amine, CH_3CN, room temperature, 2 h) led to the diazoester, which was taken up in hexane and filtered through magnesium sulfate before cyclization[19] (1 wt equiv Cu bronze powder, toluene, reflux, 2 h, 50% based on ketoester **4**) to the key cyclopropane **5**.[21-23]

On the basis of literature precedent[12-23] we expected that **5** would react readily with thiophenoxide. While orbital overlap considerations made it likely that the opening would proceed to give a cyclopentanone rather than a cyclohexanone, it was not so clear that the opening would proceed in a 1,5 as opposed to a 1,7 sense. Further, if the reaction did not proceed at ambient temperature, we did not have the option of warming it up, as allylic sulfides are quite prone to thermal racemization.

In the event, opening of cyclopropane **5** with thiophenol proved facile (1.5 equiv of thiophenol, 0.2 equiv of potassium *tert*-butoxide, ethanol, room temperature, 5 min, 69%). Oxidation and reductive rearrangement[11] of sulfide **6**[17,24] (1.1 equiv of *m*-chloroperoxybenzoic acid, CH_2Cl_2, −78 °C, 5 min; trimethyl phosphite, methanol, reflux, 30 min; 63%) then lead smoothly to the hydroxy ester **7**,[17] identical with authentic material.[25,26]

Conversion of **7** to PGA_2 has been previously accomplished. Thus, alkylation followed by retro-Dieckmann cyclization[7] gives the ketoester **8**, which can be saponified and oxidized[10] to the natural product.[27]

The control of the relative stereochemistry of an asymmetric center distant from the cyclic portion of a molecule is a problem of general interest. The method outlined here offers a versatile and efficient approach to this problem. Application of this method to the synthesis of other complex natural products is currently under investigation.

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The Electronic Structure of Chromyl Chloride: a Functional Model for Cytochrome P-450

Sir:

In a brief note, Sharpless and Flood commented on the similarity of the chemistry of cytochrome P-450 and oxotransition metal complexes of chromium and manganese.[1] Although this observation received little attention, more recent work in several areas has again suggested the possibility of an active oxidant in cytochrome P-450 which has properties similar to these reagents. Several groups have found that various peroxides couple with complexes of ferric iron including purified preparations of P-450 to give hydroxylation products.[2] The postulated intermediate in these reactions is a ferryl ion, analogous to the compound I of various peroxidases, in which atomic oxygen is formally bound to ferric iron.[3] The analogy to oxotransition metal complexes of chromium and manganese in higher oxidation states is obvious.

One of the presumable objections to the chromium and manganese complexes as models for P-450 is the radical nature of many of their reactions. The mechanism of hydroxylation by chromyl chloride (CrO_2Cl_2), for example, as well as other Cr^{VI} species is thought to initially involve a hydrogen atom abstraction to give hydrocarbon radical and a Cr^{V} species.[4] This process appears to be rate limiting in the overall reaction, as indicated by primary kinetic isotope effects in the range of $k_H/k_D = 6$–12 for several organic compounds. P-450, on the other hand, is classically thought to hydroxylate carbon hydrogen bonds by an insertion mechanism, due to the existence of low primary kinetic isotope effects and retention of configuration.[5] Evidence presented elsewhere suggests that the low isotope effects observed thus far for P-450 may only reflect a partial expression of the rate of the hydroxylation step in the overall velocity of the enzymatic process.[6] Studies of the primary kinetic isotope effect by intramolecular competition at benzylic sites resulted in $k_H/k_D > 6$. This larger value of the isotope effect suggests that abstraction–recombination be considered a possible mechanism for hydroxylation by P-450, and consequently that compounds such as chromyl chloride and chromyl acetate be reconsidered as chemical models.

As part of a systematic study of the electronic structures of chemical models for P-450, we have investigated the ground state structure of chromyl chloride (CrO_2Cl_2) with ab initio and semiempirical molecular orbital theory. Our ab initio calculations employed the Cr(14s, 11p, 5d/8s, 6p, 2d) basis of Wachters,[7] an O(9s, 5p/4s, 3p) basis,[8] and a Cl(12s, 9p/6s, 5p) basis due to Veillard.[9] Integrals were calculated in C_{2v}

Table I. Eigenvalues in the Valence Region of Chromyl Chloride[a]

