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Studies on the Bromination of Saturated Hydrocarbons Under GoAgg^{III} Conditions

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Abstract: The bromination reaction of saturated hydrocarbons under GoAgg^{III} conditions ($FeCl_3.6H_2O$, picolinic acid, H_2O_2, in pyridine/acetic acid) and under radical chain conditions (dibenzoyl peroxide in pyridine/acetic acid or initiation by UV light) are compared. Differences in the selectivity and kinetic behavior for a series of polyhaloalkanes are in agreement with a non-radical mechanism for GoAgg^{III} bromination.

Unusual chemical versatility is shown in the process of selective functionalization of saturated hydrocarbons by Gif-type systems.[1] The "natural" chemistry displayed by these systems is the ketonization of non-activated methylene groups, with quantitative yields at conversions ranging from 15 to 30%. However, if a suitable reagent is added to the reaction mixture, the formation of ketone is diverted toward the corresponding monosubstituted alkyl derivative. For instance, addition of PPh_3 affords the corresponding alcohol; with $P(OMe)_3$ the alkyl dimethyl phosphate is formed; Ph_2Se_2 produces a quantitative (in Se) yield of the alkyl phenyl selenide; sodium sulfide yields dialkyl oligosulfides.[2] Gif chemistry is also able to convert saturated hydrocarbons into alkyl halides. In this case the reagent to be added to the GoAgg^{III} reaction mixture is a polyhaloalkane, such as $CBrCl_3$, CBr_4, or CCl_4.[3]

Another interesting aspect of Gif chemistry is the mechanism of the hydrocarbon activation process. Extensive work points against a radical reaction pathway. A mechanism involving a reaction intermediate bearing a carbon-iron bond has been postulated (Figure 1).[2] We felt that additional evidence regarding this point could be collected by comparing different aspects of the well known radical pathway with the characteristics of the halogenation reaction under GoAgg^{III} conditions.

Radical chain halogenation of non-activated C-H bonds is a well investigated process in Organic Chemistry. The selectivity of this reaction, with a variety of substrates and halogenating reagents has been studied. In particular, we were interested in the efficiency of different polyhaloalkanes as carbon radical traps. To our best knowledge, data on relative reaction rates of chain radical halogenation reactions are scarce and questionable because the possibility of side reactions between the competing halogenating reagents was not taken into account.[4] Thus, we carried out the competitive experiments required to establish a kinetic order for polyhaloalkanes as radical chain halogenating agents. To avoid the above mentioned problems associated with cross-reactions between the two polyhaloalkanes taking part in the competition, they were competed against a third species, thiophenol. The latter reacts by hydrogen atom transfer to carbon radicals, affording alkanes.[5] Then, from the ratios alkyl halide/alkane the relative reactivity ratios were determined. The results obtained with a series of brominating agents are shown in Table 1. Thus, in agreement with partial reported data, the order of decreasing reaction rate for radical reactions is CBr_4 > $CBrCl_3$ (> CCl_4 [4]).

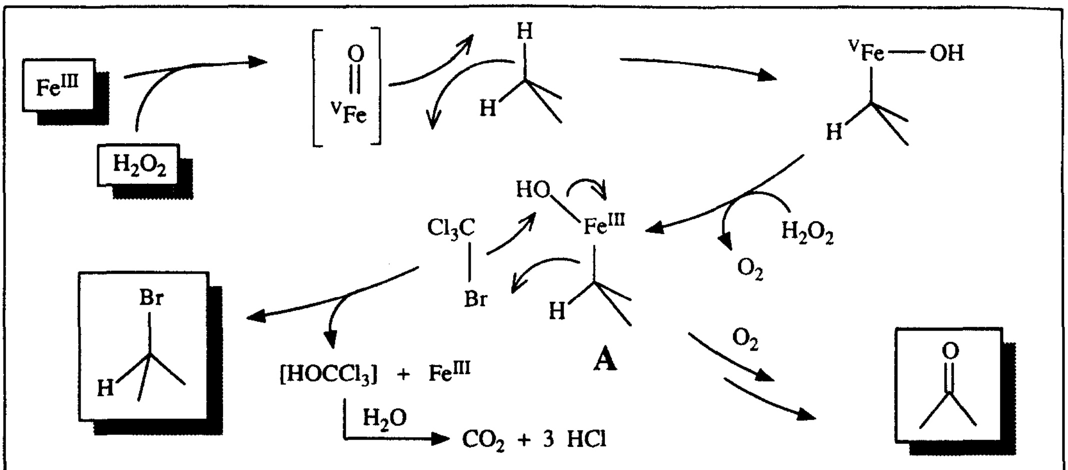
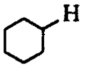
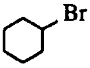


