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Molecular Orbital Studies of the Metabolism of Fluroxene and Analogous Fluorinated Ether Anesthetics

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SUMMARY

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Semiempirical molecular orbital calculations (by the modified neglect of diatomic overlap method) have been performed on the anesthetic fluroxene (2,2,2-trifluoroethyl vinyl ether, TFVE) and its analogues 2,2,2-trifluoroethyl allyl ether (TFAE) and ethyl vinyl ether to gain insight into the hepatic microsomal cytochrome P-450-catalyzed metabolism and suicide substrate functions of the ethers. The calculations indicate that the metabolic intermediate epoxides of both TFVE and TFAE require significant activation energy for ring opening. For TFVE, however, only protonation removes this energy barrier to ring opening (consistent with experimental observation). These calculated energy differences explain why TFVE metabolism can result in simultaneous product formation and destruction of the catalyzing enzyme through selective protonation. Calculated heats of reaction indicate that TFVE metabolism probably occurs via an intermediate tetrahedral hemiacetal. The calculated electronic structures of TFVE and TFAE, by providing data on the reactive sites on the molecules, have yielded insight into the mechanisms of cytochrome P-450 function.

INTRODUCTION

TFVE[1] is a volatile anesthetic agent that was used in clinical practice from 1953 until the mid-1970s (1). This anesthetic becomes toxic to some experimental animals after administration of hepatic cytochrome P-450-inducing agents (2). In man, the anesthetic is relatively nontoxic (2). TFVE undergoes metabolism to TFE, which in man is further metabolized primarily to trifluoroacetic acid, a relatively innocuous metabolite (3). In laboratory animals, TFE conjugates are the predominant urinary metabolites. TFE, rather than the parent anesthetic is thought to mediate the toxicity of TFVE (4). The CF_3 group in TFVE is metabolically inert (5), but the evidence is that toxicity resides in the trifluoroethyl moiety (6).

Metabolism of TFVE potentiates the partial destruction of the enzyme catalyzing the metabolism (hepatic cytochrome P-450) both *in vivo* and *in vitro* (7, 8). The extent of destruction is enhanced by cytochrome P-450 inducers such as phenobarbital (8). The vinyl group of TFVE is essential for destruction, since, in its absence, as with 2,2,2-trifluoroethyl ethyl ether as substrate, no destruction occurs (8). An epoxide intermediate in the metabolism of TFVE has been suggested as the possible mediator of the destruction of cytochrome P-450 (9–11).

To investigate the metabolism of TFVE and the mechanism of its destruction of cytochrome P-450, we have performed semiempirical molecular orbital calculations of the molecular and electronic structure of TFVE, its epoxide, and some analogous anesthetic fluorinated ethers, as well as the nonfluorinated analogue EVE. The objective of the study was to provide a molecular basis for the observed metabolism and toxic effects of these compounds.

Postulated metabolic pathways. Several pathways for the metabolism of TFVE are possible, including defluorination, *O*-dealkylation, and initial epoxidation. Little or no inorganic fluoride has been detected in serum after TFVE metabolism (3, 12), and thus defluorination is not a major pathway. Oxidative *O*-dealkylation, suggested for the related anesthetics methoxyflurane, enflurane, and isoflurane (13), would produce trifluoroacetaldehyde from TFVE. Trifluoroacetaldehyde would be oxidized *in vivo* to 2,2,2-trifluoroacetic acid (14), which is essentially not detectable in animals (4). Thus, *O*-dealkylation is

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[1] The abbreviations used are: TFVE, fluroxene 2,2,2-trifluoroethyl vinyl ether (fluroxene); TFE, 2,2,2-trifluoroethanol; EVE, ethyl vinyl ether; TFAE, 2,2,2-trifluoroethyl allyl ether; MNDO, modified neglect of diatomic overlap; ΔH_f, heat formation; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital.

