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THE ELECTRONIC STRUCTURE OF PERACIDS. FUNCTIONAL MODELS FOR CYTOCHROME P-450

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Abstract—An extensive set of ground state *ab initio* and semiempirical molecular orbital calculations has been performed on both peroxytrifluoroacetic and peroxyacetic acids. The equilibrium geometry of peroxyacetic acid was calculated with the STO-3G and MINDO/3 methods, and peroxide rotational barriers for both peracids were obtained with STO-3G and PCILO. Extended basis set calculations with the 6-31G** basis were performed for both peracids to compare the electronic structures of these two compounds. Electrostatic potential maps in the region of the peroxide bonds of both peracids were also calculated using INDO wavefunctions. These results are discussed with respect to the enhanced reactivity of peroxytrifluoroacetic acid relative to peroxyacetic acid and the nature of the oxygen electrophilicity in these compounds and by analogy in cytochrome P-450, for which peroxytrifluoroacetic acid is considered to be an effective chemical model.

Much of the attention which peracids have received in the past few years has stemmed from the observation that oxidative metabolism of aromatic compounds by cytochrome P-450 is similar to the chemistry of peracid epoxidations. Peroxytrifluoroacetic acid in particular, was chosen as a chemical model for P-450 based on its ability to hydroxylate alkanes and aromatic amines, and more importantly to elicit the NIH shift in the oxidation of aromatic compounds.[1,2]

Peracids are perhaps chemically the best characterized of all systems which deliver an electrophilic oxygen to a nucleophile, and the epoxidation of olefins the most studied of all peracid reactions.[3] Recent papers have examined solvent effects[4] and kinetic isotope effects[5] in epoxidation reactions and other topics have included hydrolysis[2] and decomposition of peracids,[6] and a variety of structural problems centered on the conformation of the peroxycarboxyl group and peroxide rotational barriers.[3]

Three molecular orbital treatments of peracids have appeared in the literature thus far.[7-9] All three employed semi-empirical techniques and considered problems of chemical reactivity. Two studies also considered the peroxide rotational barrier.

Our initial interest in peracids stemmed from the use of peroxytrifluoroacetic acid as a chemical model for P-450. It became apparent however, that a comparative study of peroxytrifluoroacetic acid and peroxyacetic acid might reveal changes in the electronic structure of these compounds which would reflect their differing behavior as electrophiles. This paper gives an account of our calculations concerning both the equilibrium geometry and electronic structure of peroxyacetic and peroxytrifluorocetic acid.

METHODS

Details of the choice of a crystal geometry for the peroxycarboxyl group are given in a preliminary communication.[10] Essentially, the geometry of the peroxycarboxyl group was taken from the reported cyrstal structure of peroxypelargonic acid,[11] $CH_3(CH_2)_7CO_3H$, supplemented with values for the O–O–H valence angle and O–H bond length from *o*-nitroperoxybenzoic acid.[12]. The methyl and trifluoromethyl groups were assumed to be tetrahedral and standard values of 1.09 Å for carbon hydrogen and 1.36 Å for carbon–fluorine bond lengths were assumed. Our previous calculations revealed almost no barrier to rotation about the C_5–C_6 bond, and we consequently fixed one hydrogen or fluorine in the plane of the peroxycarboxyl group cis to the carboxyl function.

INDO, PCILO and MINDO/3 are semi-empirical methods available as programs from the Quantum Chemistry Program Exchange (QCPE) and are described elsewhere.[13] Our minimal basis set *ab initio* calculations were performed with the Gaussian 70 program, developed by Hehre and Pople. General properties of calculations employing the STO-3G basis are given in a series of papers by Pople and associates.[14-17] Extended calculations involved the 6-31G** basis, also developed by Pople.[18,19] Each core orbital is approximated by six Gaussian functions, while valence orbitals are split into two groups of three and one Gaussians respectively. The 6-31G** basis also includes p-type polarization functions on hydrogen atoms and d-type functions on all heavy atoms. Standard values of 0.8 for the orbital exponents of d-type polarization functions and 1.1 for p-type functions were adopted as suggested by Pople.[19] Integrals and SCF calculations with the 6-31G** basis were performed with the IBMOL program developed by Clementi and associates.[20]

A Mulliken population analysis was used with all molecular orbital methods to obtain gross atomic charges, overlap populations, and net atomic orbital charges.[21] Contributions from the inner and outer orbitals of the valence shell functions in the 6-31G** basis were summed in the population analysis.

