Table I. Incorporation of ^{18}O from $^{18}O_2$ into the Carboxyl Group of Glycolic Acid Obtained from the Products of Bleomycin-Mediated Cleavage of DNA

activating "pulse"	reaction "chase"	% (1-^{18}O)glycolic acid[a]
$^{18}O_2$/Fe(II)	$^{18}O_2$	98.1,[b] 92.4,[c] 95.5[d]
$^{18}O_2$/Fe(II)	$^{16}O_2$	3.5[b]
$^{16}O_2$/Fe(II)	$^{18}O_2$	89.7[b]
H_2O_2/Fe(III)	$^{18}O_2$	94.8[b]

[a] Percent enrichment relative to O_2 in the chase. [b] DNA from calf thymus. [c] poly d(AT). [d] d(CGCGCG).

the thiobarbituric acid method.[5] The glycolate salt was converted to a di-TMS derivative by heating at 60 °C with 10-20 μL of 50% *N,O*-bis(trimethylsilyl)trifluoroacetamide in acetonitrile. Aliquots of 1-5 μL were then analyzed directly by GC-MS. Relative amounts of unlabeled and (1-^{18}O)glycolic acid were determined from the average intensities of the M-CH_3 ions of the silylated derivatives at *m/e* 205 and 207, respectively, after correcting the mass spectrum for the natural abundance of the other stable isotopes.[10]

When iron(II) bleomycin[11,12] was allowed to react with calf thymus DNA, poly-d(AT), or d(CGCGCG) under an atmosphere of $^{18}O_2$, 92-98% of the isolated glycolic acid was singly labeled with ^{18}O at C1 (Figure 1). No label was incorporated at C2, as indicated by the lack of enrichment at *m/e* 161,[13] nor was any doubly labeled product observed. Control experiments using (1,1-$^{18}O_2$) glycolic acid showed that approximately 2-5% of the label is lost due to exchange with solvent during the workup. We therefore believe that these values reflect full incorporation of a single atom from O_2.

In order to distinguish between the O_2 involved in drug activation and the second O_2 required for the formation of 3′-phosphoglycolate termini, a "pulse-chase" method was employed. In a typical experiment,[12] an anaerobic solution of iron(II) bleomycin was activated with a "pulse" of $^{16}O_2$ or $^{18}O_2$.[14] After allowing 60 s for all of the iron(II) bleomycin to be consumed,[1a,b] the solution was evacuated briefly and purged with $^{18}O_2$ or $^{16}O_2$ and then an anaerobic solution of calf thymus DNA was immediately added. In another experiment, DNA was combined with iron(III) bleomycin and H_2O_2 under $^{18}O_2$.[16] Under these conditions, molecular oxygen does not participate in drug activation.[1a] The results of these experiments, summarized in Table I, clearly demonstrte that the oxygen incorporated at deoxyribose C-4′ is primarily, if not exclusively, derived from the second O_2 requirement and not the bound oxygen of activated bleomycin.[1a] This supports current hypotheses[8,9] which contend that C3′-C4′ bond cleavage is initiated by the addition of O_2 to a bleomycin-induced deoxyribose C4′ radical. The course of the reaction beyond this step remains somewhat obscure. It is frequently speculated that the resulting peroxyl radical is reduced to form a 4′-hydroperoxide which then undergoes a Criegee-type rearrangement[17] or some similar decomposition[8,9,18] resulting in C3′-C4′ bond cleavage. Further experiments intended to elaborate these points are in progress.

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A Highly Selective Zeolite Catalyst for Hydrocarbon Oxidation. A Completely Inorganic Mimic of the Alkane ω-Hydroxylases

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Oxidation chemists have long envied natural oxidation enzymes which can achieve remarkable control over oxidation selectivities while using molecular oxygen and a reducing cofactor at room temperature. The natural monoxygenase enzymes, cytochrome P 450, display the ultimate in substrate selectivity[1] (choosing between substrates of different size or shape), while the ω-hydroxylases are even more remarkable in their ability to regioselectively hydroxylate the terminal methyl group of unactivated alkanes.[2] Selectivity is imposed in these natural systems by virtue of selective substrate binding or orientation relative to the active oxidant by the protein itself. We have sought to mimic the high selectivities of these natural systems by using zeolite catalysts, utilizing the similarities between cavities in a zeolite and those in the protein tertiary structure of oxidizing enzymes.[3] We have now designed a system containing Pd(0) and Fe(II) in a zeolite which, in an oxygen/hydrogen atmosphere, should generate hydrogen peroxide at the palladium sites[4] and then use that peroxide to do Fenton[5] or Udenfriend[6] type chemistry at the iron sites on any organic substrate which is concurrently present in the pore system. Since such chemistry can be constrained to occur in such a shape-selective environment, we anticipated considerable selectivity in the ensuing oxidation products. We now wish to report just such a result in the competitive oxidation of cyclohexane/*n*-octane mixtures, where dramatic substrate selectivity is evident combined with a regioselectivity of *n*-alkane oxidation comparable to the that of ω-hydroxylases.

