EI-MS fragmentation. Earlier studies focused solely on substituted esters or nitriles and maintained the olefin linkage.[7] Follow-up studies expanded this motif in cinnamic acids, but again maintained the olefin and did not vary the acid or linker/spacer moiety.[8,9] We subsequently expounded upon this theme and synthesized analogs incorporating a variety of linkers between the phenyl ring and ester, including alkane (with one or two carbon atoms), alkene, substituted alkene, and alkyne moieties. We were particularly interested in the mechanism responsible for the observed fragmentation patterns and therefore replaced the ester functionality with a nitrile, primary alcohol, or a methyl ketone. These distinct and varied chemical moieties were examined for their ability to affect the selective loss of a halogen from the *ortho* position *versus meta* or *para*. Taken together, these groups expand upon the previous work and extend the studied moiety to probe the effects of a number of functional groups that could potentially displace the halogen from the phenyl ring. On the basis of these results, we demonstrated that a variety of substituents are effective at selectively displacing the *ortho* chlorine and that the fragmentation occurs via an intramolecular radical substitution to form a benzopyrylium intermediate similar to that observed in previous studies.[7–9]

EXPERIMENTAL

Materials

All the chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless otherwise noted and were used without further purification. A summary of the synthetic methods is shown in Table 1. Further synthetic details are provided in the original papers.[1–6]

Mass spectral analysis

Samples were analyzed on a HP 6890 GC (Agilent Technologies; Palo Alto, CA) equipped with 30-m DB-17MS column (J&W Scientific; Folsom, CA), 0.25-mm internal diameter, 0.25-μm film thickness and He carrier gas at a flow rate of 0.8 ml/min. The injector temperature was 250 °C and the initial column temperature was 50 °C and was held for 5.00 min and then ramped at 15 °C/min to 320 °C and held for 2.00 min. The GC was interfaced with a HP 5973 MS that was run in full-scan mode from 50 to 550 m/z with a quadrapole temperature of 186 °C and a source temperature of 240 °C at 70 eV.

Table 1. Synthetic methods for reported compounds

No.	Synthesis
1–4	Methods reported in Sanborn *et al.*, 1998[1]
5–6	Esterification of commercially available 3-(2- and 4-chlorophenyl)propenoic acids
7	Synthetic intermediate in Sanborn *et al.*, 1998[1]
8	Treatment of 2-chloro-4-methoxy benzaldehyde with triethylphosponoacetate under basic conditions
9–12	Treatment of 6-chloropiperonylaldehyde, 2- and 3-bromobenzaldehyde, and 2-fluorobenzaldehyde with triethylphosponoacetate under basic conditions
13	Treatment of 2-chlorobenzaldealdehyde with triethyl 2-phosphonoproprionate under basic conditions
14	Treatment of 2-chloroacetophenone with triethylphosphonoacetate under basic conditions
15	Treatment of 2-chloroacetophenone with triethyl 2-phosphonoproprionate under basic conditions
16	Commercially available
17	Treatment of 2-chloro benzaldehyde with cyanoacetic acid under basic conditions
18–21	Treatment of 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 2-bromobenzadehyde and 3-bromobenzaldehyde with 3-diethyl phosphono-2-propanone under basic conditions
22–23	Lithium aluminum hydride reduction of compound **9** in tetrahydrofuran (THF)
24	Treatment of 2-chlorobenzyl chloride with di-*t*-butyl malonate followed by hydrolysis, decarboxylation and esterification
25	Esterification of commercially available 3-(3-chlorophenyl)propionic acid
26–28	Esterification of commercially available 2- and 3-chlorophenylacetic acids
29–30	Prepared according to the method of Newman and Merrill[11]

Density functional theory calculations

The molecular structure of all compounds studied were optimized using density functional theory (DFT) with the Becke 3-parameter hybrid exchange functional[12] and the Lee-Yang-Parr (LYP) gradient corrected electron correlation functional[13] (B3LYP) using a 6-31G* basis set. The B3LYP functional set has been widely demonstrated to yield accurate chemical structures and reaction energies when used with sufficient basis sets for most molecules.[14] The atomic charges were calculated from the B3LYP/6-31G* wave function at the B3LYP/6-31G* optimized geometries using natural atomic population analysis (NPA),[15] a method that yields atomic charges that validate many qualitative chemical concepts and is much more independent of molecular conformation and basis set than other methods such as Mulliken populations. These atomic charges are reported in units of electrons (e). All calculations were carried out with Gaussian 98 Version A.11.4 (Gaussian, Inc., Pittsburgh PA, 2002).

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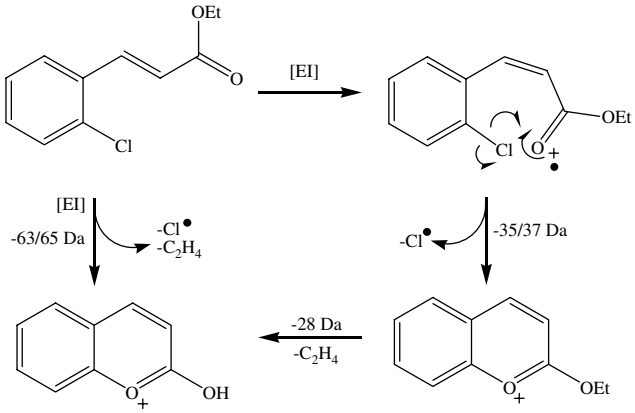


Scheme 1. Proposed mechanism for chlorine loss from ethyl 3-(2-chlorophenyl)propenoate (compound **5**). The olefin in the spacer arm of the molecule undergoes *trans* to *cis* isomerization, placing the carbonyl oxygen in a position to displace the chlorine to form the 2-ethoxy-benzopyrylium intermediate, which was observed as the *m/z* 175 fragment in Fig. 3(B). The 2-ethoxy-benzopyrylium intermediate then loses 28 Da to form 2-hydroxy-benzopyrylium (*m/z* 147), which also results from the concerted loss of *m/z* 63 observed for many other compounds in this study. The saturated analog ethyl 3-(2-chlorophenyl)propanoate (compound **24**) formed the analogous benzopyrylium structures as evidenced by the *m/z* 177 and 149 fragments in Fig. 3(A).

