by GC and ^1H NMR) was used in the formaldehyde exchange experiment. A reaction mixture consisting of **6a**-2,2-d_2 (0.0350 g, 2.34×10^{-4} mol), protioparaformaldehyde (0.0120 g), water (0.010 g, 5.88×10^{-4} mol), and acetonitrile (2.00 mL) was sealed in a Carius tube and heated at 100 °C for 40 h. After cooling, the tube was opened and the acetonitrile was evaporated. Analysis of the product by ^1H NMR indicated that the major product was **6a**-2,2-H_2, thus verifying that formaldehyde exchange does occur under these reaction conditions.

***N*-[(Cumylperoxy)methyl]-*N*-methyl-*p*-toluidine (16b).** This compound was prepared by a modification of the procedure of Kharasch and Fono.[8a] Benzene (15 mL), *N*,*N*-dimethyl-*p*-toluidine (2.57 g, 0.0190 mol), cumene hydroperoxide (8.10 g, 0.0380 mol, based on 60% pure reagent), cuprous chloride (6 mg, 6×10^{-5} mol), and four drops of water were placed in a 50-mL, round-bottom flask equipped with a reflux condenser and stirring bar. The contents were stirred vigorously at 35 °C for 15 h, giving a dark-brown solution. The benzene was removed on a rotary evaporator, and the flask contents were taken up in hexanes. The hexane solution was placed in a freezer until crystallization occurred. The crystals were collected, washed with cold hexanes, and recrystallized from hexanes after filtration of the warm hexane solution (care should be taken not to heat the hexane solution near boiling). A total of four recrystallizations gave colorless crystals, mp 64–65.5 °C, in 42% yield: ^1H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 6.86 (m, 4 H), 5.1 (s, 2 H), 3.07 (s, 3 H), 2.26 (s, 3 H), 1.57 (s, 6 H); IR ($CHCl_3$) 2984, 2924, 1616, 1518, 1448, 1362 cm^{-1}.

Proof of Formation of *N*-[(Cumylperoxy)methyl]-*N*-methyl-*p*-toluidine (16b) in Thermal Reaction of 1b with CHP. An acetonitrile solution containing 0.2 M each of **1b** and CHP was placed in a NMR tube. After the solution was purged with argon for 5 min, the tube was sealed and placed in a 100 °C oil bath. The reaction was monitored by NMR; after 1.5 h, signals corresponding to **16b** were of significant intensity. Heating was stopped, the NMR tube was opened and authentic **16b** was added. The ^1H NMR spectrum was then obtained. All of the appropriate signals corresponding to **16b** increased in intensity, thus verifying its presence in the reaction mixture.

Thermolysis of 2-(Methylphenylamino)ethyl *tert*-Butyl Peroxide (14). In a typical experiment, a 0.1 M acetonitrile solution of **14** was prepared in a volumetric flask. After transfer to a Carius tube, the solution was purged with argon for 10 min. The tube was sealed and placed in a 100 °C oil bath. After heating for 40 h, the tube was opened and the reaction mixture was analyzed by GC and NMR. In variations of this procedure, thermolysis was carried out in acetonitrile containing 0.1 M **1b** or in toluene.

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Registry No. **1a**, 121-69-7; **1b**, 99-97-8; **1b**-d_6, 84895-10-3; **1c**, 2909-79-7; **6a**-2,2-d_2, 84877-51-0; **10a** tosylate, 84877-52-1; **11a**, 84877-53-2; **11b**, 84877-54-3; **14**, 84877-55-4; **16b**, 84877-56-5; cumene hydroperoxide, 80-15-9; formaldehyde, 50-00-0; *p*-toluidine, 106-49-0; methanol-d_4, 811-98-3; potassium *tert*-butoxide, 865-47-4.