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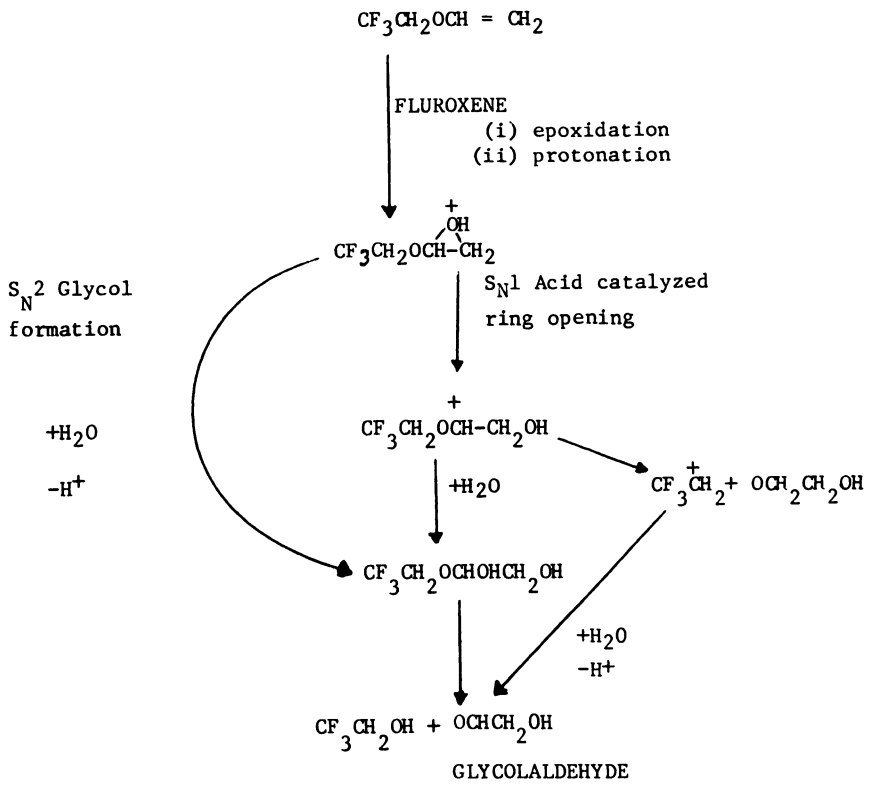

FIG. 1. *Proposed metabolic pathways for the anesthetic fluroxene (TFVE) catalyzed by hepatic microsomal cytochrome P-450*

unlikely to be a significant metabolic pathway for TFVE in animals.

The possible metabolic pathways associated with epoxidation of the vinyl group of TFVE are shown in Fig. 1. An alkoxy substituent on an epoxide ring carbon atom directs the reaction to that carbon atom (15). This occurs by a conjugative electron release from the alkoxy oxygen atom, which would stabilize an incipient positive charge on the carbon atom involved in bond breaking. Nucleophilic attack by water at this carbon atom would produce a glycol hemiacetal derivative via an S_N2 mechanism.

Acid-catalyzed epoxide hydrolysis of TFVE epoxide will occur via an A-2 mechanism in a pathway as described above or via an A-1 mechanism to give a carbocation, which would react with water to give the same glycol hemiacetal derivative. Ether cleavage of the glycol hemiacetal derivative would generate TFE and glycolaldehyde. Both products arise from TFVE metabolism in a stoichiometric 1:1 ratio.[2] The analogous anesthetic TFAE is metabolized to TFE and acrolein, with the intermediate 2,3-epoxypropyl-2,2,2-trifluoroethyl ether being at most on a minor pathway (16). The compound 2,3-epoxypropyl-2,2,2-trifluoroethyl ether has been synthesized and is stable (17). Because of the similar structure but differing properties of TFVE and TFAE, we have included the latter in the present study.