RESULTS AND DISCUSSION

Benzopyrylium ion formation

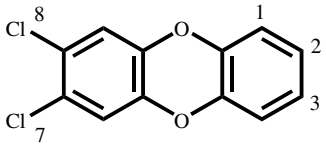
The distinct loss of a halogen observed for many of the compounds in this study occurs via a benzopyrylium intermediate as shown in Scheme 1. Formation of this ion in EI-MS has been observed for cinnamic acid esters,[16] α, β-unsaturated esters of propenoic acids and nitriles,[7] cinnamic acids,[8] methyl cinnamates,[17] α-fluorocinnamates[18] and α-phenylcinnamic acids.[9] In this mechanism, the *trans* olefin isomerizes to place the phenyl ring and ester function in a *cis* configuration.[10] The *cis–trans* isomerization of double bonds has been shown to be a facile process upon EI.[19] The carbonyl oxygen of the ester is now positioned to assist in the elimination of the halogen from the 2-position of the phenyl ring through the formation of a transitory 2-ethoxy-benzopyrylium intermediate.[8] This mechanism is consistent with the fact that skeletal rearrangements are often assisted by the presence of highly unsaturated groups.[19] To further support this mechanism, many of the compounds examined in this study lose 63 Da, ($[M]^{\bullet+} - C_2H_4 - Cl^{\bullet}$; Scheme 1). This fragment is best explained by chlorine loss and formation of the 2-ethoxybenzopyrylium intermediate, followed by loss of ethene (C_2H_4) to form 2-hydroxybenzopyrylium. It is also possible that compounds follow a concerted mechanism to directly form 2-hydroxybenzopyrylium, as many of the structures examined in this study had high abundance ions because of loss of 63 Da.

Dibenzodioxin esters

Table 2 contains EI-MS fragmentation data for four dibenzodioxin esters. The fragmentation of compound **1** is shown in Fig. 2, displaying the unique loss of chlorine *ortho* to the propenoic acid ester. Comparison of **2** and **3** with **1** demonstrates that significant loss of chlorine (35/37 Da) occurs only from the 3-position and not from the 7- or 8-positions of the dibenzodioxin ring system. Compound **4** is interesting because, even though it has a chlorine substituent *ortho* to the propenoate ester, significant loss of exclusively chlorine does not occur. The molecular ion (*m/z* 418) instead fragments with a loss of 63 Da ($[M]^{\bullet+} - C_2H_4 - Cl^{\bullet}$).

Analogs of the right hand side of the dibenzodioxin moiety were used to further probe the fragmentation patterns (shown in the boxed region in Fig. 1). Table 3 contains 11 structures that are ethyl esters of substituted 3-phenylpropenoic acids. They differ in the position, type and number of ring halogens and other substituents (e.g. methylenedioxy and methoxy) on the phenyl ring as well as methyl substitution on the olefin between the phenyl ring and the ester functionality. Multiple fragmentation pathways were reported by Schaldach

Table 2. Mass spectral data for chlorinated dibenzodioxin derivatives



No.	1	2	3	Formula	MM[a]	Ion (% abundance)[b]
1	H	$CH{=}CHCO_2C_2H_5$	Cl	$C_{17}H_{11}Cl_3O_4$	383.97	384/386/388/390(20.8/20.0/6.5/1.0); 349/351/353(37.0/24.5/4.5); 321/323/325(100/66.2/12.1)
2	H	$CH{=}CCH_3CO_2C_2H_5$	H	$C_{18}H_{14}Cl_2O_4$	364.03	364/365/366(100/20.5/66.3); 290/291/292(72.6/36.8/53.7); 115(56.9)
3	H	$CH{=}CHCO_2CH_3$	H	$C_{15}H_9Cl_2O_4$	336.00	336/338(100/69.3); 305/307(59.0/34.1)
4	$CH{=}CHCO_2C_2H_5$	Cl	Cl	$C_{17}H_{10}Cl_4O_4$	417.93	418/420/421/422(19.4/24.4/5.1/12.2); 383/385(6.4/6.9); 355/357/358/359(100/95.0/15.7/30.8)

[a] MM, molecular mass (Da), monoisotopic.

[b] Ions are given in Thompson (Th, mass to charge ratios), with the relative abundance of each ion (normalized to the base peak) shown in parentheses.

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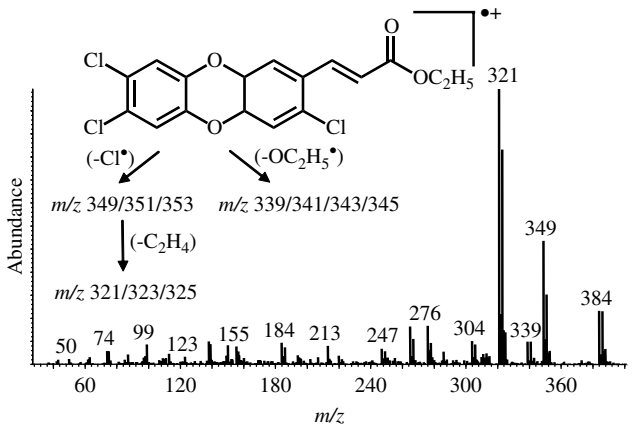


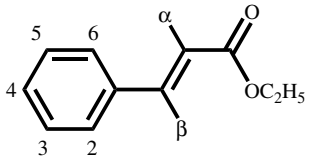
Figure 2. Mass spectral fragmentation of the dioxin hapten ethyl *trans*-3-(3,7,8-trichlorodibenzo-*p*-dioxin-2-yl)propenoate (compound **1**) showing the characteristic chlorine loss from *m/z* 384 to 349.