Figure 1. Proposed reaction mechanism for the bromination of saturated hydrocarbons under GoAgg^{III} conditions.

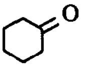
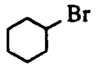
Table 1. Relative rates of bromination under radical conditions for a series of polyhaloalkanes. For reaction conditions see reference 6.

Entry	Halogenating Reagent	 mmol	 mmol	$\frac{R\text{-}Br}{R\text{-}H}$	Σ mmol
1	CBr_4	0.065	0.133	2.05	0.198
2	CBr_2Cl_2	0.108	0.093	0.86	0.201
3	$CBrCl_3$	0.099	0.072	0.73	0.171
4	$(CBrCl_2)_2$	0.124	0.072	0.58	0.196
5	CBr_2F_2	0.120	0.005	0.01	0.125

What is the reactivity order when the brominations are carried out under GoAgg^{III} conditions? The parameter selected to judge the efficiency of the different polyhaloalkanes was the ratio alkyl bromide to ketone (RBr/R=O). The rationale for this is as follows. According to the reaction mechanism proposed for Gif-type reactions[2], the trapping reagent captures a reaction intermediate (intermediate A, Figure 1). Thus, the faster the trapping reagent (in this case the polyhaloalkane) reacts with intermediate A, the higher would be the R-Br/R=O ratio. And if A were a carbon radical, the same order of reactivity as in the previous radical chain halogenations would be expected. The results from these experiments are presented in Table 2.TD 66 Tr 33.36 rim 0. Tc

From the results in Table 2, $CBrCl_3$ is the best halogenating reagent under GoAgg^{III} conditions. Although all of these compounds are partially oxidized under the reaction conditions (*e.g.*, CBr_4 and $CBrCl_3$ to CO_2, as observed by ^{13}C NMR experiments and quantification of the CO_2 as $BaCO_3$; $(CBrCl_2)_2$ to $CBrCl_2COOH$, as determined by GC-MS of its TMS-derivative), the amount of hydrogen peroxide used was small enough to assure that there was not a big variation in the concentration of the trapping reagents due to

Table 2. Relative rates of bromination under GoAgg^{III} conditions for a series of polyhaloalkanes. For reaction conditions see reference 8.

Entry	Halogenating Reagent	 mmol	 mmol	$\frac{R\text{-}Br}{R{=}O}$	Σ mmol
1	$CBrCl_3$	0.024	0.686	28.6	0.710
2	$(CBrCl_2)_2$	0.031	0.529	17.1	0.560
3	CBr_4	0.070	0.396	5.6	0.466
4	CBr_2Cl_2	0.300	0.418	1.4	0.718
5	CBr_2F_2 [a]	0.352	0.079	0.2	0.431

[a] Reaction carried out at 0°C due to the volatility of CBr_2F_2. Reaction time:48 h.

these side reactions. Clearly, the reactivity orders for the bromination of saturated hydrocarbons under radical chain conditions and GoAgg^{III} conditions are different. Thus, intermediate A could not be a carbon radical.