Geometry optimization with STO-3G was begun with the crystal structure and grid sizes of 0.05 Å and 5.0 for the parabolic search. The resulting coarse geometry obtained was further refined with grid sizes of 0.01 Å and 1.0° to calculate final values.

Electrostatic potential maps were calculated from INDO wave functions by a method developed by Weinstein and Srebrenik.[22]

RESULTS

Geometry and peroxide rotational barrier

Figure 1 shows peroxyacetic acid and the torsion angle which defines the peroxide rotational barrier. The equilibrium geometry of peroxyacetic acid calculated by STO-3G and MINDO/3 is presented in Table 1. The total energy of various geometries for both peracids calculated with STO-3G and 6-31G** are given in Table 2. Shortening of the peroxide bond and lengthening of the C–O bond relative to experimental values of these parameters are similar to errors made by STO-3G in the calculated geometry of hydrogen peroxide. The O–H bond length of hydrogen peroxide is overestimated by 0.05 Å and the peroxide bond itself is underestimated by

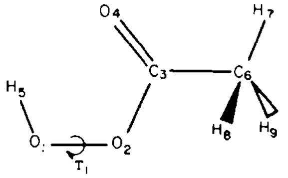

Fig. 1. Peroxyacetic acid. T_1 defines the peroxide rotational barrier.

0.08 Å.[17] Most valence angles agree with the crystal structure to within a few degrees, and this again is the expected error for skeletal angles calculated by STO-3G.[23] The O–O–H angle, however, is not well reproduced and this discrepancy might be due either to the computational method of the value taken from the crystal structure. STO-3G overestimates the O–O–H valence angle of hydrogen peroxide by 6°. On the other hand, the value of 112° for this angle was taken from the *o*-nitroperoxybenzoic acid crystal structure, and steric effects of the *o*-nitro group are certainly possible. In addition, peracids are intermolecularly hydrogen bonded species in solution or gas phase but intramolecularly hydrogen bonded in crystals. A change of several degrees in this angle on going from the crystalline to the monomeric form is therefore also possible.

The MINDO/3 geometry is roughly the same quality for bond lengths, but has larger differences with the crystal structure skeletal angles than STO-3G. A recent study by Hehre evaluated the performance of MINDO/3 vs STO-3G in calculating skeletal angles,[23] and the mean deviation of the MINDO/3 angles was found to be 8.7° for a set of 23 compounds as opposed to 0.8° for STO-3G.

In view of the inadequacy of the minimum basis set geometry of peroxyacetic acid, the crystal geometry of the peroxycarboxyl group was adopted for all further calculations on both peracids. An independent optimization of the geometry of peroxytrifluoroacetic acid by MINDO/3 gave almost exactly the same geometry for the peroxycarboxyl group as the MINDO/3 geometry of the peroxyacetic acid, and this supported our decision to regularize the structure of the peroxycarboxyl group.

Rotational barriers about the peroxide bond for both peracids calculated by STO-3G and PCILO are given in Figs. 2 and 3. The crystal geometry of the peroxycarboxyl group was used in both sets of calculations. Dipole moment calculations are summarized in Table 3.