and Grützmacher[8] for substituted cinnamic acids, which depended upon the position of the halogen substitution on the phenyl ring (Scheme 2). Compounds with *ortho* substitution formed a 2-hydroxybenzopyrylium ion in high abundance (pathway 1), while those with *meta* or *para* substitution fragmented through a number of different pathways that could produce the 2-hydroxybenzopyrylium ion in a lower abundance (pathway 1), the halogen-substituted 2-hydroxybenzopyrylium ion (pathway 2), or the halogen-substituted cinnamoylium ion (pathway 3). In this study, the propensity of the fragmentation to proceed via pathway 1, 2 or 3 was examined by varying the halogen substitution as well as the ester moiety. Displacement of a weakly bonded *ortho* substituent can occur either directly or via a short-lived intermediate.[7] Mass spectra of *ortho* isomers are therefore more likely to display reduced abundance of the molecular ion ($[M]^{\bullet+}$), but exhibit relatively abundant $[M - X]^+$ peaks (pathway 1).[7] However, in the case of *meta* or *para* substituents, additional rearrangement steps are required for cleavage. These extra steps can lead to an increase in the abundance of the $[M]^{\bullet+}$ ion and to a subsequent decrease in the $[M - X]^+$ peak intensities,[8] which are indicative of whether the fragmentation has proceeded via pathway 1 or via pathways 2 and 3.

Halogenated ethyl substituted 3-phenylpropenoates

The halogen-dependent loss was examined by compounds **5, 10**, and **12** containing the substituents, chlorine, bromine and fluorine, respectively in the 2-position of the phenyl ring of ethyl 3-phenylpropenoate. Compounds **5** and **10**, like the dioxin derivatives discussed above, lose a halogen in the 2-position (35/37 and 79/81 Da, respectively) to give a base peak of *m/z* 147. This fragment was recognized as the 2-hydroxybenzopyrylium intermediate reported by other researchers (pathway 1).[7,8] However **12**, with a 2-fluoro substituent, did not undergo significant loss of 19 Da from the molecular ion (*m/z* 194). Rather, loss of 45 Da ($[M]^{\bullet+} - C_2H_5O^{\bullet}$) preferentially occurred to yield a base peak of *m/z* 149. Similarly, Schaldach and Grützmacher[8] reported that *o*-fluorocinnamic acid did not produce the benzopyrylium intermediate, but instead fragmented via

Table 3. Mass spectral data for substituted ethyl 3-phenylpropenoates



No.	α	β	2	3	4	5	6	Formula	MM[a]	Ion (% abundance)[b]
5	H	H	Cl	H	H	H	H	$C_{11}H_{11}ClO_2$	210.04	210/212(12.0/4.4); 176(7.0); 175(49.0); 165/167(36.0/11.5); 147(100)
6	H	H	H	H	Cl	H	H	$C_{11}H_{11}ClO_2$	210.04	210/212(34.4/11.6); 182/184(21.7/7.1); 165/167(100/32.6)
7	H	H	Cl	Cl	H	H	Cl	$C_{11}H_9Cl_3O_2$	277.97	278/280(8.6/8.6); 243/245(32.9/21.1); 215/217(100/62.2)
8	H	H	Cl	H	CH_3O	H	H	$C_{12}H_{13}ClO_3$	240.06	240/242(6.9/2.3); 205(61.8); 195/197(28.3/9.6); 177(100)
9	H	H	H	OCH_2O		H	Cl	$C_{12}H_{11}ClO_4$	254.03	254/256(13.2/4.8); 219(48.8); 191/193(100/11.6)
10	H	H	Br	H	H	H	H	$C_{11}H_{11}BrO_2$	253.99	254/256(4.8/4.9); 209/211(17.2/17.6); 176(4.3); 175(34.1); 148(10.5); 147(100)
11	H	H	H	Br	H	H	H	$C_{11}H_{11}BrO_2$	253.99	254/256(42.0/41.0); 226/228(28.6/27.8); 209/211(92.3/90.5); 181/183(21.0/21.9); 102(100)
12	H	H	F	H	H	H	H	$C_{11}H_{11}FO_2$	194.07	194(31.1); 195(3.4); 166(13.2); 149(100)
13[c]	CH_3	H	Cl	H	H	H	H	$C_{12}H_{13}ClO_2$	224.06	224/226(3.3/1.1); 189(11.0); 161(100)
14[c]	H	CH_3	Cl	H	H	H	H	$C_{12}H_{13}ClO_2$	224.06	224/226(3.0/1.0); 189(52.0); 179/181(28.0/8.0); 161(100)
15	CH_3	CH_3	Cl	H	H	H	H	$C_{13}H_{15}ClO_2$	238.08	238(0.7); 203(59.9); 193/195(22.5/7.4); 175(100)

[a] MM, molecular mass (Da), monoisotopic.

[b] Ions are given in Thompson (Th, mass to charge ratios), with the relative abundance of each ion normalized to the base peak shown in parentheses.

[c] Compounds are a mixture of *cis* and *trans* isomers, which had identical fragmentation.