Oxidation of *m*-Phenoxytoluene with Ceric Trifluoroacetate

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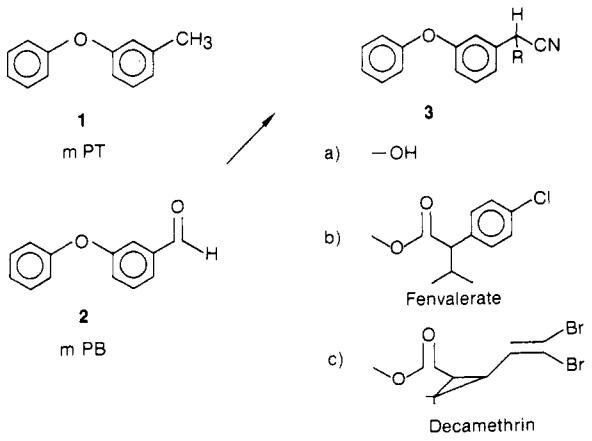
Ceric trifluoroacetate in aqueous trifluoroacetic acid has been found to be especially effective for the oxidation of activated toluenes to the corresponding aldehydes. Ceric ion is consumed in stoichiometric amounts but can be regenerated electrochemically at high current efficiencies (95%). A detailed study of the oxidation of *m*-phenoxytoluene to *m*-phenoxybenzaldehyde is presented. A study of the reaction mechanism, which involves both cations and radical cations, led to a choice of cosolvents which stabilize these intermediates and thus increase the yield of aldehyde formation.

The most potent of the pyrethroid insecticides[1] are based on esters of *m*-phenoxybenzaldehyde cyanohydrin (**3**). Efficient routes to **3** are thus in great demand. The majority of the reported syntheses rely on partial oxidation of *m*-phenoxytoluene (mPT, **1**) to *m*-phenoxybenzaldehyde (mPB, **2**, Scheme I). The most heavily investigated route involves bromination of mPT followed by hydrolysis.[2] Direct aerial oxidation of mPT has received some attention in the patent literature,[3] but like the bromination route it lacks selectivity to mPB. A third approach,[1,4] wherein

Scheme I



mPT is oxidized to *m*-phenoxybenzoic acid (**4**), reduced to *m*-phenoxybenzyl alcohol (**5**), and finally oxidized to mPB, is impractically long. In a recent paper, good yields of **5** as its propionate and butyrate esters were obtained from mPT by using a novel manganic oxidant; however, only 4% mPB was formed.[5] Synthesis of the ether linkage

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(2) (a) E. J. Smutny, T. H. Colby, and E. E. Ryder, Jr., Japanese Patent 54 112 829; *Chem. Abstr.*, **92**, 58429 (1980); (b) P. A. M. Grotenhuis and L. Menninga, Eur. Pat. Appl. 3066; *Chem. Abstr.*, **91**, 211088 (1978); (c) J. warnant and J. Jolly, German (West) Patent 2 810 305; *Chem. Abstr.*, **90**, 6064 (1979); (d) D. G. Brown and W. W. Brand, German (West) Patent 2 741 764; *Chem. Abstr.*, **89**, 59785 (1979).

(3) (a) J. Imamura, *Yuki Gusei Kagaku Kyokaishi*, **37**, 667 (1979); *Chem. Abstr.*, **92**, 6158 (1980); (b) H. Imamura, K. Onisawa, and T. Yoshimoto, Japanese Patent 7 882 734; *Chem. Abstr.*, **90**, 22596 (1979); (c) T. Matsuda, T. Shirafuji, and T. Murata, Japanese Patent 7 959 242; *Chem. Abstr.*, **91**, 211086 (1979).

(4) A. Chaintreau, G. Adrian, and D. Couturier, *Synth. Commun.*, 11, 439 (1981).