METHODS

Molecular orbital approach. The MNDO method, which represents an extension of the zero differential overlap approximation to all valence electrons, was used in the study. It is a semiempirical adaptation of the Roothaan-Hall self-consistent field-linear combination of orbitals-molecular orbital theory (18). MNDO yields reasonably accurate total energies and ΔH_f for many organic compounds, including carbocations and fluorine-containing compounds (19, 20). The mean absolute error is 6.3 kcal/mole, and three-membered rings are well treated by MNDO.

The MNDO method is a parameterization of the neglect of diatomic differential overlap approximation. MNDO does not include *d*-orbitals in its basis set. For the fluorinated molecules F_3NO, F_3CO, and F_3COH, *ab initio* calculations at the 4-31G level showed that the optimized structures are only slightly altered by the addition of *d*-orbitals (21). Energy lowering is not of the magnitude expected for significant *d*-orbital participation. Thus, lack of inclusion of *d*-orbitals in the present work should not significantly influence the calculated energy or electronic structure.

For each metabolite studied, the geometry was optimized by the Davidon-Fletcher-Powell method (22). Bond densities at the optimized geometry were computed by using the Mulliken approximation (23). The bond density is a summation of the overlap populations of each occupied molecular orbital and is a measure of bonding strength. We have employed the quantum chemistry program exchange version of MNDO (24). Computations were performed on the New York State Department of Health Burroughs 6700 computer.

RESULTS

The minimal energy geometry of TFVE is shown in Fig. 2. It prefers the *s-trans* conformation by 0.6 kcal/

[2] M. Murphy, unpublished observations.

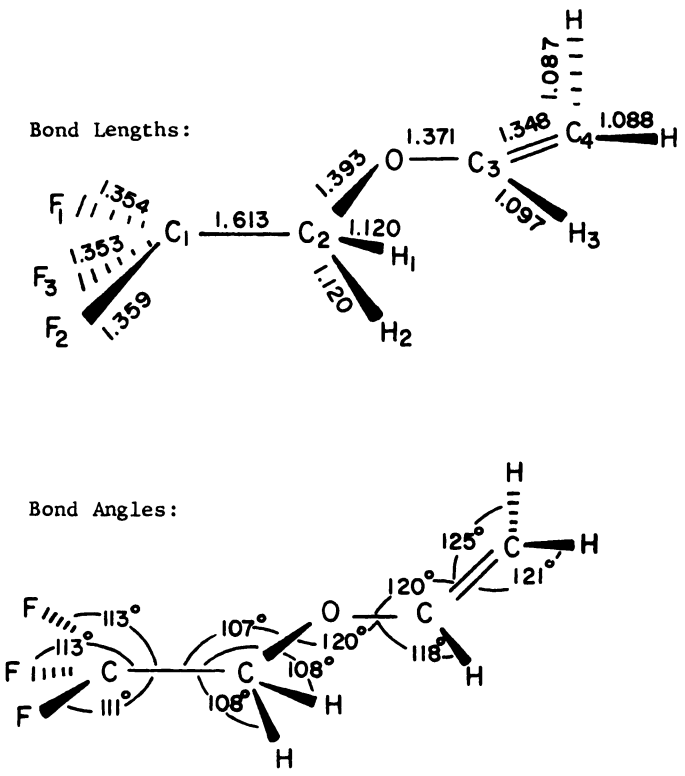

FIG. 2. *Structure of fluroxene (TFVE) calculated by MNDO*
Dihedral angles are defined with positive angles in the counterclockwise direction. Bond lengths are in angstrom units.

mole over the *s-cis* conformation. The calculated heat of formation of TFVE in this conformation is −176.6 kcal/mole.

Epoxides of EVE, TFVE, and TFAE. Calculations were performed on the epoxide derivatives, assuming epoxide formation across the unsaturated bond. This was done by assuming a trial geometry having C—O epoxide distances of 1.4 Å and a C_3C_4O bonding angle of 60°, with the epoxide oxygen atom located out of the molecular plane and in a plane perpendicular to it. This trial geometry was then optimized. It was found that the epoxides had a calculated heat of formation approximately 31 kcal/mole lower in energy than their unsaturated parent compounds (Table 1). All three epoxides had virtually equivalent C—O bond lengths of 1.42 Å, with CCO epoxide ring angles of 58°. Other bond lengths were not significantly altered upon comparison of the parent compound with the neutral epoxide.

