of **11.** The NMR spectrum shows a doublet at δ 5.92 ppm (J = 16 Hz) indicative of the trans geometry of the double bond. With **11** in hand, successful deblocking would now afford nitrone ester **2.** Indeed, we were able to deblock **11** under conditions which would simultaneously promote the intramolecular cycloaddition to follow and thereby produce cycloadduct **3.** Thus, a dilute solution of the unsaturated isoxazolidine **11** was refluxed in xylene to produce **3** in 66% yield. A one-proton doublet at δ 4.94 ppm (J = 5 Hz) was assigned to the C-1 proton. A one-proton doublet of doublets at δ 1.24 (J = 3, 12.5 Hz) was assigned to the endo proton at C-9. In addition, one-proton multiplets at δ 3.52 and 3.86 ppm were assigned to the methine protons at C-6 and C-3, respectively. The spectrum also contains a three-proton singlet at δ 3.67 ppm due to the carbomethoxyl group. The IR spectrum exhibits the expected carbonyl band at 5.79 μ.

The route described above provides adduct **3** in 40% overall yield from the readily available methyl 3-butenoate. This adduct has already been converted by us[6] into *dl*-cocaine by methylation, hydrogenolytic cleavage of the nitrogen–oxygen bond, and benzoylation.[3] The overall approach provides a stereospecific synthesis of *dl*-cocaine in very high overall yield.

Acknowledgment. We thank the National Institutes of Health (CA 14611) for financial support, the Allied Chemical Corp. for a fellowship to one of us (G.B.M.), and the National Science Foundation for their help in providing both a Varian T-60 and a Varian XL-100 NMR spectrometer to the Department of Chemistry.

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Substrate Selectivity and Orientation in Aromatic Substitution by Molecular Fluorine

Sir:

In sharp contrast to the wealth of information on aromatic substitution by other molecular halogens,[1] and despite the theoretical relevance of the problem,[2] no kinetic or mechanistic data are currently available concerning aromatic substitution by elemental fluorine. Apparently, the widespread and time-honored[3] notion that interaction of F_2 with organic compounds is a violent and uncontrollable process, leading frequently to explosions and almost invariably to the destruction of the substrate, has hampered mechanistic studies, despite substantial improvements of the experimental techniques to tame the reactivity of F_2,[4] and reports of successful preparative approaches to direct liquid-phase fluorination of aromatics.[5]

Table I. Reactivity Relative to Benzene and Isomeric Composition of Products in Aromatic Substitution by Dilute Elemental Fluorine in CCl_3F at −78 °C

Substrate C_6H_5X, X	$k_{C_6H_5X}/k_{C_6H_6}$	Isomeric composition of C_6H_4XF, %		
		Ortho	Meta	Para
CH_3[a]	4.70 ± 0.05[b]	60 ± 2	11 ± 1.5	29 ± 2
NO_2[c]	0.017 ± 0.004	9 ± 2	80 ± 3	11 ± 2
OCH_3[d]	54 ± 2	76 ± 3	0.5 ± 0.1	23.5 ± 2

[a] The search for reaction products, and their identification, was carried out with several columns. For instance, in the analysis of the fluorination products from the C_6H_6/C_7H_8 pair, the following columns were used: 12 m, Carbowax 20M, packed; 200 m, squalane, capillary; 1 m, SE-30, packed; 50 m, OV-17, capillary; 100 m, DC 702, capillary; 33 m, Carbowax 20M, SCOT, with mass spectrometric analysis of effluents. Quantitative analysis was achieved with a 76-m Carbowax 20M SCOTT column at 75 °C, until fluorotoluenes were eluted, then at 130 °C for elution of benzyl fluoride. Analysis with a short SE-30 column at high flow rates operated at 300 °C failed to detect any other high boiling or relatively nonvolatile products. These numerous column systems were used to avoid fortuitous lack of detection of other volatile products, if any, under solvent peaks. [b] Referred exclusively to ring fluorination. Benzyl fluoride was also identified in amounts corresponding to ~20% of the combined yields of ring substituted fluorotoluenes. It is a minor product under these reaction conditions. [c] Quantitative analysis on a 61-m Carbowax 20M SCOT column at 130 °C. [d] Quantitative analysis on a 30-m Carbowax 20M SCOT column, in series with a 15-m DEGS capillary column at 90 °C.