Electronic structure

Tables 4–7 give the results of Mulliken population analyses for both peracids. Although it is not appropriate to compare different basis sets with a Mulliken analysis, the comparison of similar molecules with the same basis

Table 1. Equilibrium geometry of peroxyacetic acid[a]

Method	r_{CC}	r_{CO_4}	r_{CO_2}	r_{OO}	r_{OH}	$r_{CH}{}^b$	θ_{CCO_4}	θ_{CCO_2}	θ_{COO}	θ_{OOH}	$\theta_{HCC}{}^b$
Crystal Structure	1.49	1.23	1.35	1.44	1.02	1.09	128.2	110.2	112.0	112.0	109.5
STO-3G Optimized	1.53	1.22	1.41	1.40	1.01	1.09	131.5	109.8	109.7	101.4	109.5
MINDO/3 Optimized	1.49	1.22	1.34	1.39	0.96	1.09	124.9	103.5	127.1	110.5	109.5

[a]Bond lengths in Angstroms and bond angles in degrees. [b]Not optimized.

Table 2. Total energies of peroxyacetic and peroxytriluoroacetic acids[a]

Geometry	Peroxyacetic Acid		Peroxytriluoroacetic Acid	
	STO-3G	6-31G**	STO-3G	6-31G**
Crystal Structure	-298.58970	-302.55796	-590.95058	-599.09984
STO-3G Optimized	-298.60321		-590.82398	
MINDO/3 Optimized	-298.57233		-590.92352	

[a]Energies are given in atomic units.

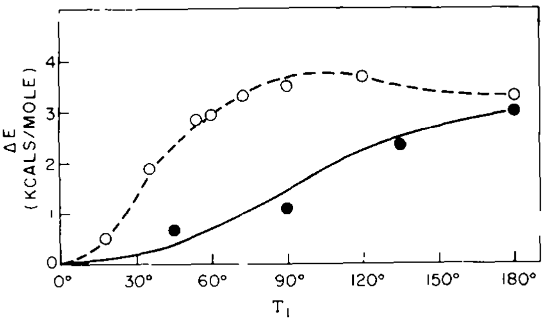

Fig. 2. Rotational barriers about the peroxide bond in peroxyacetic acid calculated by STO-3G and PCILO. Open symbols are STO-3G and closed symbols PCILO.

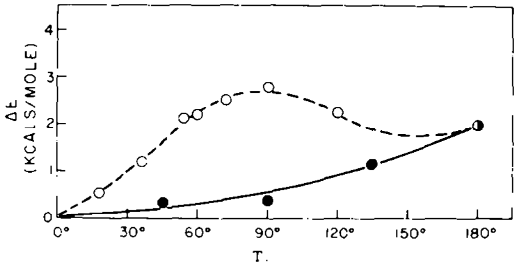

Fig. 3. Rotational barriers about the peroxide bond in peroxytrifluoroacetic acid calculated by STO-3G and PCILO. Open symbols are STO-3G and closed symbols PCILO.

Table 3. Calculated dipole moments of peroxyacetic and peroxytrifluoroacetic acids[a]

Geometry	Peroxyacetic Acid				Peroxytrifluoroacetic Acid			
	STO-3G	6-31G**	MINDO/3	INDO	STO-3G	6-31G**	MINDO/3	INDO
Crystal Structure	1.46	2.16		2.24	0.87	0.73		1.29
STO-3G Optimized	2.14				1.75			
MINDO/3 Optimized	0.42		1.56		1.52		2.18	

[a]Dipole moments are given in Debyes.

Table 4. Calculated net atomic charges of peroxyacetic and peroxytrifluoroacetic acids

	Peroxyacetic Acid			Peroxytrifluoroacetic Acid		
	6-31G**	STO-3G	INDO	6-31G**	STO-3G	INDO
O_1	-0.35	-0.17	-0.18	-0.31	-0.15	-0.22
O_2	-0.34	-0.15	-0.17	-0.35	-0.14	-0.20
C_3	0.78	0.32	0.42	0.71	0.28	0.52
O_4	-0.61	-0.28	-0.37	-0.56	-0.24	-0.35
H_5	0.41	0.22	0.19	0.42	0.22	0.17
C_6	-0.42	-0.21	-0.05	1.16	0.43	0.86
H/F_{789}	0.17	0.19	0.22	-0.35	-0.14	-0.30

set is reliable. The results indicate that the charge distributions in both molecules are much the same, with the exception of the methyl and trifluoromethyl groups. The inductive effect of the trifluoromethyl group is therefore not apparent by these criteria. Net atomic charges on the peroxide oxygens are negative and very similar in both peracids. The carboxyl carbon shows only a very slight positive shift of charge due to the