Calculated bond densities of the EVE, TFVE, and TFAE epoxides indicated that the C—O epoxide bonds of the neutral epoxides were virtually equivalent to one another within and between the compounds. Epoxidation results in an increase in the net charge at C_3 and C_4 (Table 2).

Effect of protonation. The relative energetic effects of protonation at the ether and epoxide oxygen atoms were calculated. The protonated ether of the neutral TFVE epoxide was calculated to be 17.6 kcal/mole less stable than the protonated epoxide (see below), indicating that protonation of the epoxide oxygen atom would be favored.

A proton was placed along the axis of one of the oxygen lone pairs at a distance of 0.95 Å from the epoxide oxygen atom as a trial geometrical configuration. The C_3C_4O angle was fixed at 60°. All other internal coordinates were geometry-optimized. Next, the C_3C_4O angle was optimized. Displacements of the proton in increments of 0.1A from the epoxide oxygen atom indicated a rapid increase in energy of the closed-shell singlet with increasing OH distance. A reaction surface for protonation was not investigated. Protonation lowers the bond densities of the epoxide C—O bonds and slightly enhances the C_3–C_4 bond density.

In the case of protonated TFVE epoxide, allowance for relaxation of the C_3C_4O angle gave a structure in which the C_3O bond was broken to give an epoxide ring-opened carbocation. The protonated epoxide of TFVE is thus unstable and will open, without any energy barrier, to the carbocation.

We investigated the effect of other electronic configurations on the ring opening. At C_3C_4O angles between 60° and 110°, the triplet state (T_1) was 70–120 kcal/mole higher in energy than the ground state singlet (S_0). The first excited singlet (S_1) was slightly higher in energy than T_1. However, S_1 with 3 × 3 configuration interaction (excited singlet mixed with the two configurations corresponding to single excitations) was found to be several kilocalories per mole higher than S_0 at all angles. At a C_3C_4O angle of 70°, the S_1 energy was only 1 kcal/mole higher than the S_0 energy. S_0 energies were improved by a 2 × 2 configuration interaction with the first doubly excited configuration. The improvement in energy was at most 0.3 kcal/mole. Thus, a near surface crossing of S_0 with S_1 is suggested, but it is not indicated to occur according to the calculations. Both S_0 and S_1 surfaces decreased monotonically with increasing C_3C_4O angle. This reaction path calculation demonstrates that, in the process of ring opening, the molecule loses approximately 21 kcal/mole with no intervening transition state.

TABLE 1
Changes in heats of formation Δ (ΔH_f) of epoxide metabolites

Compound	Epoxidation	Epoxide protonation	Activation energy[a]	Ring opening[b]
		kcal/mol		
EVE	−30.6	179.4	0	−23.7
TFVE	−31.0	192.1	0	−21.2
TFAE	−32.1	189.7	11	3.2

[a] Activation energy for epoxide ring opening relative to the closed, protonated epoxide ring.

[b] For EVE and TFVE, the protonated epoxide ring was fixed at a C_3C_4O angle of 60°.