	Ab initio			IEHT	
Virtual					
	9B1	0.010		18A1	−0.372
	17A1	−0.053		11B2	−0.402
	4A2	−0.070		4A2	−0.402
	11B2	−0.074		17A1	−0.407
Occupied					
	10B2	−0.488		8B1	−0.490
t_1	3A2	−0.493	t_1	10B2	−0.496
	8B1	−0.514		3A2	−0.496
a_1	16A1	−0.539	a_1	16A1	−0.514
	9B2	−0.551		7B1	−0.514
t_2	15A1	−0.575	t_2	9B2	−0.525
	7B1	−0.582		15A1	−0.533
e	14A1	−0.631	e	14A1	−0.549
	2A2	−0.641		2A2	−0.549
	8B2	−0.640		8B2	−0.552
t_2	6B1	−0.694	t_2	6B1	−0.559
	13A1	−0.700		13A1	−0.561

[a] Symmetry designations are for C_{2v} and account for core orbitals in number. Energies are in au. Bond lengths and angles for CrO_2Cl_2: r_{Cr-O} = 1.57 Å; r_{Cr-Cl} = 2.21 Å; θ_{O-Cr-O} = 105°; $\theta_{Cl-Cr-Cl}$ = 113°.

symmetry with the MOLECULE program of Almlof,[10] and SCF calculations with the ALCHEMY program.[11] Semiempirical calculations employed the iterative extended Hueckel theory program of Zerner and Gouterman.[12] The geometry of chromyl chloride was taken from the crystal structure of Palmer:[13] r_{Cr-O} = 1.57 Å; r_{Cr-Cl} = 2.12 Å; $\theta_{Cl-Cr-Cl}$ = 105°; $\theta_{Cl-Cr-Cl}$ = 113°.

Table I gives the eigenvalues of chromyl chloride in the valence region. A symmetry designation in C_{2V} is also shown for each eigenvector. Previous semiempirical calculations have demonstrated that the basic electronic structure of chromyl chloride can be considered a slight perturbation of the tetrahedral structure of chromate, the vectors grouping into T_d symmetries in a natural way.[14] These groupings are also noted in Table I. It is interesting to note that the first several virtual eigenvectors in the SCF calculation actually have negative eigenvalues. This is unusual for SCF calculations of transition metal complexes, and presumably reflects the high oxidation state of the complex. Since Cr^{VI} complexes are formally d^0, we might expect the first several virtual orbitals to have only d character. This is not the case. Both methods give substantial ligand character to the 4A2 and 11B2 vectors, with oxygen being relatively more important than chlorine and accounting for 25–33% of the electron density in these orbitals. In the 17A1 vector, all ligands have the same distribution of charge density due to the A1 symmetry, but the relative importance of the ligands decreases and the d character of this orbital consequently increases. The appearance of ligand character in these low lying virtual orbitals is a consequence of covalency in the metal ligand bond. Table II gives the results of Mulliken population analyses for the two calculations. The strong covalency of the metal ligand bonds is again reflected in the substantial overlap populations. Similar calculations for ionic complexes such as NiF_6^{4-} give essentially no net overlap population for the metal ligand bond.[15] An analysis of the Cr–O bond reveals substantial π character and this appears to account for both the high covalency of the bond and the low lying virtual orbitals with ligand character.

A major concern in these calculations was to learn something of how chromyl chloride functions as an oxidant, and in what fashion the oxygen ligands might participate in electrophilic reactions. The ligands are clearly not electrophilic in the sense of having positive charges which participate in electrostatic interactions with negatively charged centers. Rather, the large amount of oxygen character in the empty 4A2 and 11B2 orbitals and their relative stability suggest that the electrophilic reactions of chromyl chloride involve charge-transfer interactions in which these orbitals are the principal electron acceptors.

Table II. Population Analysis for Chromyl Chloride

	Ab initio	IEHT
Net charge		
Cr	+1.15	+0.57
O	−0.37	−0.27
Cl	−0.20	−0.01
Overlap populations		
Cr–O	0.601	0.995
Cr–Cl	0.607	0.742

In previous work with chemical models of P-450, a similar type of "neutral" electrophilic reactivity was identified.[16] Peroxytrifluoroacetic acid was found to be activated toward electrophilic reactions by the presence of low lying virtual orbitals involving the peroxide bond rather than peroxide bond polarization due to inductive effects as previously suggested.

A subsequent paper[17] describes the electronic structure of heme containing models of biologically active P-450 intermediates which are analogues to compound I of peroxidases. In these models for the enzymes the oxygen bound to the iron is similar to that in chemical models with a net negative charge and low-lying, electron accepting orbitals with significant oxygen character. Thus, it seems that in all four systems a consistent description of the electrophilic oxygen is obtained based on covalent rather than electrostatic interactions with the substrate.

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