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LETTERS

Lack of Molecular Selectivity in Gif-Type Oxidations

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***Abstract*:** The relative molecular reactivities of cycloalkanes in Gif-type reactions correspond to the cross-sections of the substrates indicating an absence of selectivity expected for a highly exothermic, diffusion controlled rate-limiting step.

In a recent Letter concerning continuing studies of the Gif family of oxidants, Barton *et al.* reported the intermolecular selectivities found for reactions of iron-activated hydroperoxides with cyclohexane, cyclooctane, and cyclododecane.[1] The relative reactivity of the cycloalkanes towards *t*-BuOOH in the presence of Fe(III) (formerly known as GoAgg^{IV} and GoAgg^{V} systems) was distinctly different than that observed in reactions of H_2O_2 and either Fe(II) or Fe(III) salts (Gif^{III}, Gif^{IV}, GoAgg^{I}, GoAgg^{II}, GoAgg^{III} systems). The reactivities of the cycloalkanes in the *t*-BuOOH systems, known to involve production of alkyl free radicals via H-atom abstraction by the *t*-BuO• radical,[1,2] were taken to demonstrate the normal reactivity of the cycloalkanes under radical conditions. In this context, the differences in cycloalkane reactivities in the iron-H_2O_2 systems appears to be evidence that cycloalkyl radicals were not produced by H-atom abstraction by the hydroxyl radical. The selectivities for the H_2O_2 systems were tacitly ascribed to effects arising in formation of iron-carbon bonded intermediates produced by addition of iron-oxo species to C–H bonds, and production of similar Fe–C species was proposed for both Fe(II) and Fe(III) salts on the basis of similar cycloalkane reactivities.[1]

In this Letter, we demonstrate that the reported reactivities of cycloalkanes in iron-H_2O_2 systems are consistent with an *absence* of intermolecular selectivity expected for a highly exothermic reaction. Thus, the observed relative reactivities of cycloalkanes in Gif-type oxidations do not provide *prima facie* evidence that H-atom abstraction by hydroxyl radical can be excluded as a mechanistic possibility.

Barton *et al.* listed the product ratios resulting from reactions of H_2O_2 (or molecular oxygen and a reductant) with both Fe(III) and Fe(II) salts in competition experiments between cyclohexane and cyclooctane and between cyclohexane and cyclododecane (10 competitions each).[1] Earlier, the relative amounts of ketones produced in competition experiments with cyclopentane and cyclohexane reacting with iron-H_2O_2 systems were compared (3 competitions).[3] The results were normalized to a "per hydrogen" ratio, and the average "per hydrogen" reactivities are listed in Table 1 below. The "per hydrogen" reactivities have been converted back into relative molecular reactivities that are also listed in Table 1.

Table 1. Molecular Reactivities in Gif-type Reactions and Cross Sections of Cycloalkanes.

Substrate	Rel. Reactivity per H[a,b]	Rel. Molecular Reactivity[a]	radius[c] (Å)	Relative Cross Section[d] (dens)	(vdw)
cyclopentane	0.75 ± 0.11	0.6 ± 0.1	3.34	0.91	0.89
cyclohexane	1.00	1.0	3.50	1.00	1.00
cyclooctane	0.82 ± 0.14	1.1 ± 0.2	3.76	1.15	1.21
cyclododecane	0.69 ± 0.16	1.4 ± 0.3	4.27	1.49	1.59

[a] Errors are 1σ. [b] Averages of reported "per hydrogen" reactivities.[1,3] [c] Radii calculated from the densities at 20 °C and the molecular weights assuming closest neighbor packing.[4] [d] Relative cross sections from radii determined from densities (dens) and by the van der Waals increments method (vdw).[4]

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For highly exothermic bimolecular reactions in solution, the activation energies of the reactions can be so small that the processes become diffusion controlled; that is, the activation energy for reaction is less than the apparent activation energy for diffusion (2-3 kcal/mol). In a diffusion controlled reaction, an encounter complex exists for thousands of vibrations allowing the two entities to access all possible orientations, and reaction will occur irrespective of the number of reactive centers. The important factor for intermolecular competition studies under diffusion control is the relative probability of encounters between the active agent and each of the competing substrates. The identity and diffusional coefficient of the active agent are immaterial in this case, and the probabilities of encounter are proportional to the "size" of the competing targets, the molecular cross sections. The cross sections can be estimated from the molecular volumes which, in turn, can be calculated from the densities and molecular weights of the pure agents.[4] In Table 1, we list the radius of each cycloalkane thus calculated and the resulting relative cross section for each cycloalkane (from the squares of the radii). An alternative method for estimating molecular volumes, the van der Waals increments method,[4] gives similar relative cross sections that are also listed in Table 1.

The correspondence between the relative molecular reactivities and the relative cross sections of the cycloalkanes is quite good. The apparent disparate reactivity of cyclopentane might result from the fact that the average reactivity value comes from only three studies and the listed error at 1σ for this data set is only at the 50% confidence interval. We believe the agreement between reactivity and "size" is clear evidence that the rate-limiting step in reactions of iron-H_2O_2 with the cycloalkanes is highly exothermic and under diffusion control. Further evidence that Fe-H_2O_2 oxidations involve diffusion controlled reactions is found in the apparent lack of a kinetic isotope effect in the *functionalization* step for reactions of cyclohexane-d_0 and -d_{12}.[5]

The results indicate a highly exothermic initial step in Gif-type reactions. Whereas one might formulate a variety of highly reactive agents that could be produced in these reactions, the hydroxyl radical is clearly one member of this group. Reaction of hydroxyl with cyclohexane is quite exothermic ($\Delta H = -24$ kcal/mol),[6] and the much less exothermic reaction of the *t*-BuO• radical with cyclohexane ($\Delta H = -10$ kcal/mol)[6] has a rate constant of 1.2×10^6 M^{-1} s^{-1} at 30 °C in various solvents.[7] Hundreds of diffusion controlled reactions of hydroxyl radicals with hydrocarbons and other organic substrates in water are known.[8]

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