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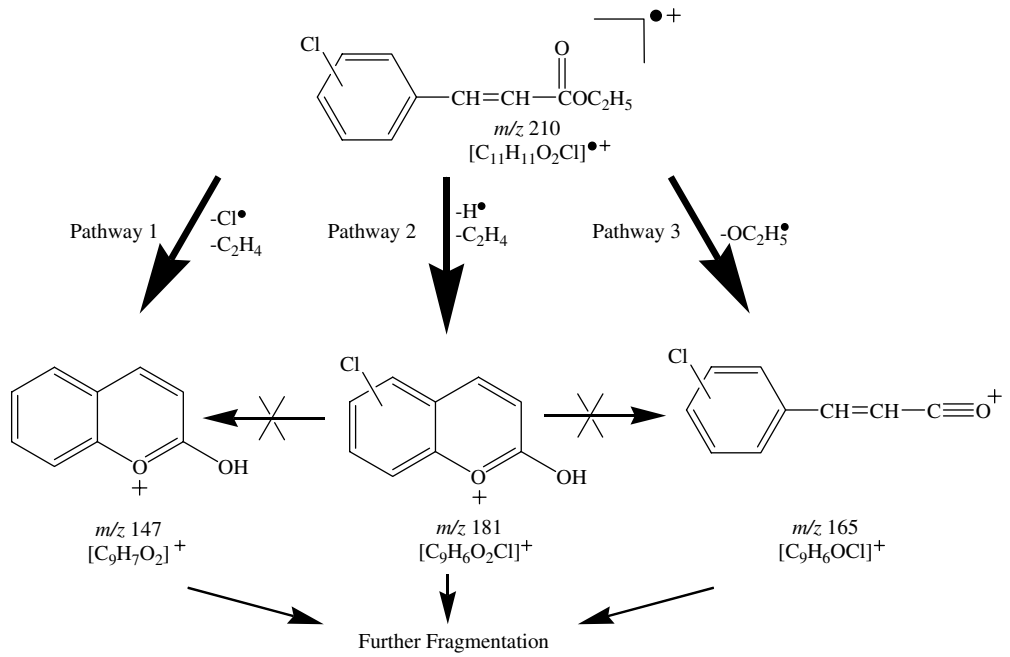

Scheme 2. Fragmentation pathways for the chlorine-substituted ethyl 3-(2-chlorophenyl)propenoate. Pathway 1 is mainly observed for *ortho*-substituted compounds, whereas Pathways 2 and 3 are for *meta*- or *para*-substituted compounds.).

a coumarin. We did not observe a coumarin for 3-(2-fluorophenyl)propenoate ethyl ester (m/z 146), which instead fragmented similar to the *m*- and *p*-chlorocinnamic acids reported by Schaldach and Grützmacher (pathway 3),[8] producing a peak at m/z 166. This peak was most likely the 2-fluorocinnamic acid ion, which further fragments to form the 2-fluorocinnamoylium ion (m/z 149). This lack of fragmentation is most likely due to the stronger C–F bond energy compared to C–Cl or C–Br.[20]

Compound **6** with a chlorine in the 4-position did not exhibit significant chlorine loss, instead losing a 45 Da fragment ($[M]^{\bullet+} - C_2H_5O^{\bullet}$) via pathway 3 to give the 2-chlorocinnamoylium ion base peak (m/z 165). The chloro-substituted benzopyrylium ion was not observed (m/z 181) and the compound instead lost C_2H_4 (28 Da) to give the 2-chlorocinnamic acid ion (m/z 182). The mass spectrum of **7** provides an interesting comparison to the data discussed previously for **4**. Both of these compounds have chlorine substituents in the 2- and 3-positions of the phenyl ring and exhibit simultaneous loss of 63 Da ($[M]^{\bullet+} - C_2H_4 - Cl^{\bullet}$) to form their respective base peaks (pathway 1). However, the mass spectrum of **7**, in contrast to **4**, shows selective chlorine loss from the molecular ion (m/z 278) to give m/z 243 (32.9%) as opposed to **4** for which no selective chlorine loss was observed. The fragmentation of compound **7** is consistent with compound **5** in that the base peak consists of a benzopyrylium ion, which in this case is the dichloro-substituted 2-hydroxybenzopyrylium cation (pathway 2). This fragmentation pattern is particularly interesting in that the presence of multiple halogen substituents does not interfere with the previously observed fragmentation pathway in which *ortho*-substituted compounds fragment via pathway 1.

Compounds **8** and **9** are structurally related; however, **8** has a single electron-donating methoxy substituent while **9** contains a mixture of electron-donating (*para*) and electron-withdrawing (*meta*) groups in the benzo[d][1,3]dioxole substituent. The benzo[d][1,3]dioxole ring in **9** provides similar substituent electronic effects as occurs in the dichlorodibenzodioxin in **1**. Hence, it is not unexpected that **9** shows significant loss of *ortho* chlorine from the molecular ion (m/z 254) to give m/z 219 (48.8%). Again, as in the previous structure, there is also loss of 63 Da to provide the base peak at m/z 191 (pathway 1). However, the lack of the electron-withdrawing oxygen in the *meta* position in **8** did not prevent the loss of chlorine from the molecular ion (m/z 240) to give m/z 205. This observation demonstrated that the mixture of electron-donating and electron-withdrawing oxygens present in the dioxin structure (**1–4**) were not necessary for the characteristic loss of the chlorine. Similar results were observed with **5**, which does not contain an oxygen substituent, and had essentially the same fragmentation pattern as molecules containing either one or two oxygen substituents on the phenyl ring. Both **8** and **9** produced the equivalent substituted benzopyrylium ion as the base peak (m/z 177 and 191, respectively), showing that benzopyrylium ion formation is variable and does not depend upon an unsubstituted phenyl ring.

Structures **13**–**15** were prepared to investigate whether steric effects, resultant from the replacement of the hydrogens on the olefinic side chain with methyl groups, affected the mass spectral fragmentation. All three structures lost the characteristic *ortho* chlorine to some extent. Compound **14** (*β*-methyl) and **15** (*α*,*β*-methyl) had higher abundance ions from loss of 35 Da (*β*-methyl, 52%; *α*,*β*-methyl 60%) than **13** (*α*-methyl, 11%). There are minimal steric effects on chlorine loss. These results agree with those of Madhusudanan *et al*.[9] who showed that phenyl substitution on the olefin of cinnamic acid (*α*-phenylcinnamic acid) also resulted in the phenyl-substituted benzopyrylium ion (m/z 223).