TABLE 2

Calculated atomic charges of EVE, TFVE, and their corresponding epoxides

Atom	EVE	EVE epoxide	TFVE	TFVE epoxide	Protonated TFVE epoxide	TFVE ring-opened carbocation
C_1	0.02	0.02	0.58	0.57	0.58	0.61
C_2	0.17	0.17	0.17	0.18	0.14	0.12
O_{ether}	−0.28	−0.32	−0.28	−0.31	−0.27	−0.16
C_3	0.06	0.18	0.05	0.17	0.31	0.45
C_4	−0.12	0.09	−0.09	0.10	0.18	0.15
F_1(H)	0.01	0.01	−0.22	−0.22	−0.23	−0.21
F_2(H)	0	0	−0.24	−0.23	−0.20	−0.19
F_3(H)	0.01	0.01	−0.22	−0.23	−0.20	−0.19
H_1	−0.01	−0.01	0.03	0.03	0.10	0.12
H_2	−0.01	0	0.03	0.04	0.06	0.09
H_3	0.06	0.07	0.06	0.08	0.13	0.14
H_4	0.06	0.05	0.07	0.06	0.14	0.07
H_5	0.05	0.04	0.05	0.05	0.11	0.07
$O_{epoxide}$	—	−0.30	—	−0.30	−0.18	−0.32

TFAE epoxide was found to be stable in its protonated form. The protonated epoxide of TFAE gained approximately 3 kcal/mole upon epoxide ring opening (Table 1). According to a reaction path calculation, the barrier to ring opening was 11 kcal/mole. Thus, for TFVE and TFAE epoxides, the similar energy changes occurring upon epoxidation become differentiated upon protonation of the epoxide rings. Protonation induces TFVE epoxide ring opening, with no calculated energy barrier, to form the trifluoroethyl hydroxy ethyl ether carbocation ($CF_3CH_2O^+CHCH_2OH$), but leaves the TFAE epoxide stable.

Bond densities for the neutral and protonated TFVE epoxide demonstrate that protonation diminishes epoxide bond strength. The C_1—C_2 bond, which from metabolic studies is expected to be stable, was assigned the highest bond density. In contrast, the epoxide C—O bonds in the protonated epoxide had the lowest bond density, with the C_3O epoxide bond having a lower value of bond density than the C_4O bond.

EVE epoxide was similar to TFVE epoxide; protonation caused epoxide ring opening with no intervening transition state. Thus, the spontaneous epoxide ring opening calculated for protonated TFVE epoxide was caused not by the presence of fluorine, but probably by the presence of the alkoxy substituent.

Hemiacetal formation and ether cleavage. As is indicated in Fig. 1, the carbocation resulting from epoxide ring opening may undergo ether cleavage directly without the necessity for attack by H_2O and subsequent hemiacetal cleavage. Alternatively, nucleophilic attack by H_2O may result in the formation of the hemiacetal, which subsequently cleaves to form TFE and glycolaldehyde in the case of TFVE. The latter possibility appears more likely, based on the computed MNDO heats of reaction (Table 3). Ether cleavage of the carbocation to form glycolaldehyde and TFE cation has a computed heat of reaction of 72.2 kcal/mole. This extremely endothermic reaction is unlikely to compete with the exothermic hydroxylation of the carbocation.

TABLE 3

Heats of reaction calculated by MNDO

Reaction	ΔH
	kcal/mole
$CF_3CH_2CH\text{-}CH_2{+}H_3O^+ \rightarrow CF_3CH_2O^+CHCH_2OH + H_2O$	−24.1
$CF_3CH_2O^+CHCH_2OH \rightarrow CF_3CH_2^+ + CHCH_2OH$	72.2
$CF_3CH_2O^+CHCH_2OH + OH^- \rightarrow CF_3CH_2OCHOHCH_2OH$	−254.2
$CF_3CH_2OCHOHCH_2OH \rightarrow CF_3CH_2OH + HCCH_2OH$	2.7

DISCUSSION

Comparison of semiempirical with ab initio calculations. The transition state for the opening of the protonated epoxide ring in the oxiranium cation, the simplest protonated epoxide, is 25 kcal/mole higher than the epoxide, based on an *ab initio* calculation (25). The calculated value for protonated TFAE epoxide of 11 kcal/mole is consistent with this. The calculated energy gain of 3 kcal/mole on protonated TFAE epoxide ring opening is similar to that determined by *ab initio* calculations for the oxiranium cation, 7 kcal/mole (25).

