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Regio-and Chemo-Selectivity of Adamantane Halogenation by Gif-Barton and Metalloporphyrin Catalysis and by Classical Free-Radical Reactions.**

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Abstract. The halogenation of adamantane by $CBrCl_3$ with Gif-Barton and metalloporphyrin catalysis is compared with classical free-radical halogenations (Br_2, NBS, t-BuOCl, R_2NCl) and with the behaviour of simple alkanes (n-hexane, 2,3-dimethylbutane, cyclohexane); the free-radical mechanism is discussed.

Free-radical functionalization of adamantane has been the subject of several investigations[1], but the factors affecting the intra- and intermolecular selectivity are not yet clear. In the Gif oxidation of adamantane, Barton and coworkers[2] reported: "the ratio C^2/C^3 is 1.1, much higher than typical values for radical reactions", and that would exclude a radical nature of the oxidation; on the opposite, we[3] have reported evidences concerning the radical character of the Gif oxidation. Our interpretation would certainly be invalidated if the free-radical reactivity of adamantane was comparable to that of simple alkanes or cycloalkanes. Thus we have investigated the halogenation of adamantane according to the Gif reaction, metalloporphyrin catalysis and

Table 1. Selectivity in 1-chloro (I), 2-chloro (II), 1-bromo (III) and 2-bromoadamantane (IV) with several radical sources*

RADICAL SOURCE	I %	II %	III %	IV %	C^2/C^3
Gif reaction[a] + $CBrCl_3$	4.1	---	69.2	26.7	0.36
Mn-porphyrin[b] + $CBrCl_3$	3.8	---	66.6	29.6	0.42
Fe-porphyrin[c] + $CBrCl_3$	2.9	---	63.4	31.5	0.50
t-BuOCl[d]	47.7	52.3	---	---	1.09
Br_2/H_2O[e]	---	---	48.9	51.1	1.04
Br_2/H_2O_2[f]	---	---	48.7	51.3	1.05
NBS[g]	---	---	65.9	34.1	0.52
iPr_2NCl/H_2SO_4	91.3	8.65	---	---	0.09

*) The balance of the reacted adamantane is in all cases > 90%. Experimental conditions: a) 2.5 mmol adamantane, 2.5 mmol $CBrCl_3$, 2.5 mmol t-BuOOH, 0.1 mmol $FeCl_3$ in 14 mL pyridine and 1.15 mL AcOH at 60°C for 18 hrs; b) 5 mmol adamantane, 5 mmol $CBrCl_3$, 5 mmol t-BuOOH, 0.01 mmol Mn(III)-tetra-(2,6-dichlorophenyl)porphyrin-acetate = TDClPP-OAc, 3 mmol pyridine in 6 mL CH_2Cl_2, at 0°C for 30', then at r.t. for 30'; c) same as in b), with Fe(III)-TDClPP-OAc; d) 4 mmol adamantane, 2 mmol t-BuOCl in 10 ml CH_2Cl_2, irradiated at 254 nm for 4 hrs; e) 5 mmol adamantane, 1 mmol Br_2, 15 mL H_2O and 15 mL $ClCH_2CH_2Cl$ refluxed for 4 hrs; f) as in e) with 1 mmol H_2O_2; g) 5 mmol adamantane, 2 mmol NBS, 0.05 mmol Br_2, 10 ml CH_2Cl_2, irradiated at 254 nm for 4 hrs; h) 2 mmol adamantane, 1 mmol iPr_2NCl in 6 mL 85% H_2SO_4 and 4 mL CCl_4, 0.5 mmol $FeSO_4$ 7 H_2O at r.t. for 30'.

classical free-radical reactions (Br_2, NBS, t-BuOCl, R_2NCl); the results are reported in Table 1. Moreover, we have determined the relative rates of adamantane, n-hexane, 2,3-dimethylbutane and cyclohexane halogenation and the results are reported in Table 2.