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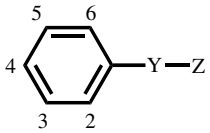
Table 4. Mass spectral data for structures related to substituted ethyl 3-phenylpropenoates



No.	2	3	4	5	6	Y	Z	Formula	MM[a]	Ion (% abundance)[b]
16	Cl	H	H	H	H	CH=CH	CN[c]	C_9H_6ClN	163.01	163/165(53.8/17.3); 136/138(8.3/2.8); 128(100)
17	H	H	Cl	H	H	CH=CH	CN[c]	C_9H_6ClN	163.01	163/165(100/33.0); 136/138(20.2/6.9); 128(97.0)
18	Cl	H	H	H	H	CH=CH	$C(O)CH_3$	$C_{10}H_9ClO$	180.03	180/182(9.4/3.1); 165/167(28.9/9.7); 145(100)
19	H	H	Cl	H	H	CH=CH	$C(O)CH_3$	$C_{10}H_9ClO$	180.63	180/182(28.3/9.9); 165/167(100/33.0); 145(37.6)
20	Br	H	H	H	H	CH=CH	$C(O)CH_3$	$C_{10}H_9BrO$	223.98	224/226(4.7/4.7); 209/211(13.1/12.6); 181/183(10.1/9.7); 145(100); 102(40.3)
21	H	Br	H	H	H	CH=CH	$C(O)CH_3$	$C_{10}H_9BrO$	223.98	224/226(21.8/21.1); 209/211(61.4/59.9); 181/183(20.3/20.9); 145(68.7); 102(100)
22	H	OCH_2O	H	Cl		CH=CH	CH_2OH	$C_{10}H_9ClO_3$	212.02	212/214(31.1/13.3); 196/198(30.5/9.3); 169/171(100/32.1)
23	H	OCH_2O	H	Cl		CH_2CH_2	CH_2OH	$C_{10}H_9ClO_3$	214.04	214/216(37.2/12.8); 169/171(100/32.8)
24	Cl	H	H	H	H	CH_2CH_2	$CO_2C_2H_5$	$C_{11}H_{13}ClO_2$	212.06	212/214(1.1/0.4); 177(100); 167(20.6); 149(76.7)
25	H	Cl	H	H	H	CH_2CH_2	$CO_2C_2H_5$	$C_{11}H_{13}ClO_2$	212.06	212/214(36.5/12.4); 167/169(14.1/4.5); 138/140(100/35.4); 141(44.4)
26	Cl	H	H	H	H	CH_2	$CO_2C_2H_5$	$C_{10}H_{11}ClO_2$	198.04	198/200(1.6/0.5); 163(35.4); 135(8.3); 125(100)
27	H	Cl	H	H	H	CH_2	$CO_2C_2H_5$	$C_{10}H_{11}ClO_2$	198.04	198/200(73.4/31.6); 153/155(11.2/3.1); 125/127(100/35.7)
28	Cl	H	H	H	H	CH_2	CO_2CH_3	$C_9H_9ClO_2$	184.62	184/186(5.2/1.7); 149(80.7); 125(100)
29	Cl	H	H	H	H	C≡C	$CO_2C_2H_5$	$C_{11}H_9ClO_2$	208.03	208/210(10.1/2.8); 163/165(87.5/30.6); 136/138(100/33.4)
30	H	H	Cl	H	H	C≡C	$CO_2C_2H_5$	$C_{11}H_9ClO_2$	208.03	208/210(14.6/4.8); 163/165(91.9/31.3); 136/138(100/33.4)

[a] MM, molecular mass (Da), monoisotopic.

[b] Ions are given in Thompson (Th, mass to charge ratios), with the relative abundance of each ion normalized to the base peak shown in parentheses.

[c] Compounds are a mixture of *cis* and *trans* isomers, which had identical fragmentation.

The reason for the lower abundance of the ion resulting from chlorine loss from **13** compared to **14** or **15** is unknown. It would be expected that steric congestion is greatest for **15**, which contains methyl substituents at both the α- and β-positions. However, the data for **15** are most similar to those for **14**, which contains a methyl in the β-position. All three of these structures have a base peak that results from the simultaneous loss of 63 Da ($[M]^{\bullet+}-C_2H_4-Cl^{\bullet}$), corresponding to their equivalent methyl-substituted benzopyrylium ions formed from pathway 1 (m/z 161 for **13** and **14**, m/z 175 for **15**).

Other analogs related to ethyl 3-phenylpropenoates

Compounds **16** and **17**, which have a nitrile in place of the ester group, contain the chlorine substituent in the 2- and 4-positions, respectively (Table 4). The mass spectra for these two structures were similar, with the molecular ion (m/z 163) losing chlorine to give (m/z 128), which was the base peak for **16** and 97.0% abundant for **17**. A similar fragmentation pattern was reported for 1-cyano-2-phenylethylene methyl ester, which also produced the m/z 128 fragment.[7] These nitrile-substituted olefins were the only compounds in this study that exhibited 100% chlorine loss in the *para* position. Another interesting observation is that compound **17** fragmented less than **16**, with similar trends repeated for compounds **18** and **19** as well as **5** and **6**. These data consistently show that less fragmentation is observed when chlorine is in the *para versus ortho* position.