The planar CH_2^+ group of the 2-hydroxyethyl cation (the epoxide ring-opened form of the oxiranium cation) has two possible conformational states: one in which the hydroxyl oxygen atom and the CH_2^+ group are coplanar (eclipsed) and another with the oxygen atom and the empty *p*-orbital of the carbocation coplanar (oxygen staggered relative to the hydrogens). *Ab initio* calculations indicate that the eclipsed conformation is favored by 15 kcal/mole over the staggered conformation (25). This difference is caused by a more favorable interaction in the eclipsed conformation of the π-component of the two hydrogen atoms on the carbon atom adjacent to the empty *p*-orbital relative to the interaction of the empty *p*-orbital with the polarized C—O bond in the staggered conformation. Calculations in this study were in agreement with these results and demonstrated that the eclipsed conformation was favored in every instance in which the epoxide ring-opened carbocation was calculated. The proton of the hydroxy group was calculated to be in an *s-trans* conformation relative to the C—C single bond, also in agreement with *ab initio* calculations (25). In this conformation, the minimal repulsive interaction

between the positively charged proton and carbon atom is achieved.

Differences in reactivity of the fluorinated ethers. Experimental observations of cytochrome P-450-catalyzed metabolism indicate that TFVE is epoxidized, whereas, in contrast, TFAE is preferentially hydroxylated at the allylic methylene carbon (16). The calculated electronic structures of the two compounds were examined to gain insight into this difference and into the absence of metabolism at C_2 in both compounds. Calculated energy changes on epoxidation of TFVE and TFAE were similar; thus, net energy loss does not provide a reason for the metabolic diffrences. Furthermore, the π-bond orders are close to unity for both compounds, indicating similar electron densities in the π bonds.

Reactivity can sometimes be inferred from considerations of electronic distribution in the frontier orbitals, in particular the HOMO and LUMO (26). In both TFVE and TFAE, virtually all of the electron density in the HOMO is associated with the unsaturated carbon atoms and the ether oxygen atom; virtually no electron density is situated on the trifluoroethyl moiety. The electrons in the HOMO would be expected to participate in a reaction with an activated electrophilic oxygen atom in the formation of an epoxide.

In a MINDO/3 study of the mechanism of action of cytochrome P-450, it was suggested that hydroxylation may occur by an "attachment-rearrangement" mechanism, rather than by direct insertion of an oxygen atom on a carbon (27). Such a mechanism could involve attack by an electrophile at the most electron-rich hydrogen atom. In TFAE, the allyl methylene hydrogen atoms are the most electron-rich, with a net charge of 0.01 and HOMO coefficients of ± 0.22. The hydrogen atoms on the unsaturated carbon atoms do not appear in the HOMO. The C_2 methylene hydrogen atoms of the trifluoroethyl moiety have coefficients of only ± 0.07. Attack by an electrophile on a hydrogen atom, if dictated by frontier orbital considerations, is thus predicted to be at the allyl methylene hydrogen. In TFVE, none of the vinyl hydrogen atoms contributes to the π-HOMO (because of their location in the nodal plane of the π-orbitals), and the methylene hydrogen atoms of the trifluoroethyl moiety have a linear combination of atomic orbitals coefficient of only ± 0.1, thus discouraging any possible attachment-rearrangement reaction.

Although it is an unlikely possibility, nucleophilic attack may occur with TFVE and TFAE. According to the LUMO electron distribution, both TFVE and TFAE have significant electron density on the unsaturated carbon atoms. The LUMO is the unoccupied molecular orbital which most readily accepts electron density and is used to determine the most probable site of nucleophilic attack by comparisons of LUMO coefficients. As with the HOMO, the LUMO has virtually no electron density associated with the trifluoroethyl moiety. Thus, nucleophilic attack cannot explain the differences in methbolism of TFVE and TFAE; however, TFAE hydroxylation can be explained by the HOMO electron density governing electrophilic attack.