Several new relevant aspects of the free-radical reactivity of adamantane arise from these results:

i) The ratio C^2/C^3 (1.09) for the chlorination of adamantane by t-BuOCl is in excellent agreement with Barton's results and strongly supports our interpretation of the Gif reaction, in which the selectivity would be determined by the rate of hydrogen abstraction by t-BuO• radical.

ii) The results of bromination by Br_2 are quite striking because the ratio C^2/C^3 is much higher than those observed for simple alkanes and cycloalkanes and the sequence of reactivity is quite different compared with chlorination by t-BuOCl: for C^2-H, hexane > cyclohexane > adamantane while for C^3-H, 2,3-dimethylbutane > adamantane; even C^2-H of hexane is more reactive than C^3-H of adamantane. With NBS the selectivity changes somewhat compared to that observed with Br_2, because it is well-known[4] that two reaction paths occur: one is a bromine atom chain in which NBS acts merely as Br_2 source, and it is most easily observed with reactive substrates bearing allylic and benzylic hydrogens; the other is a succinimide radical chain, acting mostly on the less reactive alkanes. The selectivity of bromination by Br_2 depends on the rate of hydrogen abstraction by Br• (eq.1), which is in all cases endothermic and therefore strongly affected by the energies of the involved bonds; it can be also influenced by reversal both within the solvent cage and through reaction of cage escaped pairs[5]

$$Br^{\cdot} + R\text{-}H \rightleftarrows Br\text{-}H + R^{\cdot} \qquad (1)$$

The external reversal is minimized by working in a two-phase system in the presence of water or H_2O_2, which rapidly extracts and oxidizes HBr, keeping its concentration low during the reaction. The results obtained for bromination support the reported evaluation[6] of the energy for C^3-H bond in adamantane (3.7 kcal/mol greater than the C^3-H bond energy in isobutane): the selectivity would reflect the sequence of C-H bond energies. We suggest that the different intermolecular selectivity with t-BuO• radical should be ascribed to a prevalence of the polar over the enthalpic effect; this should reflect a high electron availability of the C-H bonds in adamantane.

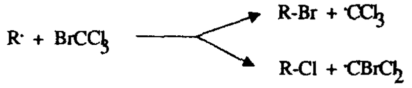
In order to support this interpretation we have investigated a free-radical chlorination much more affected by the polar effect: the Minisci chlorination[7] by N-chloroamines in acidic medium. The C^3-H bond of adamantane is more reactive than the C^3-H bond of 2,3-dimethylbutane towards $iPr_2NH^{\cdot +}$ radical, in spite of the higher bond energy, supporting a higher sensitivity to polar effects. The C^2-H bond of adamantane appears, however, to be deactivated compared to C^2-H of cyclohexane and n-hexane, suggesting that also steric effects[8] can play a role in this chlorination.

iii) Under Gif and metalloporphyrin catalyzed halogenation by $CBrCl_3$ the interpretation of the selectivity is less clear, leading Professor Barton[9] to exclude a radical mechanism also for this halogenation; that, in our opinion, is simply due to several radical and redox chains superimposing on hydrogen abstraction (eqs.2-6)

$$\text{t-BuOOFe(III)} \longrightarrow \text{t-BuO}^{\cdot} + \left[{}^{\cdot}\text{O-Fe(III)} \longleftrightarrow \text{O=Fe(IV)} \right] \qquad (2)$$

$$\text{t-BuO}^{\cdot} + \text{HOOBu-t} \xrightarrow{k} \text{t-BuOH} + {}^{\cdot}\text{OOBu-t} \qquad k = 2.5\ 10^{8}\ M^{-1}s^{-1} \qquad (3)$$

$$XO^{\cdot} + H\text{-}R \longrightarrow X\text{-}OH + R^{\cdot} \qquad (4)$$



$$R^{\cdot} + BrCCl_3 \longrightarrow \begin{cases} R\text{-}Br + {}^{\cdot}CCl_3 \\ R\text{-}Cl + {}^{\cdot}CBrCl_2 \end{cases} \qquad (5)$$

$$R\text{-}H + {}^{\cdot}CCl_3 \longrightarrow R + CHCl_3 \qquad (6)$$

We[3,10] have trapped t-BuOO· and t-BuO· radicals by styrene and α-methylstyrene, and $\cdot CCl_3$ by cyclohexene under the same reaction conditions. The main difference between Gif and metalloporphyrin catalysis concerns reaction (3), which is very fast[11] in CH_2Cl_2, but it is inhibited in pyridine solution by hydrogen bond formation[10]. The radical character of these halogenations is strongly supported by the very peculiar behaviour of the 1-adamantyl radical in chlorine and bromine abstraction from $CBrCl_3$,quite different from that of simple alkyl radicals, as first reported by C.Ruchardt[12] and confirmed by I.Tabushi[13]: the observed selectivity reported in Tables 1 and 2, are in excellent agreement with Tabushi's results, 1-adamantyl radical abstracting both chlorine and bromine atoms from $CBrCl_3$, in about 1:17 ratio, while 2-adamantyl radical only abstracts bromine atoms.