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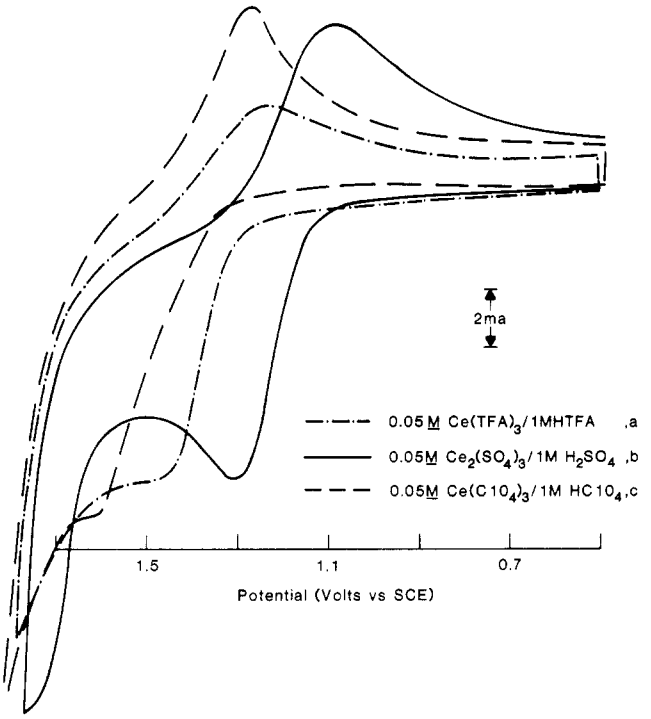

Figure 1. Cyclic voltammetric response of Ce(IV) at Pt in (a) 1 M HTFA, (b) 1 M H_2SO_4, (c) 1 M $HClO_4$.

of mPB subsequent to formation of the aldehyde function has also been reported.[6] We have studied an unreported route, the ceric oxidation of mPT to mPB, as part of a program on indirect electrochemical synthesis using ceric salts as mediators.

While ceric sulfate,[7] ceric perchlorate,[8] and ceric nitrate[9] are known to be excellent reagents for benzylic oxidation, we were not able to produce mPB using these salts, even under conditions where toluene was oxidized to benzaldehyde in good yield. We report here an electrochemical study of ceric ion in various acids as well as the electrochemistry of mPT and mPB. Particular attention is paid to the relative electrochemical potentials of the ceric oxidant and organic substrate. We describe how such information can be used to choose a ceric salt which can oxidize mPT to mPB in good yield.

It has been noted that the oxidizing strength of ceric ion varies drastically as the composition of the acid is changed.[10] We therefore examined the electrochemistry of the Ce(III)/Ce(IV) couple in a series of different acids. By determining the equilibrium potentials ($E°$) of the redox couple, a quantitative measure of the oxidizing power could be obtained.

Figure 1 shows the voltammetric behavior of soluble Ce(III)/Ce(IV) in several different acid media. In all cases both cerium valence states are electroactive, and the couple exhibits reversibility. Coulometric studies demonstrate that Ce(III) can be electrochemically oxidized to Ce(IV)

Table I. Effect of Acid on the Ce(III)/Ce(IV) Potential

electrolyte	concn, M	$E°$, V (vs. SCE)
H_2SO_4[a]	1	1.20
	4	1.19
	8	1.18
CF_3COOH	1	1.36
	3	1.33
	6	1.31
HNO_3[a]	1	1.37
	4	1.37
	8	1.32
CH_3SO_3H	1	1.40
	3	1.41
	6	1.39
$HClO_4$[a]	1	1.46
	4	1.51
	6	1.57
	8	1.63

[a] G. F. Smith and C. A. Getz, *Ind. Eng. Chem.*, **10**, 191 (1938).

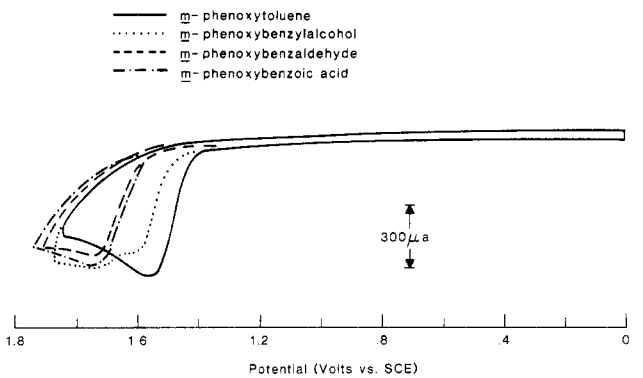

Figure 2. Cyclic voltammetric response of *m*-phenoxytoluene and derivatives in trifluoroacetic acid/acetonitrile/water (1/1/2) at glassy carbon.

at high current efficiencies. In perchloric acid current efficiencies of 90%+ were measured at current densities of 20 mA/cm^2 and a potential of 1.6 V vs. SCE.