In summary, the metabolic pathways for TFVE and TFAE differ, notwithstanding the similar electron densities of their π-bonds. Presumably, the allylic carbon atom of TFAE has sufficient susceptibility to hydroxylation to be preferred over the epoxidation reaction. The reason for this could possibly be the high electron density in the allylic methylene C—H bonds. The atomic charge on this carbon atom does not indicate any particular susceptibility to electrophilic attack.

Comparisons of theoretical and experimental results. The calculated differences in stabilities of the TFVE and TFAE protonated epoxides are consistent with experimental observation. TFVE epoxide has not been isolated in solution, and attempts to synthesize it have failed.[2] This lack of success is probably a consequence of the absence of any requirement of activation energy for protonated ring opening. In contrast, TFAE epoxide is relatively stable, can be synthesized readily, and has been demonstrated to exist in solution (16), although it decomposes in acidic solution at a measureable rate (16). The slow decomposition in acidic solution probably results from the ability of solvolytic nucleophilic attack by water to overcome this energy barrier. Thus, the calculated ability of the epoxide rings to withstand protonation parallels their observed presence in solution.

EVE epoxide has been isolated in the gas phase (28), but has not been unequivocally demonstrated to exist in solution. Its instability as calculated by MNDO would probably preclude its isolation.

Reactivity of the TFVE epoxide ring-opened carbocation. The obvious candidate for the site of nucleophilic attack on the ring-opened carbocation of TFVE epoxide is C_3, which has a formal positive charge. The calculated C_3 charge of 0.45 indicates that the resonance structures with the adjacent oxygen atom ($F_3CCH_2O^+CHCH_2OH \rightleftarrows F_3CCH_2O^+ = CHCH_2OH$) leads to a delocalization of part of the charge. Nucleophilic attack on this carbocation would be directed to C_3 according to frontier orbital considerations and also by electrostatic charge. It has been suggested that, when both charge and orbital contributions are significant, the charge will control the reactivity (26).

Summary and implications for cytochrome P-450 destruction. A metabolite of TFVE, rather than TFVE itself, is the causative agent for destruction of cytochrome P-450 (7). Since neither of the isolated metabolites, TFE or glycolaldehyde, causes destruction, the epoxide of TFVE has been suggested as the possible activated intermediate. The results presented here suggest that protonation of the epoxide would lead to formation of a carbocation which would react to form an inactivating complex with cytochrome P-450.

The mechanism of metabolite formation from TFVE after formation of a carbocation can be inferred from the heats of reaction (Table 3) and the electronic structure. The carbocation would preferentially react exothermically with hydroxide ion (contributed by solvent water) to form a tetrahedral hemiacetal derivative about the C_3 carbon atom. Hemiacetal cleavage was calculated to require only 2.7 kcal/mole. Protonation has been suggested to promote decomposition of hemiacetals (29) and would thus be expected to lower further the calculated heat of reaction.

A possible mechanism to explain both TFVE-mediated

destruction of the enzyme and the generation of product which occur simultaneously involves cytochrome P-450-catalyzed production of the neutral epoxide. In the absence of an adequate supply of protons, the neutral epoxide can diffuse away from the active site of the enzyme and, upon protonation by solvent and subsequent carbocation trapping, decompose to TFE and glycoaldehyde. However, should some molecules of TFVE epoxide become protonated at the active site, the resulting carbocation can become covalently attached to a nucleophilic group on the heme, thus destroying the cytochrome P-450. This would differentiate this system from a typical suicide substrate reaction in which each molecule of activated substrate inactivates a molecule of enzyme.

In summary, application of molecular orbital theory has, by differentiating between the stabilities of the protonated epoxides of TFVE and TFAE and between the protonated and neutral epoxides of TFVE, provided possible mechanisms for the metabolism of these two compounds and for the production of metabolites simultaneously with enzyme destruction. The calculations have also indicated a possible mechanism for hydroxylation at the allylic carbon atom of TFAE that involves an attachment-rearrangement reaction.

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