Table 2. Relative reactivity of adamantane, cyclohexane, n-hexane and 2,3-dimethylbutane per H atom[a]

RADICAL SOURCE (mmol)	*ALKANE*	C^2_{ad}/C^2_{alk}	C^3_{ad}/C^2_{alk}	C^3_{ad}/C^3_{alk}
t-BuOCl	cyclohexane	0.73	2.37	
NBS	cyclohexane	0.49	4.03	
Br_2/H_2O_2	cyclohexane	0.07	0.22	
$i\text{-}Pr_2NCl$	cyclohexane	0.07	8.89	
t-BuOCl	n-hexane	0.536	1.893	
NBS	n-hexane	0.129	1.406	
Br_2/H_2O_2	n-hexane	0.012	0.044	
$i\text{-}Pr_2NCl$	n-hexane	0.010	3.230	
t-BuOCl	2,3-dimethylbutane			0.612
NBS	2,3-dimethylbutane			0.030
Br_2/H_2O_2	2,3-dimethylbutane			0.029
$i\text{-}Pr_2NCl$	2,3-dimethylbutane			4.067
Gif reaction + $CBrCl_3$[b]	cyclohexane	1.16	3.01	
Gif reaction + $CBrCl_3$[b]	n-hexane	2.30	6.95	
Mn-porphyrin[b]	cyclohexane	1.48	9.95	
Mn-porphyrin[b]	n-hexane	2.10	3.62	
Mn-porphyrin[b]	2,3-dimethylbutane			3.47

a) the experimental conditions are the same reported in Table 1.

b) 1-bromo and 1-chloroadamantane are formed in about 1:17 ratio.

In conclusion, the behaviour of adamantane and adamantyl radical towards free-radical reactions are quite peculiar and the observed selectivity is not always a reliable diagnostic criterion for the mechanism.

***dedicated to prof.Christoph Rüchardt on the occasion of his 65th birthday.*

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References.

1. Perkins, R.P.; Pincock, R.E. *Can.J.Chem.* **1978**, *56*, 1269; Smith, C.V.; Billups, W.E. *J.Am.Chem.Soc.* **1974**, *96*, 4307; Owens, P.H.; Gleicher, G.J.; Smith, L.M., Jr. *J.Am.Chem.Soc.* **1968**, *90*, 4122 and references cited therein.
2. Barton, D.H.R.; Doller, D. *Acc.Chem.Res.* **1992**, *25*, 504.
3. Minisci, F.; Fontana,F. *Tetrahedron Lett.* **1994**, *35*, 1427; Minisci, F.; Fontana,F.; Araneo, S.; Recupero, F. *Tetrahedron Lett.*, **1994**, *35*, 3759-3762; Minisci, F.; Fontana,F.; Araneo, S.; Recupero, F. *J.Chem.Soc., Chem.Commun.*, in press.
4. Tanner, D.D.; Meintzer, C.P.; Dionarian, N.; Singh, H.; Tsai, E.C.; Oumar-Mahamat, H. *J.Am.Chem.Soc.* **1990**, *112*, 2736-2739.
5. Tanner, D.D.; Reed, D.W.; Tan, S.L.; Meintzer, C.P.; Walling, C.; Sopchik, A. *J.Am.Chem.Soc.* **1985**, *107*, 6576-6584.
6. Kruppa, G.H.; Beauchamp, J.L. *J.Am.Chem.Soc.* **1985**, *108*, 2162-2169.
7. Deno, N.C. *Methods in Free-Radical Chemistry*; Huyser, E.S., ed.; M.Dekker: New York. 1975; p. 143.
8. Bernardi, R.; Galli, R.; Minisci, F. *J.Chem.Soc. (B)* **1968**, 324; Minisci, F. *Substituent Effects in Free-Radical Chemistry*; Viehe, H., ed.; D.Reidel: Dordrecht. 1986, p.391.
9. Barton, D.H.R.; Bèvière, S.D.; Chavasiri, W. *Tetrahedron* **1994**, *50*, 31.
10. Evidence for this aspect will be provided in a full paper.
11. Paul, H,; Small, R.D.; Scaiano, J.C. *J.Am.Chem.Soc.* **1978**, *100*, 4520-4527.
12. Ruchardt, C.; Herwig, K.; Eichler, S. *Tetrahedron Lett.* **1969**, 421.
13. Tabushi, I.; Aoyama, Y; Kojo, S.; Hamuro, J.; Yoshida, Z. *J.Am.Chem.Soc.* **1972**, *94*, 1177-1183.

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