From the voltammetric data the $E°$ for the Ce(III)/Ce(IV) couple was determined and is found to differ by as much as 0.45 V between $HClO_4$ and H_2SO_4 media. In 6 M sulfuric acid the wave corresponding to the oxidation of Ce(III) is well-defined ($E°$ = 1.18), whereas in 6 M perchloric acid ($E°$ = 1.57) the wave is partially obscured by oxygen evolution which makes the determination of the $E°$ difficult. Measurement of the open-circuit cell potential of acid solutions containing equimolar Ce(III) and Ce(IV) gave more accurate results. These $E°$ potentials are given in Table I; increasing positive potential indicates a stronger oxidant.

The oxidation potentials of mPT and other pertinent oxidized forms of this substrate were determined in an aqueous mixture of trifluoroacetic acid (HTFA, 25%) and acetonitrile (AN, 25%) and also in a solution of acetonitrile containing 0.1 M tetrabutylammonium perchlorate (TBAP). Cyclic voltammetric experiments carried out in each of the solutions show all the substrates to be electroactive. A typical set of voltammograms obtained in the HTFA/AN mixture is shown in Figure 2. Similar voltrammetric behavior is obtained in AN/TBAP except that all the waves are shifted by 0.36 V to more positive potentials. The important feature to be noted in the voltammograms is the oxidation potential of each material relative to that of the other materials. The relative ease at which these compounds are oxidized either on platinum or glassy carbon anodes is *m*-phenoxytoluene > alcohol >

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Table II. Yield and Selectivity of Ceric Oxidations of mPT in Several Acids

substrate	aqueous phase[d]	yield,[a] %	selectivity,[b] %
mPT	H_2SO_4 (50%)	2	5
mPT	HOAc (35%)	*c*	*c*
mPT	HCO_2H (35%)	*c*	*c*
mPT	CF_3CO_2H (35%)	37	58
mPT	CH_3SO_3H (40%)	1	3.7
mPT	$HClO_4$ (35%)	0	0
pPT	H_2SO_4 (50%)	40	56
p-methylanisole	CF_3CO_2H (35%)	81	82
m-methylanisole	CF_3CO_2H (35%)	22	25

[a] Yield is defined as aldehyde produced/initial toluene. [b] Selectivity is defined as aldehyde produced/toluene consumed. Analysis was by GC against a Ph_2O internal standard. [c] No reaction. [d] The cosolvent was benzene in all cases.

Table III. Effect of Cosolvent on Yield and Selectivity of Ceric Oxidation of mPT in Trifluoroacetic Acid

cosolvent[a]	yield,[b] %	selectivity,[c] %
none	34	35
cyclohexane	28	50
benzene	37	58

[a] The substrate was mPT, and the aqueous phase was CF_3CO_2H (35%) in all cases. [b] Yield is defined as aldehyde produced/initial toluene. [c] Selectivity is defined as aldehyde produced/toluene consumed. Analysis was by GC against a Ph_2O internal standard.

aldehyde ≥ acid. On the assumption that this same order holds for homogeneous oxidants, the optimal reagent will have a redox potential positive enough to oxidize mPT but at which mPB is stable.

Ceric oxidation of mPT was carried out in several acids; Table II summarizes the results. The limiting cases are represented by perchloric acid, in which Ce(IV) and mPT reacted rapidly but with no selectivity to mPB, and by sulfuric acid, in which the reaction was very slow and only a few percent of mPB could be obtained. The optimal situation was attained in trifluoroacetic acid where the selectivity to mPB was as high as 50%.[11]

The data in Table III illustrate how the selectivity to mPB may be further improved by using cosolvents. The selectivities are consistently better by 10% when cyclohexane is added to the reaction mixture. Under similar conditions, reactions with benzene as a cosolvent give selectivities higher by about 10% than when cyclohexane is used as cosolvent.