Table 5. Calculated overlap populations of peroxyacetic and peroxytrifluoroacetic acids

	Peroxyacetic Acid		Peroxytrifluoroacetic Acid	
	6-31G**	STO-3G	6-31G**	STO-3G
O-O	0.16	0.33	0.17	0.33
C-O	0.45	0.53	0.46	0.53
C=O	1.14	0.85	1.11	0.85
O-H	0.55	0.47	0.55	0.47
C-C	0.72	0.72	0.74	0.64
C-^{H} $_{F}$	0.78	0.76	0.55	0.42

Table 6. Calculated atomic orbital charges on the peroxide oxygens of peroxyacetic and peroxytrifluoroacetic acids

	Peroxyacetic Acid			Peroxytrifluoroacetic Acid		
	6-31G**	STO-3G	INDO	6-31G**	STO-3G	INDO
O_1						
2S	1.82	1.86	1.80	1.82	1.87	1.80
$2P_x$	0.92	0.94	1.01	0.88	0.92	0.90
$2P_y$	1.57	1.38	1.37	1.57	1.38	1.38
$2P_z$	1.98	2.00	2.00	1.98	2.00	2.00
O_2						
2S	1.84	1.84	1.75	1.86	1.84	1.74
$2P_x$	1.07	1.05	1.06	1.10	1.06	1.08
$2P_y$	1.51	1.41	1.49	1.49	1.39	1.45
$2P_z$	1.85	1.86	1.88	1.84	1.85	1.87

trifluoromethyl group. Contributions of individual orbitals to the gross charge of peroxide oxygens (see Table 6) are again, very similar for both peracids. The P_x orbitals which are aligned with the peroxide bond show the least total occupation, and a slight polarization of these values can be seen in trifluoroperacetic acid.

Figures 4 and 5 are maps of the electrostatic potentials in the plane of the peroxycarboxyl group for each of the peracids. The potential minima associated with the oxygen atoms in peracetic acid are deeper than the corresponding minima in peroxytrifluoroacetic acid. In a similar manner, the positive potential which is primarily due to the peroxide hydrogen extends further as a result of net charge movement towards the trifluoromethyl group. Both molecules have regions of low potential which are roughly associated with the axis of the peroxide bond, but this potential is positive for peroxytrifluoroacetic acid and negative for peroxyacetic acid.

In Figs. 6 and 7, similar maps are given in a plane perpendicular to the peroxycarboxyl group extending through the peroxide bond. Again the movement of negative charge towards the trifluoromethyl group is reflected by changes in the minima associated with oxygen electrons. It is interesting to note that while both oxygens of the peroxide group have non-bonding electrons in the mapping plane, only O_1 at the edge of the molecular frame generates a negative potential. The negative potential associated with electrons on O_2 is more than compensated for by nuclear repulsion terms, resulting in positive potentials. This is a typical pattern of potentials for regions which are in effect "inside" of a molecule.

Table 7. 6-31G** Frontier orbitals of peroxyacetic and peroxytrifluoroacetic acid[a]

	Peroxyacetic Acid						Peroxytrifluoroacetic Acid				
Energy	O_1	O_2	C_3	O_4	H_5	Energy	O_1	O_2	C_3	O_4	H_5
σ^* 0.192	0.91	.40	.03	.06	.00	σ^* 0.157	.92	.40	.05	.07	.49
π^* 0.159	.00	.20	1.16	.58	.00	π^* 0.097	.00	.22	1.00	.60	.00
π -0.464	.70	.75	.03	.51	.00	π -0.497	.73	.76	.03	.47	.00
σ -0.475	.02	.16	.11	1.45	.01	σ -0.526	.01	.20	.09	1.46	.01
π -0.526	.56	.01	.27	.81	.00	τ -0.578	.76	.01	.35	.84	.00
σ -0.561	.87	.21	.13	.03	.05	σ -0.608	1.19	.21	.16	.08	.09

[a] Energies are given in atomic units and distribution of orbitals on the peroxycarboxyl group in fractions of electrons.