In compounds **18**–**21**, the ester functionality was replaced with a methyl ketone to test if other carbonyls could cause the characteristic halogen loss. It was speculated that the ketone in a substituted 4-phenylbut-3-en-2-one, with an oxygen in a similar sp^2 hybridization as the carbonyl oxygen of the ester, might facilitate the loss of the halogen. Compound **18**, with a chlorine substituent located in the 2-position of 4-phenylbut-3-en-2-one, underwent significant loss of 35/37 Da. The loss of 15 Da from the molecular ion (m/z 180) provided an ion at m/z 165 suggesting loss of a methyl group, which is to be expected from a terminal methyl ketone. These data agree with the ester-containing **5**, which also lost the 2-chloro fragment. The methyl ketone was, therefore, able to effect the same unique fragmentation as an ester moiety. However, compound **19**, which had the chlorine substituent in the 4-position, also lost a significant amount of chlorine unlike **6**. Interestingly, **19** exhibited less chlorine loss then **18** (37.6% *vs* 100% respectively). The phenomenon was further examined with compounds **20** and **21**, which contain bromine substituents in the 2- and 3-positions of 4-phenylbut-3-en-2-one. Both compounds selectively lost the bromine constituent (79/81 Da), concurring with that observed for the ester-containing **10**, which also lost bromine from the 2-position. The observed amount of halogen loss was similar to compounds **18** and **19**, in that halogen substitution in the 2-position resulted in 100% loss (base peak), whereas substitution in the 3-position (**21**) or 4-position (**19**) had significantly less halogen loss. All four compounds **18**–**21**

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formed the methyl benzopyrylium ion (m/z 145), which was either the base peak or second most abundant peak (pathway 1).

Compounds **22** and **23** contain a 1,3-dioxole substituent and are similar to **9** in structure. However, both of these compounds contain a primary alcohol moiety instead of the ester. Compound **22** still contains the olefin (molecular ion m/z 212) and did not readily lose the characteristic chlorine. Compound **23** is the saturated analog of **22** and did not lose the 2-chloro substituent either, instead losing 45 Da to give a base peak at m/z 169. A significant ion was observed at m/z 171 indicating loss of the saturated ethylene spacer (43 Da) from the molecular ion (m/z 214). Both **22** and **23** have the same base peak (m/z 169), which retains the chlorine substituent and may be a stable benzyl or rearranged tropylium cationic species $[C_8H_6ClO_2]^+$. Neither compound formed the benzopyrylium ion intermediate.

The mass spectra of four additional structures were used in the investigation of the effect of two (**24, 25**) and one (**26, 27**) carbon-saturated spacers between the ester and the phenyl ring on the fragmentation pattern. Comparison of the mass spectral data for **24** and **26** again shows that loss of 35/37 Da occurs to a significant extent when the chlorine is in the 2-position of the phenyl ring, but not in the 3-position (compounds **25** and **27)**. This observation shows that it is possible to have a variable length spacer between the ester and phenyl ring and still achieve chlorine loss. Compound **24** formed the saturated analog of the benzopyrylium ion of compound **5** (m/z 149). Compound **25** fragmented similar to the *m*-chlorocinnamic acid reported by Schaldach and Grützmacher[8] and **26** formed the benzofuran analog (m/z 135), which had also been previously reported.[21] The mass spectra of 2- and 3-chlorobenzoic acid were downloaded from the National Institute of Standards and Technology (NIST) EI-MS library, and neither one showed selective loss of chlorine. Examination of the acid derivatives of halogen-displacing compounds in this study showed that the acid forms also lost the halogen (data not shown) as had been earlier reported.[8] Therefore, the fact that 2-chlorobenzoic acid did not lose chlorine suggests that compounds lacking at least one carbon spacer are unable to displace the halogen. This observation is most likely due to the ring being sterically unable to form a 4-membered structure. Compound **28** (the methyl ester of **26**) shows that the carbonyl of the methyl ester is also efficient at effecting chlorine loss in the 2-position. However, compound **28** did not evidence direct loss of the methyl ester (seen as loss of methanol as was observed with *o*-hydroxy cinnamic acid methyl esters.[22] These data further support the hypothesis that the loss of halogens, and chlorine in particular, occurs through a concerted mechanism.

The alkane analogs with 1 or 2 carbons between the phenyl ring and ester function both underwent significant halogen loss, indicating that the length of the spacer can be somewhat flexible. These analogs are less rotationally constrained compared to the esters with a *trans* olefinic linkage and it is not necessary to undergo the initial olefin-isomerization step. This observation may be reflected in the relative ion abundances of different fragments. Compound **5** contains an olefin and has loss of 63 Da as the base peak ($[M]^{\bullet+} - C_2H_4 - Cl^{\bullet}$) as opposed to **24**, the saturated analog, which has loss of 35/37 Da as the base peak ($[M]^{\bullet+} - Cl^{\bullet}$). The less constrained alkane can more easily effect sole loss of chlorine, whereas the *trans* olefin must undergo isomerization first thus producing more of the 63 Da fragment. The intermediate proposed in Scheme 1 may also form a 5-membered ring as suggested by the results for **26**.