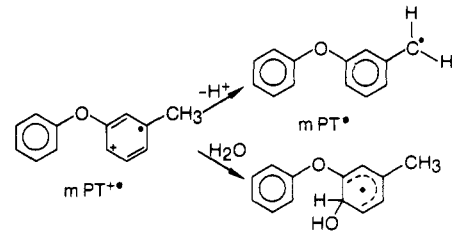
In contrast to the difficulties encountered with mPT oxidation, the para isomer, *p*-phenoxytoluene (**6**), could be converted in 80% yield to the aldehyde **7**. Under similar conditions *p*-methylanisole gave much better yields of anisaldehyde than *m*-methylanisole (Table II).

An attempt was made to identify the byproducts of the reaction between ceric trifluoroacetate and mPT by using field-ionization mass spectrometry. Aside from mPB and alcohol **5**, no single substance amounting to more than 2% of the total was detected. Essentially complete mass balance was attained, the major fraction being molecules lighter than mPT, indicating fragmentation. The most abundant of these fragments appeared at mass 98, which we tentatively assign to maleic anhydride, a product of overoxidation.

(11) Anhydrous trifluoroacetic acid has been used as a solvent for Ce(IV) oxidation of toluenes.[12] No aldehydes were produced.

Discussion

The differences in the reactivity of mPT and pPT can be understood after examination of the reaction mechanism. It is well documented[12,13] that the first step in oxidation of toluenes by Ce(IV) is a one-electron transfer to give a radical cation. This is rapidly followed by loss of a proton (see below) to form a benzyl radical which can



then be oxidized to a benzyl cation, an alcohol equivalent. These steps are then repeated to oxidize the alcohol to an aldehyde. The phenoxy group activates the tolyl ring to oxidation in both the meta and para isomers. However, the resulting radical cation is stabilized in $pPT^{+}\cdot$ relative to $mPT^{+}\cdot$. There is an even greater difference in stability between the radicals mPT· and pPT·, giving a greater driving force for $pPT^{+}\cdot$ to lose a proton. Nucleophilic attack by water occurs more readily for $mPT^{+}\cdot$ than $pPT^{+}\cdot$, a path which leads to degradation. Nucleophiles are known to add to the *m*-methylanisole radical cation,[14] and addition of water to other toluene radical cations has been discussed.[15]

Given the above, we formulated two criteria to follow in attempting mPT oxidations: the oxidant should be not stronger than is necessary for the first step, and the solvent should stabilize radical cations. Both of these criteria are satisfied by trifluoroacetic acid. The ability of trifluoroacetate to enhance the stability of cation and radical cations is well documented.[16] Table I illustrates the range of potentials available to the ceric/cerous couple. The best yields of aldehyde should result when this potential matches that of the toluene to be oxidized. Our measurements do not give a direct value for the $E°$ of mPT because it cannot be oxidized reversibly; therefore, we can only assign a relative order to the reactivity of the various ceric salts; the optimal value can only be determined by experiment. Table II shows that the predicted trend is followed, and ceric trifluoroacetate with an $E°$ of 1.3 V is the optimal choice for mPT oxidation.

The choice of cosolvent provides an additional variable, which has yet to be optimized or even fully understood. If the organic phase is diluted with benzene or cyclohexane, more of the desired aldehyde can be produced. We presume that such inert cosolvents prevent or slow self-condensation of radicals in the organic phase. (Under anhydrous conditions biaryl coupling products can be formed

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(14) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Am. Chem. Soc.*, **91**, 6830 (1969).
(15) C. Walling and R. A. Johnson, *J. Am. Chem. Soc.*, **97**, 363 (1975).
(16) A. Ronlan, O. Hammerlich, and V. D. Parker, *J. Am. Chem. Soc.*, **95**, 7132 (1973), and references therein.

almost exclusively.[12]) Cosolvents could also affect selectivity by altering relative concentrations of starting materials, products, and intermediates in the aqueous phase. Presumably the best cosolvent would extract product from the aqueous phase without lowering the concentration of starting material and would be inert to reactive intermediates.

Conclusions

The oxidation of mPT to mPB proceeds in good yield *only* in trifluoroacetic acid. In other acids the redox potential of ceric ion is either too high ($HClO_4$, CH_3SO_3H) and leads to overoxidation and tars or too low (H_2SO_4, AcOH, HCO_2H), leading to little or no reaction. Yields of mPB can be further improved by using a cosolvent. The cosolvent does not simply dilute the product, as benzene gives significantly better results than cyclohexane. Further work on cosolvents is clearly called for and is in progress.