Iron(II) ion exchanged zeolite 5A[7] (Si/Al ~ 1.2) is subsequently ion exchanged with palladium(II) tetramine chloride, to give a material containing ~1 wt % Fe and ~0.7 wt % Pd.

[†] Contribution No. 4237.
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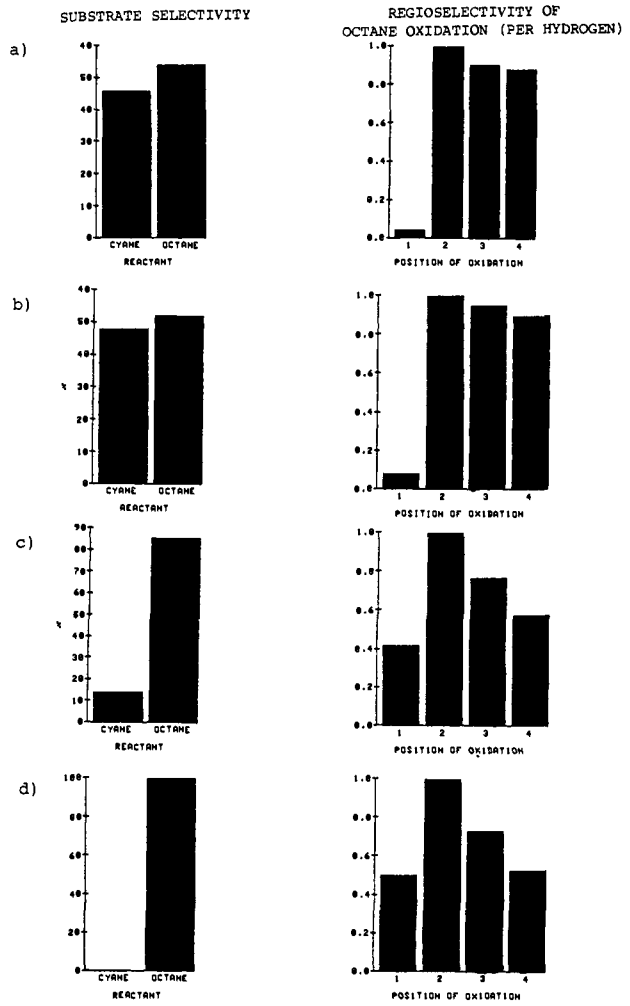

Figure 1. Selectivities in the oxidation of a 1:1 (volume) mixture of *n*-octane and cyclohexane. Substrate selectivitites are on a molar basis. Regioselectivities along the chain have been normalized for the relative number of hydrogens at each chain position with the activity at the 2-position in the chain assigned a nominal activity of 1.0. Bars represent the total of all products (alcohols plus ketones) derived from a given reactant or at a given position within each reactant: (a) amorphous silico–aluminate support; (b) zeolite 5A support after water addition; (c) zeolite 5A after acid dissolution; (d) zeolite 5A with 2,2′-bipyridine as poison after acid dissolution.

Calcination in oxygen (400 °C) followed by reduction in hydrogen (150 °C) generates a well-dispersed Pd(0) phase.[8] A typical oxidation run used 500 mg of such a catalyst in 10 cm^3 of hydrocarbon subjected to a pressure of 15 psig hydrogen and 40 psig oxygen at 25 °C for 4 h in a glass-lined shaker tube (**Beware** of explosion hazard; all such procedures must be carried out in an appropriately rated barricade area). Samples were worked up by a preliminary addition of water (4 cm^3) to displace hydrophillic oxidation products from the zeolite surface with subsequent GC analysis of the organic phase. A further addition of concentrated sulfuric acid (1 cm) with stirring for 1 h to dissolve the zeolite particles released any oxidation products trapped inside the pore system, which were then detected with a second GC analysis of the organic phase. As a means of estimating the selectivity imposed by the zeolite, a control catalyst was also prepared with an amorphous silico–aluminate (Si/Al ~ 1.2) as the oxide support where there is no internal pore system and so all chemistry must occur on the "non-shape-selective" exterior surface.