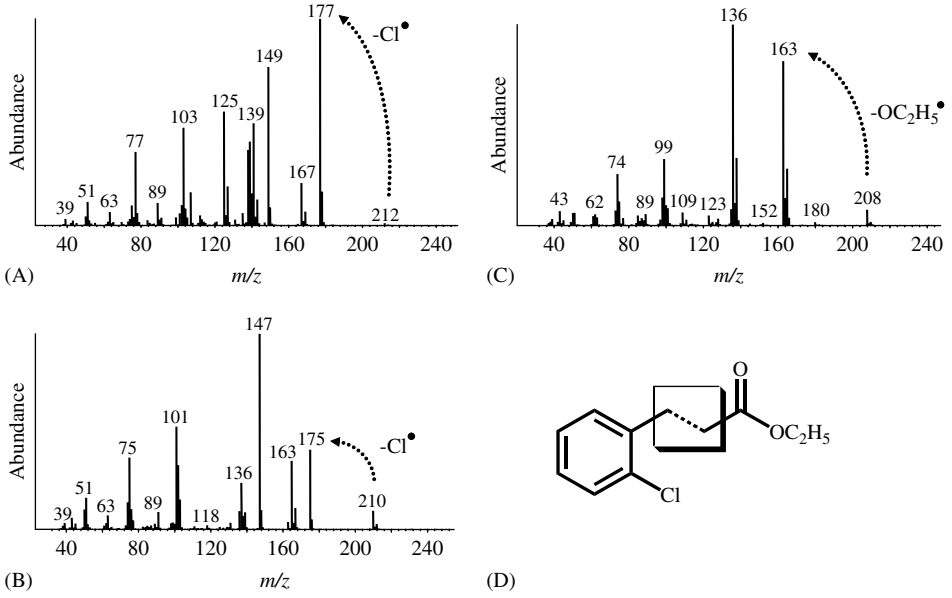

Figure 3. Mass spectral fragmentation of (A) ethyl 3-(2-chlorophenyl)propanoate (compound **24**), (B) ethyl 3-(2-chlorophenyl)propenoate (compound **5**), and (C) ethyl 3-(2-chlorophenyl)propynoate (compound **29**). Spectra A and B show the characteristic chlorine loss from the molecular ion to give *m/z* 177 and 175 respectively, while spectra C does not show loss of chlorine. The 2-hydroxybenzopyrylium cation is observed in spectra B (*m/z* 147) and the saturated analog is observed in spectra A (*m/z* 149), whereas no corresponding ion is observed in spectra C. Figure (D) gives the base structure of compounds **24**, **5** and **29**, and the boxed area highlights the region of variable saturation.

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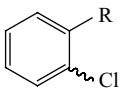
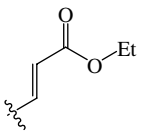
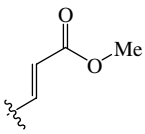
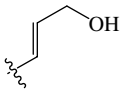
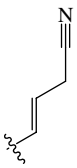
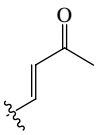
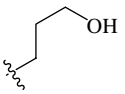
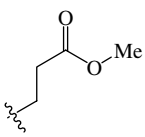
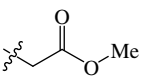
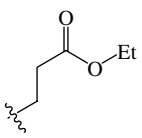
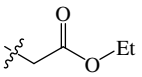
Table 5. Atomic charges and molecular ionization potentials calculated using density functional theory. The atomic charges listed are for the atom presumed to be involved in halogen displacement (usually the carbonyl oxygen)



		Ortho[a]				*Meta*				*Para*			
R	No.	Charge[b] (neutral)	Charge (cation)	Excess α spin[c]	IE[d]	Charge (neutral)	Charge (cation)	Excess α spin	IE	Charge (neutral)	Charge (cation)	Excess α spin	IE
	**31**	−0.61	−0.54	0.10	−186.1	−0.61	−0.54	0.09	−187.9	−0.61	−0.55	0.09	−183.7
	**32**	−0.60	−0.54	0.10	−187.1	−0.61	−0.54	0.09	−188.8	−0.61	−0.54	0.09	−184.6
	**33**	−0.75	−0.71	0.03	−177.8	−0.75	−0.71	0.03	−179.2	−0.75	−0.72	0.02	−175.2
	**34**	−0.30	−0.12	0.26	−194.0	−0.30	−0.12	0.23	−195.5	−0.31	−0.13	0.24	−191.1
	**35**	−0.55	−0.40	0.28	−186.4	−0.55	−0.40	0.27	−188.3	−0.56	−0.42	0.23	−184.4
	**36**	−0.75	−0.63	0.17	−189.2	−0.75	−0.63	0.16	−189.8	−0.75	−0.64	0.15	−186.2
	**37**	−0.60	−0.52	0.13	−192.5	−0.60	−0.52	0.13	−192.2	−0.60	−0.53	0.11	−189.3
	**38**	−0.59	−0.54	0.09	−193.3	−0.60	−0.54	0.15	−191.3	−0.61	−0.55	0.07	−190.5
	**39**	−0.60	−0.51	0.15	−191.5	−0.60	−0.52	0.15	−191.2	−0.60	−0.53	0.13	−188.3
	**40**	−0.61	−0.53	0.11	−191.9	−0.61	−0.53	0.17	−190.2	−0.61	−0.53	0.10	−189.3

[a] *Ortho, meta* and *para* refer to the position of the chlorine substitution on the phenyl ring.
[b] Charge units are electrons (e).
[c] Units are electrons (e).
[d] Ionization energy, units are kcal/mole.

Compounds **29** and **30** are the 2- and 4- chlorine substituted 3-phenyl alkynoate esters, which have nearly identical mass spectra. The molecular ion (m/z 208) loses a 44 Da fragment, suggesting loss of the ester moiety to provide a m/z 163 ion with ~90% abundance for both the compounds. This fragment does not undergo the characteristic chlorine loss seen for the propenoic and propanoic acid esters (Fig. 3). Examination of the mass spectrum of ethyl 3-phenylpropiolate from the NIST library showed loss of 45 Da as the base peak, indicating that cleavage of the ester linkage is the major route of fragmentation for these structures. The observation that the 2-chloro substituted alkyne ester does not preferentially lose chlorine is likely related to the sp geometry of the alkyne

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linkage between the ethyl ester and the phenyl ring. This rigid spacer prevents the carbonyl of the ester moiety from interacting with the halogen in the 2-position (Fig. 3).

Density functional theory calculations

A particularly interesting observation was the position-dependent loss of chlorine from the different structures examined. Both the chemical moiety attached to the olefin as well as the position of the halogen on the phenyl ring appeared to affect the overall percentage of halogen loss. To further examine this effect, we calculated a number of chemical properties that may be associated with the fragmentation process. These properties include the electronic charge on the atom assumed to be involved in halogen displacement – in most cases the carbonyl oxygen – for both the neutral and cationic forms of the molecule. We also calculated the excess α-spin on the relevant atom (for the cationic form) and overall ionization energy of the molecule. These calculations were performed with the halogen (chlorine) in the *ortho, meta*, and *para* positions (Table 5). There were essentially no differences between charges calculated on the presumed reactive atom as the chlorine position was varied from *ortho* to *meta* and *para*, and only small differences were observed in the excess α -spin and ionization energy. This suggests that any differences in halogen displacement for these different isomers are because of nonelectronic effects.