The difficulties encountered in the oxidation of mPT are expected to be general to benzylic systems containing activating groups in a meta position. In these cases the ring is more easily oxidized, but the resulting radical cation cannot be stabilized by the activating group.

Good yields of *m*-anisaldehyde from *m*-methylanisole suggest that ceric trifluoroacetate will generally be the reagent of choice when an activating group occupies the meta position with respect to the oxidizable side chain.

Experimental Section

The phenyl ethers *m*-phenoxybenzyl alcohol (98% Aldrich), *m*-phenoxybenzaldehyde (95% Aldrich), *m*-phenoxybenzoic acid (99% Aldrich), and diphenyl ether (99% Aldrich) were all used without further purification. Ceric perchlorate (G. F. Smith Co.), cerous perchlorate (G. F. Smith Co.), ceric sulfate (Alfa), and cerous sulfate (G. F. Smith Co.) were all used as received. Other cerium salts ($CH_3SO_3^-$, NO_3^-, and CF_3COO^-) were prepared from the aqueous perchlorate salt by addition of the corresponding acid. Toluene, benzene, cyclohexane, perchloric acid and trifluoroacetic acid were reagent grade and were used without further purification. Water was deionized. The *m*-phenoxytoluene (Aldrich) was distilled on a 1-m spinning-band column at 0.25 mmHg and 84 °C. Only minor traces of diphenyl ether remained as well as *o*- and/or *p*-phenoxytoluene (as determined by GC/MS of the corresponding aldehydes after oxidation with Ce(IV)).

Gas chromatographic analysis was performed on a Perkin-Elmer Sigma 1B with a 20 ft × $^1/_8$ in. stainless steel column packed with Supelco 10% SP-2100 on 80/100 Supelcoport. The analyzer was programmed for injector and FID detector temperatures of 300 °C and an oven temperature programmed from 195 to 265 °C at 5 °C/min with a helium carrier flow rate of 30 cm^3/min. Field-ionization mass spectrometry was performed at SRI by their Mass Spectrometry Development Program group using an activated tantalum foil source and a 60° magnetic sector.

Electrochemical studies were conducted in a three-compartment electrochemical cell. The working electrodes for the voltammetric studies were of the disk type and were fabricated in-house (platinum, glassy carbon, and pyrolytic graphite).

Coulometric experiments were performed with a platinum-mesh electrode (52 mesh, 1.5 × 1.5 cm). The auxiliary electrode was a platinum coil, and the reference electrode was a saturated calomel electrode. All electrochemical experiments were conducted with a Princeton Applied Research (PAR) Model 173 potentiostat equipped with a PAR Model 179 digital coulometer and used in conjunction with a PAR Model 175 potential programmer. Cyclic voltammograms and current–time curves were displayed on a PAR Model 9002A X-Y-t recorder. Potentiometric measurements were made by using two electrodes in conjunction with a high-impedance electrometer (Keithley Model 616). A platinum wire served as the indicating electrode, and the reference electrode was used via a salt bridge which contained the appropriate acid of the same concentration as that in the reaction mixture. The Ce(III) and Ce(IV) concentrations were both held to 25 mM. Trifluoroacetic acid (1–6 M) was supersaturated with Ce(IV) in the 25 mM range. These supersaturated solutions can be prepared by adding Ce(IV) (0.5 M) in 6 N $HClO_4$ to trifluoroacetic acid or by electrochemical oxidation of cerium(III) trifluoroacetate solutions. The reported potentials change by less than 10 mV on lowering the concentration of Ce(III) and Ce(IV) to 2.5 mM, where Ce(IV) is soluble.

p-Phenoxytoluene (6, pPT). *p*-Phenoxytoluene was prepared via an Ullman condensation.[17] Sodium metal (12 g, 0.52 mol) was added with stirring to *p*-cresol (50 g, 0.47 mol) in a 1-L flask under argon. After steam ceased to evolve, bromobenzene (90 g, 0.57 mol) was added. It was necessary to add additional sodium (9 g) to achieve complete drying of the mixture, which was then refluxed for 5 h. The internal temperature rose from 165 to 180 °C as bromobenzene was consumed.

