Conformational Calculations and the Oxidation of Fatty Acid Esters by Chromium Trioxide

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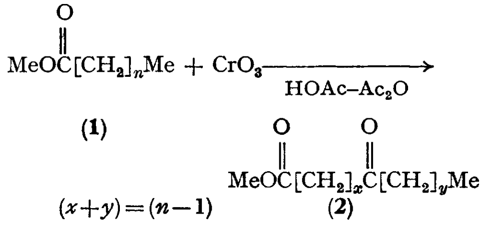
Summary Random walk calculations on a diamond lattice are used to suggest that the principal mode of oxidation in the direct conversion of fatty acid methyl esters into monoketo esters could be an intramolecular process occurring within a tetrahedral complex of the ester with Cr^{VI}.

Money and his co-workers recently reported a novel oxidation by CrO_3 of unactivated methylene groups in fatty acid methyl esters.[1] Unlike photochlorination,[2] the oxidation was not uniform among the CH_2 groups of the various chains. While mixtures of keto esters were produced, oxidation predominated at C(7)—C(10) of the chains. This peculiar result is unlikely to be due to a long-range electronic effect of the ester group.

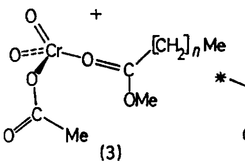
The distribution of oxidation sites in (**1**) appeared to us to have the characteristics of an intramolecular reaction[3] in which some carbon atoms could not reach the reactive oxygen atoms on chromium. Were this the case, we could apply our Monte Carlo method,[4] using random walks on a diamond lattice, to simulate the relative probability that the *i*'th CH_2 group in an *n* carbon chain would occupy the reactive volume about the reactive oxygen atom attached to Cr^{VI}.



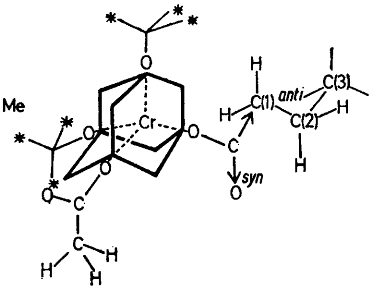
$$\underset{(\mathbf{1})}{\mathrm{MeO\overset{O}{\overset{\|}{C}}[CH_2]_nMe}} + CrO_3 \xrightarrow[\text{HOAc–Ac}_2\text{O}]{} \underset{(\mathbf{2})}{\mathrm{MeO\overset{O}{\overset{\|}{C}}[CH_2]_x\overset{O}{\overset{\|}{C}}[CH_2]_yMe}}$$

$(x+y) = (n-1)$

Cr^{VI} forms tetrahedral complexes. In $HOAc–Ac_2O$ solvent, it forms diacetylchromium dioxide[5] (**5**). The results of calculations presented here are based on the assumption that methyl stearate and other fatty acid esters undergo a ligand substitution reaction with (**5**), forming (**3**), the reactive complex. We assume that each of the CH_2 groups in (**3**) is equally reactive. The distribution of oxidation sites reported by Money *et al.*[1] would then reflect the relative probability that each CH_2 group occupies the reactive volume about the monosubstituted chromate oxygen atoms. We model (**3**) in the diamond lattice as (**4**), with the CH_2 groups numbered to correspond to the sites of oxidation in Figures 1 and 2. The chromium atom is situated at the centre of an adamantane structure, with the four oxygen atoms directed toward the four tertiary intersections. The dark lines indicate space excluded from the chain for steric reasons. The six lattice sites designated * in (**4**) were taken to be the reactive sites. Occupancy of



(3)



(4)

one of these sites by an H of a chain methylene indicated a reactive conformation. To simplify the calculations, the ester methyl was not considered in (**4**). Chains were grown as previously described.[4] Monte Carlo techniques were used as before to estimate the relative number of conformations leading to reaction at each CH_2 group.[4] These values are presented in Figures 1 and 2.

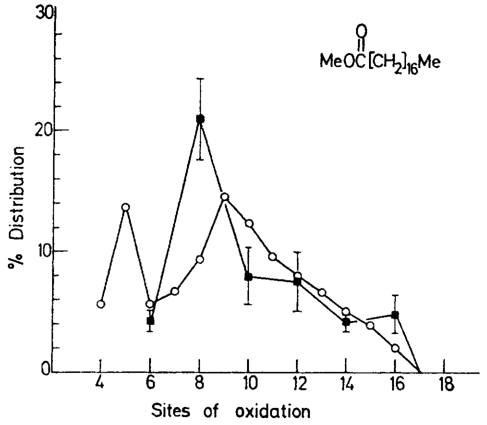


FIGURE 1. Oxidation of methyl stearate. ○, Experimental data from ref. 1; ■, random walk calculations showing relative number of conformations reactive at the sites indicated. 20,000 chains were examined, half with $C(1)H_2$ *syn* to the acetyl group in (**4**); half with the first chain vector *anti*. These were averaged. The calculations were reweighted to room temperature by assigning *gauche* bonds a statistical weight of $\exp(-\Delta E/RT)$, taking ΔE — 0·5 kcal/mol. Error bars represent the standard deviation.

There are several difficulties to bear in mind when comparing the experimental data in the Figures with our random walk calculations. First, in the experimental work, a different chemical and mass spectrometric analysis was used for methyl stearate oxidation than for methyl docosanote oxidation.[1] Second, some bimolecular oxidation may have occurred in competition with the intramolecular process simulated in our calculations. These may be responsible for differences in the general shapes of the experimental curves in Figures 1 and 2. Third, since only even-membered rings can be formed on a diamond lattice, we can be concerned with comparing only gross features of the theoretical and experimental curves in the Figures.

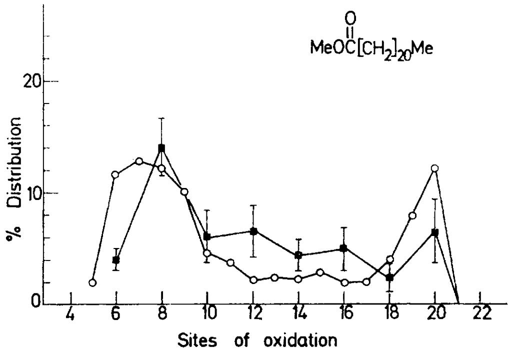


FIGURE 2. Oxidation of methyl docosanoate. ○, Experimental data from ref. 1; ■, random walk calculations as described in the caption to Figure 1.

The peak at C(5) in methyl stearate oxidation is most peculiar since it does not appear in the same reaction of methyl docosanote. The peak near the chain end is simulated by the random walk calculations, and has been seen in other intramolecular chain oxidations.[3,4] If we ignore the peak at C(5) in Figure 1, the agreement in general features between theoretical and experimental results are quite good. The calculations reproduce sufficient features of the experimental results to lend strong support to our assumption that the oxidation occurs intramolecularly through a complex such as (**3**). As more experimental results become available, we hope that better understanding of the Cr^{VI} chemistry will lead to substantial improvement in the model and the conformational calculations.

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