The predicted atomic charges for neutral and cationic forms of the molecules are strongly correlated ($R^2 = 1.000$) and, therefore, only the cation data are shown in Fig. 4. In the following analysis, we will assume that the net charge on an atom is indicative of its electrophilicity, and that an atom with a more negative charge is less electrophilic. The net atomic charge of the key atom proposed to be involved in the halogen displacement (usually the oxygen, except for the nitrile-containing compounds **16** and **17**) was found to be correlated with both the selectivity and % of halogen displacement. The only compound not capable of effecting chlorine displacement was the primary alcohol, which was the most negatively charged proposed electophilic atom (−0.71 e), as opposed to the nitrile (−0.12 e) that effected 100% chlorine loss in both *ortho*- and *para*-substituted compounds. Both the unsaturated and saturated ethyl 3-(4- or 3-chlorophenyl)propenoate compounds (**6** and **25**) did not evidence any chlorine loss as would be expected, given that the halogen was not in the *ortho* position. However, the ketone (**18**) contained sufficient electrophilicity to effect some chlorine loss (37%) and the nitrile exhibited 100% loss for *para* chlorine. Results from these calculations indicate that there is a correlation between the net charge on the presumed halogen-displacing atom and the loss of chlorine, and therefore provide support for the proposed electrophilic mechanism for the formation of the benzopyrylium ion.

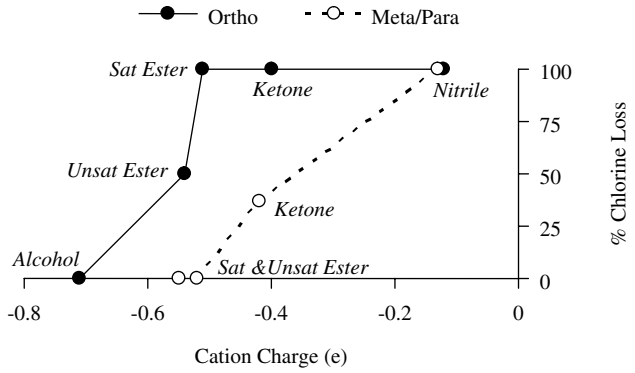

Figure 4. Relationship between % of chlorine loss and the charge on the cation of the chemical moiety attached to the phenyl ring. Cation charges are from Table 5 using either the *ortho*, *meta* or *para* values as appropriate for the following compounds: Unsat ester (**31**), alcohol (**33**), nitrile (**34**) and ketone (**35**), and sat ester (**39**). The % chlorine loss values are from Tables 3–5 and for *ortho* values include compounds **5**, **16**, **18**, **22** and **24**; for *meta* values include compound **25**; for *para* values include compounds **6**, **17** and **19**. Nitrile-containing compounds exhibited 100% chlorine loss with substitution in either the *ortho* (**16**) or *para* (**17**) position. Sat, saturated; Unsat, unsaturated.

CONCLUSIONS

The observation of an interesting mass spectral fragmentation with loss of 35/37 Da for substituted *ortho*-chlorinated dibenzodioxin propenoate esters lead to an exploration of the structural fragmentation requisites using a series of substituted ethyl 3-(substituted phenyl)propenoates. A proposed mechanism, based upon previous studies, suggests that an ester moiety linked to a phenyl ring facilitates halogen loss from the 2-position. With respect to halogen substitution, chlorine and bromine, but not fluorine (substituents on phenyl) in the 2-position are lost. Methyl substituents on the olefin of ethyl 3-(2-chlorophenyl)propenoate did not preclude chlorine loss. Saturation of ethyl 3-(2-chloropheny)propenoate to give ethyl 3-(2-chloropheny)propanoate also resulted in preferential *ortho* chlorine loss. In addition, reduction in the spacer length between the ester and phenyl ring to form ethyl 2-chlorophenyl acetate also provided the characteristic chlorine loss. Positioning of the halogens in the 3- or 4-position of the phenyl ring resulted in other fragmentations, such as cleavage of the ester with a loss of 45 Da. The replacement of the ester moiety in ethyl 3-(2-chlorophenyl)propenoate with a methyl ketone, but not a primary alcohol, also resulted in selective chlorine loss. The substitution of a nitrile for the ester moiety resulted in isomer nonspecific chlorine loss in both the 2- and 4-positions of the phenyl ring. Finally, ethyl (2-chlorophenyl)propynoate did not lose chlorine, indicating that the rigid alkyne spacer with sp bond geometry between the phenyl ring and the ester prevents the ester-facilitated loss of chlorine from the 2-positon of the phenyl ring. These results suggested that geometric constraints are important because rigid sp-hybridized groups are too inflexible to allow the carbonyl oxygen to be in the required position to effect the loss of the halogen. However, these data show that the selective chlorine loss from the 2-position of the phenyl ring is only achieved by the ester moiety and that other sp^2 hybridized atoms or moieties in the spacer are unable to effect the chlorine loss.

Further work could examine the effects of increased spacer length and ring saturation upon halogen loss. The

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increased electrophilicity of the cation involved in halogen displacement resulted in decreased selectivity of halogen loss (in terms of *ortho versus meta* or *para*) and increased percentage of halogen loss. Examination of the structural requirements for the preferential loss of a phenyl ring halogen *ortho* to a variable spacer arm showed that this process can only be selectively achieved by an ester moiety. Results showed that a number of different chemical moieties were capable of effecting the intramolecular radical substitution to form a substituted benzopyrylium ion. These observations greatly expand earlier studies that had focused on only esters and acids. The correlations between cation charge (electrophilicity) and selectivity of halogen loss were very strong, providing support for the proposed intramolecular radical substitution.

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