After the mixture cooled, 400 mL of H_2O and 300 mL diethyl ether were added, and the mixture was transferred to a separatory funnel. The organic phase was collected and the aqueous phase extracted twice with 10 mL of diethyl ether. The organic fractions were combined, washed twice with 2 M NaOH, water, 0.5 M HCl, and again with water, and dried over $MgSO_4$, and the solvent was removed. The resulting brown oil was fractionated on a spinning-band column. A total of 5 mL of pPT was collected: bp 85–86 °C (0.5 torr); yield 6%.

$Ce(CF_3CO_2)_2O\cdot H_2O$, Ceric Trifluoroacetate. Ceric trifluoroacetate was prepared by adding 100 mL of trifluoroacetic acid to 500 mL of 0.5 M ceric perchlorate in 6 N perchloric acid. After the mixture was stirred and warmed (60–70 °C) for 1 h, the light yellow precipitate was filtered, washed with 25% trifluoroacetic acid, and oven dried at 100 °C overnight to give 84.5 g of ceric trifluoroacetate. The product was found to contain 34.3% Ce(IV) by dissolving the solid in 1 M H_2SO_4 and titrating the clear yellow solutions with ferrous ammonium sulfate against ferroin indicator. The yield of ceric trifluoroacetate was 90%.

Oxidation of Toluenes with Ceric Trifluoroacetate. Typical Procedure. Ceric trifluoroacetate (0.90 g, 2 mmol) was added to 25 mL of 25% aqueous trifluoroacetic acid in a 50-mL round-bottomed flask and deaerated with N_2 for 15 min. To this was added *m*-phenoxytoluene, 87.5 μL (0.50 mmol). The resultant three-phase system was refluxed under nitrogen with stirring by heating it in a 90 °C oil bath. The approximate course of the reaction could be followed by observing the disappearance of the solid phase. If any solids remained, they were filtered and washed with water and CH_2Cl_2. The liquids were extracted three times with 25 mL of CH_2Cl_2 after dilution with 25 mL of water. The organic layer was reduced in volume to 3 mL, and diphenyl ether (79.5 μL, 0.50 mmol) added to it as an internal standard for GC analysis. For analysis of any acid product the dichloromethane was removed on a rotary evaporator, 1.5 mL of 1 M tetramethylammonium hydroxide in dimethylformamide (DMF) was added with agitation, and then 5 mL DMF and finally 0.25 mL of CH_3I[18] were added. After 5 min this mixture was subjected to GC analysis. Control experiments showed *m*-phenoxybenzoic acid could be detected in this manner as its methyl ester.

Oxidations with Ce(IV) in Solution. Typically 5 mmol of the ceric salt of interest, most often Ce(IV) in $HClO_4$ or ceric trifluoroacetate, was dissolved or suspended in the acid of interest and water to make 50 mL of a solution 6 M in acid and 0.1 M in Ce(IV). The solution was transferred to a 100-mL round-bottomed flask immersed in a 90 °C water bath, magnetically stirred, and purged with N_2 through the top of the attached condensor for 10–15 min. Benzene (5 mL) was then added through the top of the condenser to effect vigorous reflux at which time 0.2 mL of mPT in 5 mL of benzene was slowly (30 min) dripped into the reaction vessel from an addition funnel on top of the condenser. After 1 h, the reaction mixture was taken out of the bath to cool, diluted to 150–200 mL with H_2O, extracted three times with CH_2Cl_2, and dried over $MgSO_4$. Dichloromethane was removed on a rotary evaporator, 0.181 mL of diphenyl ether (calculated 1:1 molar ratio) as an internal standard was added, and 5 mol DMF was added as well. The solution was throughly

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mixed and 1-2 μL of the resultant clean light yellow to dark red-brown liquid was subjected to GC analysis.

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Registry No. *m*-phenoxytoluene, 3586-14-9; ceric trifluoroacetate, 70236-93-0.