We wish to report the preliminary results of a study on substrate selectivity and orientation in aromatic substitution by elemental fluorine. Fluorine (Matheson Co.) having a stated purity of 98.5 mol %, containing N_2 and O_2 as the major impurities, was diluted with a large excess of an inert gas (Ar or N_2), the F_2 concentration being typically 0.75 mol % (determined by iodometric titration[6]). The gas scrubbed of HF by passage through a NaF trap was slowly bubbled through a dilute (0.01–0.1 M) solution of the aromatic substrate(s) in inert solvents (CCl_3F, CH_3CN, C_6F_6, or C_7F_8) maintained at low temperature (typically −78 °C). The purity of the solvent and of the substrate(s) was determined by GLC, on the same columns used for the analysis of products. The reactions were carried out in the dark, at extremely low [F_2]:[substrate] ratios, calculated to obtain correspondingly low substrate conversions, approaching the limit of analytical sensitivity. Typical conversions were below 0.01%, rising only in a few cases to 0.1–0.3%. Such stringent conditions were chosen to minimize further interaction between F_2 and primary fluorination products, to achieve effective *local* control of temperature, and to reduce *local* modifications of the reaction medium by products, e.g., HF.

It should be emphasized that the results reported in this contribution are typical of aromatic fluorination carried out at low temperatures, in the dark, at nearly "infinite" F_2 dilution, and at substrate conversions approaching zero. An entirely different product pattern is obtained from reactions performed under photochemical, or preparative conditions, or at considerably higher [F_2]:[substrate] ratios, characterized by the occurrence of polymerization, addition, predominant side-chain attack, etc., at the expense of ring substitution.[4,5]

When the desired conversion was accomplished, the cold solution was thoroughly outgassed with dry N_2 and allowed to come to room temperature and the products were analyzed by GLC, using a Model 900 Perkin-Elmer chromatograph equipped with capillary columns and an FI detector.

The products were identified by comparison of their retention volumes with those of authentic samples, and their yields

Table II. Effect of Solvent and Reaction Temperature on the Competitive Fluorination of Benzene and Toluene

Solvent	t, °C	kT/kB	Isomeric composition of fluorotoluenes, %		
			Ortho	Meta	Para
C_7F_8	40	2.4 ± 0.3	54 ± 2	17 ± 2	29 ± 2
C_6F_6	0	2.7 ± 0.3	52 ± 3	15 ± 2	33 ± 2
C_7F_8	0	2.8 ± 0.2	56 ± 3	15 ± 2	29 ± 2
CCl_3F	0	4.2 ± 0.3[a]	60 ± 3	13 ± 2	27 ± 2
CH_3CN	−23	3.4 ± 0.4	56 ± 2	14 ± 2	32 ± 2
CCl_3F	−23	4.2 ± 0.3	62 ± 3	11 ± 1	27 ± 2
CCl_3F	−78	4.70 ± 0.05[b]	60 ± 2	11 ± 1.5	29 ± 2
CCl_3F	−97	5.2 ± 0.2	60 ± 3	9 ± 2	31 ± 3
CH_2F_2	−154	5.9 ± 0.3	59 ± 3	7 ± 2	34 ± 3

[a] Yield of benzyl fluoride at this temperature ≃50% of the combined yields of fluorotoluenes. [b] Yield of benzyl fluoride at this temperature ≃20% of the combined yields of fluorotoluenes.

calculated from the areas of the corresponding elution peaks, making use of individual calibration factors to correct for the variable FID to the different products.

In several cases, the identification of the products was confirmed using a Hewlett-Packard Model 5985A mass spectrometer, equipped with a dual CI/EI source. Except in the case of toluene, where measurable but small yields of benzyl fluoride were obtained (vide infra), ring-substituted monofluorinated products were the only ones detected in significant amounts by GLC.

Table I summarizes the results of the competition experiments involving benzene and, respectively, toluene, nitrobenzene, and anisole. The data listed are the mean values of the results from separate competitive fluorinations, where the relative concentrations of the two substrates was systematically varied over a range that covered, for the benzene/toluene pair, almost three orders of magnitude. In all cases, such changes in the relative concentrations failed to significantly affect the ratio of rate constants, consistent with a first-order dependence of the fluorination rate on the concentration of the aromatic substrate.

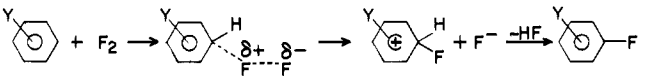
The relative reactivity of the substrates listed in Table I, namely nitrobenzene ≪ benzene < toluene ≪ anisole, together with the substituent orientations observed, predominantly meta in nitrobenzene and ortho–para in toluene and anisole, characterizes the aromatic halogenation by elemental fluorine as a typical, if highly unselective, electrophilic substitution.