Another well known aspect of radical chain bromination of alkyl halides is the "Skell-Walling effect". This describes the fact that radical chain bromination of alkyl monobromides is characterized by preferential bromination in the β-position with retention of configuration.[9] Thus, we compared the radical chain bromination of cyclohexyl bromide (dibenzoylperoxide, $CBrCl_3$ in pyridine/acetic acid) with the bromination under GoAgg^{III} conditions. The results are presented in Table 3. Again, the pattern of dibromocyclohexanes obtained under GoAgg^{III} conditions differs from the pattern observed under radical chain bromination conditions, in agreement with a non-radical hydrocarbon activation step. Although the high selectivity for the formation of the *trans*-1,2-dibromo-cyclohexane reported in the literature[9] was not observed either in the [redacted] products. Under GoAgg^{III} bromination conditions the former is a minor product while the latter is not seen. Also, the GoAgg^{III} bromination shows a preference for equatorial substitution. Authentic samples of the dibromides were obtained according to published procedures;[10] control experiments proved that they are stable under GoAgg^{III} reaction conditions.

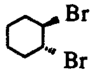
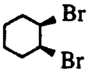
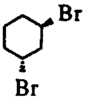
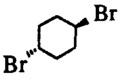
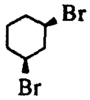
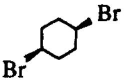
Thus, this incursion into the halogenating chemistry of the GoAgg^{III} system exposes once again the differences in behavior between carbon radical chemistry and Gif chemistry. The reaction mechanism presented in an abbreviated form in Figure 1 is in agreement with every experimental fact known to-date about Gif chemistry.

Acknowledgments. We are indebted to Professor K. U. Ingold for his valuable suggestions. We thank the National Science Foundation, TATRAP, British Petroleum, and Quest International for financial support of this work. One of us (D.D.) is grateful to Merck Sharp & Dohme for a post-doctoral fellowship.

References

1. The nomenclature of Gif systems is as follows: *GoAgg^{II}* is a solution of the hydrocarbon in pyridine/acetic acid, containing a catalytic amount of $FeCl_3.6H_2O$ and using H_2O_2 (30% in water) as

Table 3. Comparison of the distribution of dibromocyclohexanes for a radical chain reaction and a GoAgg^{III} reaction.

Entry						
1[a]	94.0	3.5[b]	0.9	0.5	0.5	0.5
2[c]	7.7	---[f]	1.9	45.2	27.9	17.3
3[d]	41.0	14.0	0.8	21.0	16.0	7.2
4[e]	33.0	25.0	7.0	15.0	13.0	7.0

a. Values for radical chain bromination (from reference 9). The conversion was 20%. *b.* 1,1-dibromocyclohexane and *cis*-1,2-dibromocyclohexane could not be distinguished. *c.* Values obtained in the GoAgg^{III} reaction on cyclohexyl bromide (for reaction conditions see reference 8). *d.* Cyclohexyl bromide (1.0 mmol) and $CBrCl_3$ (4.0 mmol) irradiated in a Rayonet photoreactor with four 3000 Å light tubes under Ar at 35-38°C for 22 hs. *e.* Radical reaction initiated by $(PhCOO)_2$ in Py/AcOH. *f.* Not detected

the oxidant. *GoAgg^{III}* is the same as GoAgg^{II} but including picolinic acid as a catalyst in a ratio 3:1 to iron. For a recent review, see: Barton, D. H. R.; Doller, D. *Pure & Appl. Chem.* **1991**, *63*, 1567-1576.

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6. PhSH (10 mmol) and the halogenating reagent (1 mmol) were dissolved in freshly distilled CH_2Cl_2. The system was purged with Ar for 10 min at 0°C. The *N*-hydroxy-2-thiopyridone derivative of cyclohexane carboxylic acid[7] (0.2 mmol) was added and the solution was irradiated using a W lamp (150W)in a Pyrex glass round bottomed flask stoppered with a rubber septum while cooling in an ice-water bath. An internal standard was added (naphthalene) and the mixture was analyzed by GC.
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8. $FeCl_3.6H_2O$ (0.1 mmol) and cyclohexane (20 mmol) was dissolved in pyridine (14 mL). Picolinic acid (0.3 mmol) and acetic acid (1.15 mL) was added, followed by the brominating agent (2.5 mmol). H_2O_2 (250 μL, 30% in H_2O, 2.5 mmol) was added and the mixture was stirred overnight at room temperature in a 125 mL Erlenmeyer flask stoppered with a rubber septum. After the usual workup[2] the mixture was analyzed by GC.
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