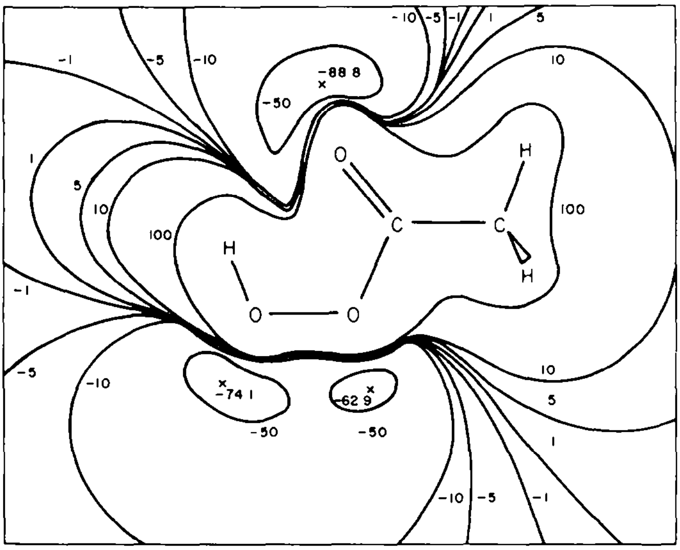

Fig. 4. Electrostatic potentials in the plane of the peroxycarboxyl group of peroxyacetic acid.

Table 7 gives a summary of the properties of several 6-31G** eigenvectors in the frontier region for both peracids. An indication of either π or σ character is shown along with contributions to the gross charge of individual atoms in the peroxycarboxyl group. The contributions from virtual orbitals were calculated as if they were occupied for simple comparison with the filled orbitals. This table demonstrates that the vectors in the frontier region are similar for both peracids, and this is not surprising in view of the similarity of the charge distribution between the two. The most striking change is the systematic lowering of the eigenvalues of 0.03–0.05 a.u. or about 20 kcal/mol in peroxytrifluoroacetic acid.

DISCUSSION

Geometry and peroxide rotational barrier

Our calculations of the equilibrium geometry of peroxyacetic acid are essentially in agreement with the crystal structure of peroxypelargonic acid. Most of the discrepancies are within the errors which should be expected from a minimum basis set geometry for highly functional components like peracids.

The finding of an energy minimum in the peroxide rotational barrier corresponding to a planar conformation of the peroxycarboxyl group is in disagreement with Swern, who predicted a stable conformation with $\tau = 72°$.[24] His methodology, however, employed the calculation of molecular dipole moments using ideal bond moments taken from molecules with widely varying electronic structures. The conformation of the peroxycarboxyl group was varied until the calculated dipole moment was in agreement with a value of 2.34 D observed for several fatty peracids. The 6-31 G** value of 2.16 D for the planar conformation of peroxyacetic acid is in quite good agreement with this value. In general, dipole moments calculated even at the Hartree-Fock level have a mean error of about 0.6 D, and better values can only be obtained with the inclusion of configuration interaction in the wave function.[25]