When a 1:1 mixture (by volume) of *n*-octane and cyclohexane is subjected to this oxidation the results are as shown in Figure 1a. The amorphous silico–aluminate control catalyst shows moderate activity (~75% yield based on iron, ~205% based on palladium, or ~0.5% based on hydrogen at 0.15% conversion), with the expected lack of any real substrate selectivity (octane/cyclohexane oxidation = 0.9), and a regioselectivity of octane oxidation products (primary H/secondary H oxidation = 0.05) which is not typical of hydroxyl radical oxidation in an aqueous system (prim/sec ~0.2[9]). The detected products did not change in either quantity or distribution from the initial water addition to the dissolution in the acid step of the workup. All products are released from the catalyst surface following the initial water addition in this case. With the 5A catalyst this is not the case. Analysis of the organic phase after initial water addition detects a small quantity of oxidized products with a distribution (Figure 1b) almost identical with the amorphous silico–aluminate control which we ascribe to that oxidation which has occurred at the exterior surface of the zeolite particles. Following dissolution in acid, however, the product quantity and distribution are dramatically changed with a 5-fold increase in products being entirely due to octane oxidation species (Figure 1c). The substrate selectivity now shows an octane/cyclohexane ratio of 6 while the regioselectivity of octane products shows primary/secondary oxidation of 0.54. Presumably, all of the additional oxidized products from the acid dissolution have come from the zeolite interior where they were trapped because of their physical size (zeolite 5A has 5-Å eight-ring windows which are extremely selective for adsorption or release of unsubstituted linear alkanes to the exclusion of cyclic or branched species[7]). Thus this increase in products represents those which were generated inside the zeolite.

The addition of a small amount of 2,2′-bipyridine to the oxidation medium acts as a poison of the iron activity, presumably due to coordination to produce a redox inactive complex. The poison's size dictates that *only* exterior surface iron sites are accessible, and we find no evidence of oxidation products prior to the acid dissolution of the zeolite when the bipyridine is used. This provides a means of establishing the intrinsic selectivity of the interior zeolite sites only (Figure 1d). This shows a substrate selectivity of octane/cyclohexane of >190 and a regioselectivity primary/secondary oxidation of 0.67. Such regioselectivity is superior to that reported by Suslick[10] for (porphyrinato)iron (0.3) and the best manganese systems (0.53) with iodosobenzene oxidant.

Comparison of the oxidation products from the linear alkanes pentane, octane, and decane by such a zeolite system (Figure 2) shows that the regioselectivity of the oxidation is almost independent of chain length. In all three cases, the prim/sec oxidation ratio is very close to 0.6 for the first three atoms in the chain. This result stands in contrast to that of Suslick et al.,[10] who noted a marked chain length dependence in regioselectivity with hindered porphyrin systems. This implies that the rigid zeolite framework is exerting a much tighter control over the substrate conformations during oxidation of short-chain alkanes than the flexible organic periphery of the porphyrin systems can impose.

The mechanism for oxidation in these systems appears to involve the expected generation of hydrogen peroxide at Pd(0)[4] rather than reduction of an iron-coordinated dioxygen species by a palladium hydride,[11] since a physical mixture of a Pd zeolite and a Fe zeolite is also capable of hydrocarbon oxidation in solvents in which hydrogen peroxide is somewhat soluble and hence migratory.[12] The nature of the actual oxidizing species as either anhydrous hydroxyl radicals or a high-valent iron–oxo unit (which we prefer) is unknown, but our results do confirm that very selective oxidation can be achieved with a very nonselective potent