Table II illustrates the influence of the reaction temperature and the nature of the solvent[7] on the selectivity of the fluorination. It is worth noting that the extreme reactivity of F_2 allows investigation over an unusually wide temperature range, the lower limit being in most cases the temperature at which the solvent freezes. Incidentally, the temperature of −153.7 °C, used in the experiments where difluoromethane was the solvent, represents perhaps the lowest ever reported in the study of aromatic substitution. From the data of Table II the F_2 selectivity appears to undergo a regular, though modest *increase* as the temperature is decreased, while the selectivity undergoes an appreciable decrease when the reaction is carried out in a more polar solvent (e.g., acetonitrile). The small number of substrates employed in this preliminary study prevents a statistically meaningful derivation of free-energy correlations; it is nevertheless of interest, pending further investigation, to plot the logarithms of the partial rate factors deduced from the data of Table I, namely $f_m = 1.55$ and $f_p = 8.2$ for toluene, $f_m = 0.041$ and $f_p = 0.011$ for nitrobenzene, $f_m = 0.81$ and $f_p = 76.1$ for anisole vs. the appropriate σ^+ values.[1]

In so doing one obtains a surprisingly good fit, resulting in a ρ^+ value of approximately −2.4, for F_2 substitution. This can be regarded as a convenient, if inexact, way to numerically express the highly unselective nature and the extreme electrophilic character of the elemental fluorine reactivity. A comparison with the ρ^+ values of molecular chlorination and bromination, respectively −10.0 and −12.1 in acetic acid/water at 125 °C, shows consistency with the high reactivity, and correspondingly lower selectivity, of molecular fluorine, already demonstrated in electrophilic aliphatic substitution.[8]

In view of the multiple reaction pathways allowed by the chemical reactivity of elemental fluorine, and taking into account the preliminary nature of this report, detailed mechanistic discussion of the aromatic halogenation by F_2 must await the results of further investigation.

However, the present data provide per se some interesting mechanistic clues. *Referring exclusively to ring substitution*, the selectivity of the electrophile, in particular the high meta:para ratio in the fluorination of nitrobenzene, is inconsistent with a radical mechanism involving the intermediacy of fluorocyclohexadienyl radicals.[9] It should again be noted that no "dimers" were found under our reaction conditions. A more plausible mechanism, consistent with the observed orienting effects of both electron-donating and electron-withdrawing substituents, involves the electrophilic attack of a polarized fluorine molecule on the aromatic ring, leading to the formation of an arenium ion and a fluoride ion, possibly forming a "contact" [10] pair in the aprotic solvent.



Further investigation of the mechanistic aspects of direct fluorination of aromatics and extension of the study to a larger number of substrates is currently under way in our laboratories.

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(8) Cf. ref 4a, p 109, and 4b, p 41.
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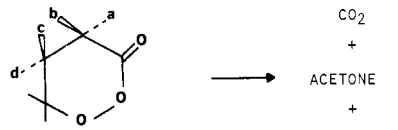
Thermolysis of γ-Peroxy-γ-butyrolactones: Alternate Modes for Fragmentation

Sir:

With acyclic peroxy esters or their cyclic analogues, the peroxylactones, the principal means by which thermal decompositions take place involve O–O bond homolysis followed by or concerted with β scission leading to CO_2 loss.[1] We present evidence here for two alternate fragmentation paths in a series of γ-peroxy-γ-butyrolactones functionally substituted at the β position of the ring.

The thermally induced homolytic cleavages of β-peroxy-β-propiolactones have been studied intensively by Adam.[2] The results of these studies are consistent with a path having O–O bond breaking as the first step followed by a step in which migration of a β substituent is concerted with CO_2 loss. Activation enthalpies for the compounds studied were 31.0–31.7 kcal/mol and $\Delta S^{\ddagger}$ values varied from −1.0 to 0.3 eu.

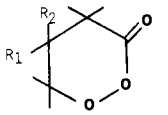
A few γ-peroxy-γ-butyrolactones have been reported[3,4] and Adam and Szendrey[5] have studied the thermolysis of **1a** in detail. The $\Delta H^{\ddagger}$ for **1a** is 34.1 kcal/mol and $\Delta S^{\ddagger}$ is 6.6 eu.



1 a: a, b, c, d = H
b: a, b, c, d = D

Thermolysis proceeds as shown. Consistent with the observation of a secondary deuterium isotope effect of 1.27 ± 0.2 for **1b,** they proposed a reaction path in which C_{acyl}–C_{α} bond breaking is concerted with O–O scission. The mechanism derives further support from the observation that the cis and trans dideuterio derivatives of **1** produce deuterated ethylenes nonstereospecifically, thus ruling out concerted three-bond scission.