Based on the variability of dipole moment calculations,

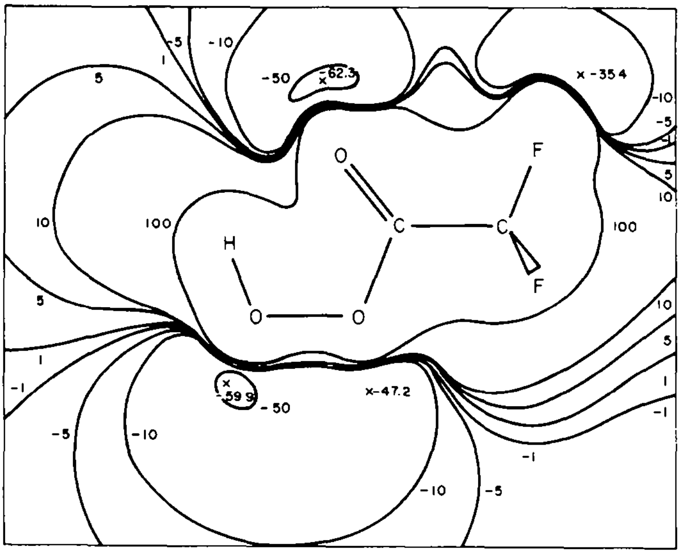

Fig. 5. Electrostatic potentials in the plane of the peroxy carboxyl group of peroxytrifluoroacetic acid.

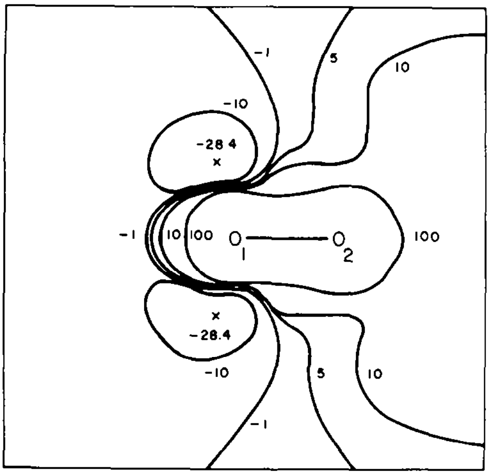

Fig. 6. Electrostatic potentials in a plane perpendicular to the peroxycarboxyl group and including the peroxide bond in peroxyacetic acid.

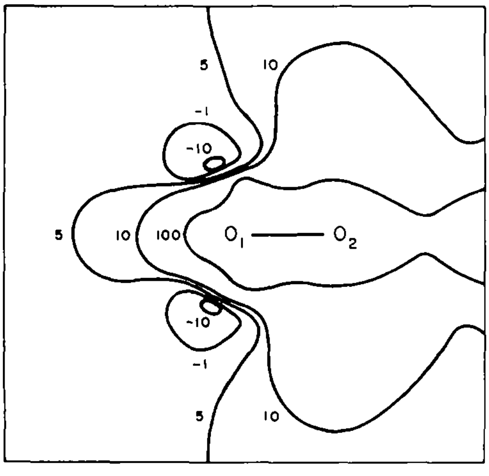

Fig. 7. Electrostatic potentials in a plane perpendicular to the peroxycarboxyl group and including the peroxide bond in peroxytrifluoroacetic acid.

we felt that total energy was much better criterion for the prediction of the peroxycarboxyl group conformation. Some caution must be used, though, in examining rotational barriers of peroxides calculated with minimum basis sets. The accurate prediction of the barrier heights of hydrogen peroxide for example, requires a double zeta quality basis set which includes polarization functions and the complete optimization of the geometry at each conformation studied.[26] The general shape of the barrier, however, is correctly given by minimal basis set calculations although the energies involved are not accurately predicted. These trends indicate that the planar conformation of the peroxycarboxyl group in both compounds is probably most stable but that our calculated barrier heights are very likely to be inaccurate.

Electronic structure

Our primary reason for examining the peracids was to see what aspects of their ground state structure might reflect electrophilic behavior. Faced with the problem of having only ground state wave functions, it seemed that the use of an approach involving perturbation theory would be the most useful. Perturbation methods utilize ground state functions in a natural way, and provide at the same time a convenient vehicle for the discussion of electrophilicity. The interaction energy between two reacting molecules is commonly expanded as a power series in both overlap and intermolecular potential, and the resulting energy expression truncated after second order.[27,28] Five terms remain, three of which are classical electrostatic interactions and do not involve overlap. Two terms specifically contain overlap, and are usually denoted as charge transfer and exchange polarization effects. These approaches were originally designed for regions of small overlap between the reacting species, and several authors have commented on problems with the use of perturbation methods in the transition state region.[27,28]