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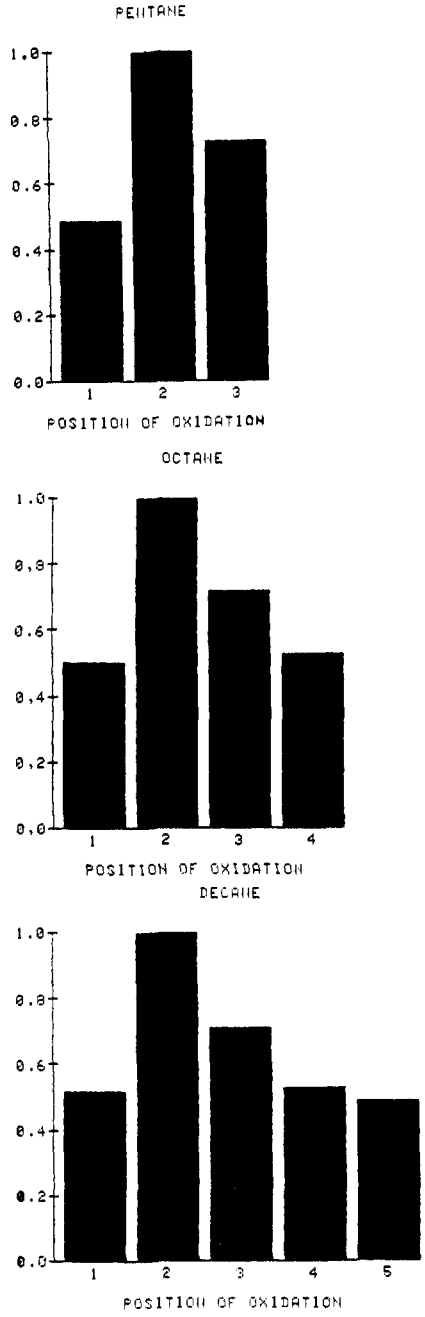

Figure 2. Regioselectivities along the chain of *n*-pentane, *n*-octane, and *n*-decane normalized for the relative number of hydrogens at each chain position (with activity at the 2-position normalized to 1.0).

oxidant by forcing such an oxidant to operate in a shape-selective environment.[13] We believe the substrate selectivity observed is a consequence of the sorption selectivity of the 5A zeolite while the ω oxidation selectivity arises from the very close fit of alkane to pore size which essentially constrains it to have an extended "linear" conformation. Thus the methyl end groups are the first to encounter (and so be oxidized by) the iron active sites in the six-ring faces of the zeolite supercages.

The overall activity of the 5A zeolite system is lower than the control, with 30% yield based on iron in this batchwise experiment. However, a recovered, calcined, and dried catalyst can be reused with the same initial activity as virgin material. We believe that a combination of organic oxidation products and the water by-product of the H_2/O_2 reaction fills the zeolite interior and eventually stops access of further hydrocarbon substrate to the active sites. It should be noted that, on the basis of the pressure drop during the course of the reaction, more than 95% of the H_2/O_2 mixture consumed gives water rather than oxidized organics.

This completely inorganic system demonstrates a remarkable similarity to the natural monoxygenase enzymes in that (1) it will take molecular oxygen at room temperature in the presence of a reducing agent and perform partial oxidation on an unactivated alkane and (2) such oxidations can be made to exhibit tremendous substrate selectivity combined with a regioselectivity reminiscent of the ω-hydroxylases. Preliminary results with other zeolite hosts (e.g., ZSM-5) have already demonstrated that if the pore system is larger, then products can be completely removed without zeolite dissolution. However, in such cases the selectivities are reduced. Finally, we note that the oxidation of aromatic substrates with identical systems is much more efficient, giving up to 30 catalytic turnovers based on iron with good substrate selectivities and regioselectivities. Full details of such studies will be reported in a future publication.

Acknowledgment. The excellent technical assistance of J. B. Jensen and J. M. Williams is appreciated as are discussions with Prof. G. D. Stucky, Dr. M. J. Nappa, and Dr. L. W. Gosser. We wish to thank K. S. Suslick for communication of his results with porphyrin systems prior to their publication.

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Absolute Stereochemical Control in Allylic Oxidation via Ene Reactions of *N*-Sulfinylcarbamates

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The ene reaction of the *N*-sulfinylcarbamate of *trans*-2-phenylcyclohexanol[2,3] with simple *cis*-alkenes proceeds to form allylic sulfinamides with high levels of both absolute stereochemical as well as regiochemical control. In turn, these products can be readily converted to allylic alcohols. Overall, these two processes represent a net allylic oxidation with retention of double-bond regiochemistry that is effected with reagent-based control of absolute stereochemistry.

Over the past 15 years, Kresze[1] has studied extensively the thermal ene reactions of *N*-sulfinylcarbamates, from which it can be concluded that, in general, the regiochemical outcome can be predicted based upon a concerted transition-state model that is quite productlike. Thus, the major product from the reaction with unsymmetrical alkenes is that with the more highly substituted double bond. Our initial attempts to impose the absolute stereochemical bias[2] of chiral auxiliaries in thermal ene reactions with the *N*-sulfinylcarbamate of phenylcyclohexanol (**1**)[3,4] led to only modest levels of control. In contrast, reaction of **1** with a number of alkenes in the presence of slightly more than 1 molar equiv of tin tetrachloride[5] led to adducts with practical levels of

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