Dynamic Nuclear Magnetic Resonance and Empirical Force Field Studies of Podophyllotoxin

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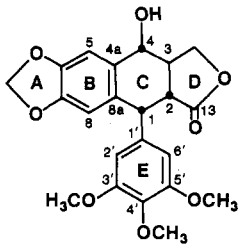
Proton dynamic nuclear magnetic resonance (DNMR) spectra (250 MHz) of the biologically active podophyllotoxin (1) at low temperatures reveal long sought evidence for hindered rotation of the pendant E ring. Under conditions of slow E-ring rotation on the NMR time scale at 137 K, the 2′- and 6′-protons of the E ring show two different NMR singlets of equal area separated by a substantial chemical shift difference ($\Delta\delta$ = 1.08 ppm). Simulation of the DNMR spectrum at 156 K gives a barrier ($\Delta G^{\ddagger}$) to E-ring rotation of 7.0 ± 0.2 kcal/mol. The NMR data suggest that in the stable conformation of 1, the E ring is essentially perpendicular to the rigid framework of the remainder of the molecule. Empirical force field calculations presented here are in qualitative agreement with the NMR data. Decoalescence of the 3′- and 5′-methoxyl proton resonances is also assigned to restricted E-ring rotation, but it is apparent that another lower barrier rate process (i.e., rotation about the phenyl–oxygen bonds of the E ring) contributes to additional broadening of the DNMR spectra especially at the lower temperatures employed in this study.

Podophyllotoxin (1) and most of the other members of

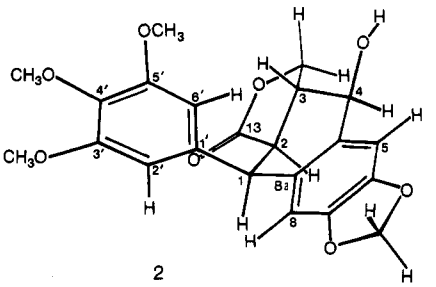


1

Podophyllotoxin

the podophyllotoxin family are constituted as lignans of the 1-phenyltetralin variety. Although the chemistry, stereochemistry, syntheses, and diverse biological activities of these compounds have been extensively investigated,[1-3] an apparent discrepancy between the ^1H nuclear magnetic resonance (NMR) spectrum observed at room temperature and the expected spectrum has persisted. Specifically, an examination of models suggests convincingly that the 2′- and 6′-protons of the E ring should be fixed at diastereotopic locations. However, at room temperature, the ^1H NMR signal for these two hydrogens consists of *one* sharp two-proton singlet. This paper addresses the apparent discrepancy.

A scaled molecular model built with space-filling atoms (Courtauld) shows that fused rings A–B–C–D of podophyllotoxin (1) form a strained, rigid framework which, on the average, is coplanar with the B ring. The rigidity of the A–B–C–D fused rings system of 1 is also evident from an examination of Dreiding models. In constructing the Courtauld model, it is especially difficult to attach the E ring of 1 to the tetralin 1-position, and once attached, the E ring is forced into a conformation in which it is essentially perpendicular to the average plane of the fused rings A–B–C–D. Structure 2 is a perspective of this geometry



2

of podophyllotoxin viewed with ring A closest and ring D farthest from the eye. According to the Courtauld model, the E ring has no torsional freedom; rotation about the 1–1′ bond appears to be severely restricted.

This preferred geometry (2) places the two aromatic protons of the E ring at different molecular and magnetic environments, i.e., the inner or endo position ($H_{6'}$ of 2) and

(1) For example, two semisynthetic derivatives, prepared by Sandoz, Ltd. (Basel), and designated as VP-16-213 (4′-demethylepipodophyllotoxin ethylidene-β-D-glucoside) and VM-26 (4′-demethylepipodophyllotoxin thenylidene-β-D-glucoside), are currently in use as clinical anticancer agents.

(2) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004. Also cf.: Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 7082.

(3) See the reviews by: Jardine, I. In "Medicinal Chemistry Monographs", Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Vol. 16, Chapter 9, p 319. Ayres, D. C. *Chem. Lignans* **1978**, 123; *Chem. Abstr.* **1980**, *93*, 220493. Hartwell, J. L.; Schrecker, A. W. *Fortschr. Chem. Org. Naturst.* **1958**, *15*, 83. We are indebted to Professor Ayres for providing a copy of his review.

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