Due to the use of potential and overlap as expansion parameters, terms which include overlap can be separated from those which do not. This provides a means of lumping electrophilic behavior into two broad classes based on the predominance of the potential terms or the overlap terms in the energy expression. Klopman and Hudson have specifically used the nomenclature of charge controlled vs overlap controlled reactions in relation to the same idea.[30] Protonation is an example of a reaction involving a charge controlled electrophile and the common use of electrostatic potential maps to study protonation reflects the dependence of this reaction on charge interactions.[31] Reactions between neutral closed shell species, however, are expected to show very little charge interaction and relatively more dependence on the overlap terms. Perturbation treatments of the interaction of carbon dioxide and formaldehyde with ethylene,[32] methylene dimerization,[29] and reactions of $^1\Delta_g$ molecular oxygen [33] as well as benzyne[34] bear out the expected trends in the relative importance of overlap terms in the reactions of these neutral electrophiles.

Our results indicate that overlap terms must be the more significant in reactions at the peroxide bond. Although previous discussion of the enhanced reactivity of peroxytrifluoroacetic acid compared to peroxyacetic acid have centered mostly on trifluoroacetate as a better leaving group, or "strong polarization" of the peroxide bond,[3] our results do not support this idea. The charge distribution in both the peracids is very similar, and only very small changes in the polarity of the peroxide bond or the associated overlap populations could be detected. The possibility that the peroxide group is electrophilic in the sense of charge interaction is clearly not viable in view of the negative charges of the peroxide oxygens, and the regions of low potential associated with the axis of the peroxide bond as shown in the potential maps. The relative electron deficiency of the oxygen p_x orbitals, the low lying peroxide σ^* orbitals, and the dramatic lowering of the eigenvalues of these orbitals in peroxytrifluoroacetic acid, however, support the view that electrophilic reactions on the peroxide group involve overlap control and help explain the greater reactivity of the peroxytrifluoroacetic acid in reactions similar to those of cytochrome P-450.

Peracids are evidently ambident electrophiles, however, and nucleophilic attack also occurs at the carbonyl carbon of the peroxycarboxyl group. Such reactions are not at all analogous to those involving cytochrome P-450s. Hydrolysis, for example, has been shown by ^{18}O-labelling experiments to occur almost exclusively at this site for both peroxyacetic and peroxytrifluoroacetic acid.[2,35] This site has the largest positive charge of the peroxycarboxyl group, and this suggests the importance of charge effect in these reactions.

The complete separation of charge and overlap effects in the reactions at the two electrophilic centers is an obvious oversimplification. Reactions at the peroxide group have a polar component as evidenced by ρ values of around -1.0[35] and the dependence of epoxidation rates on solvent polarities.[4] The electrostatic potential maps of trifluoroperacetic acid which show regions of positive potential in the peroxide bond direction are also indicative of possible electrostatic interactions with an approaching nucleophile. Similarly, our results indicate charge effects at the carbonyl carbon are probably complemented by the presence of the low lying π^* orbital which is centered at this position. This orbital is again significantly stabilized in peroxytrifluoroacetic acid and must account in some fashion for the greatly enhanced hydrolysis rates of peroxytrifluoroacetic acid compared to peroxyacetic acid.[2]

Finally, the question may be posed as to what bearing these results might have on the production of an electrophilic oxygen species by cytochrome P-450. Because of their similar reactivities, we might expect enzymatic activation by cytochrome P-450 to produce an electrophilic oxygen species similar to the electrophilic peroxide oxygen described for peroxytrifluoroacetic acid. That is, the oxygen species bound to the iron would not have a net positive charge nor a region of large positive potential around it. Hence it would not act as an electrophile in charged controlled reactions. Rather the electrophilic activity of the oxygen would reside mainly in its participation in low energy virtual orbital which can serve as incipient electron acceptors in predominantly covalent electrophilic reactions. Covalent binding of oxygen to transition metals involving substantial d-orbital mixing could clearly create complementary low lying antibonding orbitals with oxygen and iron d orbital character. Examination of chemical models of cytochrome P-450 which include transition metals is now in progress.

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