We have prepared the γ-peroxy-γ-butyrolactones **2a–d** and studied their thermal fragmentations.[6] The reaction products



2a: $R_1 + R_2 = O$
b: $R_1 + R_2 = CH_2$
c: R_1 = AcO, R_2 = H
d: R_1 = HO, R_2 = H

from **2a** were acetone, tetramethyl-1,3-cyclobutanedione (the dimer from dimethyl ketene) and CO_2. The principal products (>80%) from **2b** are dimethylallene, acetone, and CO_2.

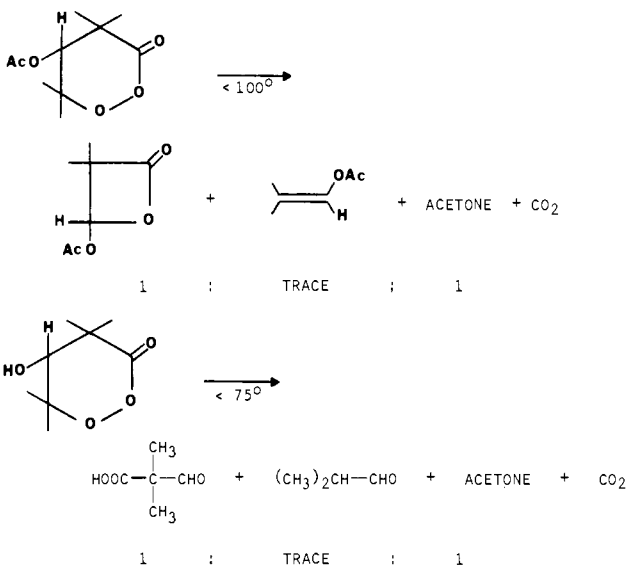
The fragmentations of **2c** and **2d** take a very different course from those of the first two with deketonation being preferred to decarboxylation (Scheme I).[7] Reactions conducted at temperatures higher than those indicated in the sequences in Scheme I do show larger amounts of the enol acetate or isobutyraldehyde. These compounds are formed as decarboxylation products from the β-propiolactone[8] and the malonic aldehydic acid, respectively; however, it is not yet clear whether small amounts of them can be formed directly from **2c** and **2d** by a minor competing thermolysis path.

The thermolyses of compounds **2a–c** in benzene solution follow first-order kinetics. Rate constants were obtained at three temperatures and activation parameters were found as follows: **2a,** $\Delta H^{\ddagger} = 26.96 \pm 0.15$, $\Delta S^{\ddagger} = 5.27 \pm 0.07$; **2b,** $\Delta H^{\ddagger} = 34.18 \pm 0.17$, $\Delta S^{\ddagger} = 8.99 \pm 0.04$; **2c,** $\Delta H^{\ddagger} = 33.15 \pm 0.12$, $\Delta S^{\ddagger} = 0.55 \pm 0.06$. The thermal behavior of **2d** is erratic and we have not been able to obtain satisfactory kinetic data for it. The low temperatures at which complete decomposition[9] of **2d** takes place (1 h at 74 °C in benzene) suggest that this compound may have the lowest $\Delta H^{\ddagger}$ of any γ-peroxylactone yet prepared. Further work on **2d** is in progress.

In a classic work on thermolyses of acyclic peresters Bartlett and Hiatt[10] showed that substituents capable of providing resonance stabilization could effectively lower both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in systems substituted at the acyl center. These observations led to a proposed reaction path in which O–O bond breaking was concerted with CO_2 formation in systems with stabilizing substituents. More recently, Pryor and Smith[11] have proposed a scale for peroxy esters using $\Delta H^{\ddagger}$ values to differentiate one-bond (O–O) cleavage processes from those involving multibond homolyses in the transition state. One-bond cleavage is proposed to obtain for compounds having $\Delta H^{\ddagger} >$ 33 kcal/mol and multibond cleavage is suggested when $\Delta H^{\ddagger} <$ 27 kcal/mol.

Since a limited number of compounds have been studied thus far, such a scale cannot be devised for either the peroxypropiolactones or the peroxybutyrolactones. However, Adam's studies of **1** suggest a lower limit for $\Delta H^{\ddagger}$ for one-bond homolyses with the latter compounds. The observation of a secondary deuterium isotope effect here together with the

Scheme I



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