Tetrahedron Letters, Vol 32, No 31, pp 3811-3814, 1991
Printed in Great Britain

0040-4039/91 $3 00 +
Pergamon Press plc

On the Mechanism of Carbon-Hydrogen Activation in Gif-type Reactions. Kinetic Isotopic Effects in Pyridine Solution.

Derek H. R. Barton [a], Darío Doller [a] and Yurii V. Geletii *[a,b]

a. Department of Chemistry, Texas A&M University, College Station, Texas 77843-3255, USA

b. Institute of Chemical Physics, USSR Academy of Sciences, Chernogolovka, Moscow region 142 432 USSR

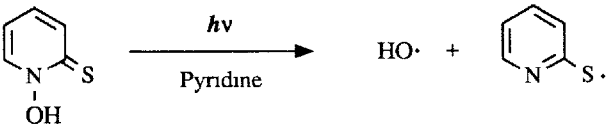
Abstract: Kinetic isotopic effects (KIE) were measured for oxidation, bromination and selenylation of $c\text{-}C_6H_{12}/c\text{-}C_6D_{12}$ in pyridine solution for different Gif-type, Fenton and other systems. The comparison of KIE and relative reactivity data for the pair $c\text{-}C_5H_{10}/c\text{-}C_6H_{12}$ proved that the mechanism of activation in Gif-type reactions is different from a hydrogen atom abstraction.

The hydrogen kinetic isotopic effect (KIE) is widely used for establishing the mechanism of chemical reactions[1]. A value of KIE different from unity indicates that the rate determining step involves the removal of an hydrogen atom, proton or hydride anion during a C-H bond cleavage. The quantitative analysis of KIE values for alkane oxidations has shown clearly its utility as a criterion for the understanding of the nature of the reactive species involved in the process of C-H activation[2]. The pair *cyclo*hexane/*cyclo*hexane-d_{12} is commonly used for quantification of KIE in oxidation processes and nearly all of the available data were obtained for these hydrocarbons.

The relative reactivity of *cyclo*pentane and *cyclo*hexane (C_5/C_6) is another very useful criterion for establishing the mechanism of C-H bond cleavage[2]. This ratio depends on whether a carbocation or an alkyl radical is involved as an intermediate in the C-H bond cleavage, as it reflects the different changes in conformational ring strain for *cyclo*pentane and *cyclo*hexane.

In previous papers we have described a number of systems for alkane functionalisation with unusual selectivity which we named Gif[3]. In the Gif^{IV} system hydrocarbons are oxidized by dioxygen in the presence of Zn powder and an Fe^{II} complex; in GoAgg^{II} (or GoAgg^{III}) the oxidant is hydrogen peroxide and the catalyst is an Fe^{III} complex. GoChAgg systems are the same as GoAgg but Fe^{III} is replaced by Cu^{II}. The nomenclature used is purely geographical, after the places where each system was first discovered: ***G****if-sur-Yvette and* ***O****rsay in France,* ***Agg****ieland in Texas, and* ***Ch****ernogolovka in the USSR[3c]. In these systems hydrocarbons are oxidized to ketones with minor amounts of alcohols, and the presence of pyridine is essential. A reaction intermediate can be trapped by, for example, $CBrCl_3$ or Ph_2Se_2, yielding alkylbromides or alkylphenylselenides, respectively, instead of ketones and alcohols[4].

There is practically no KIE or relative reactivity data in the literature on alkane oxidations carried out in pyridine as the solvent The equimolar mixture of H_2O_2 and Fe(II), known as Fenton's system, has been thoroughly studied and it is supposed to produce hydroxyl radicals as the reactive species[5-7]. It was recently found that hydroxyl radicals can be generated under mild conditions by irradiation (W-lamp) of N-hydroxy-2-thiopyridone **1**[8]. The reactivity of the hydroxyl radical and its KIE *in water* are well known[6] However, as a solvent dependence could be expected for both, we decided to measure the KIE in pyridine solution using both Fenton's system and photolytically generated hydroxyl radicals:



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The data obtained in our experiments and those available in the literature are shown in the Table. All the oxidative systems can be separated into three groups according to their KIE values. The lowest KIE obtained, of about 1.6, is for Fenton's system. It is slightly higher than the value reported in water (1.1)[6]. This small difference can be attributed to complexation of hydroxyl radicals with pyridine. Such a behavior is well established for chlorine atoms in pyridine[13]. The highest values of KIE (2.0-2.4) are observed for the oxidation and bromination reactions under Gif-type conditions, the KIE being the same within experimental accuracy. These data suggest that the same reactive species is involved in the cleavage of the C-H bond, and the mechanism of cleavage is the same regardless of the final product.

Here it is worth mentioning that *cyclo*hexyl hydroperoxide was recently proved to be an intermediate in the GoAgg^{II} oxidation of *cyclo*hexane, the iron-catalyzed *cyclo*alkyl hydroperoxide decomposition leading to ketone[14]. In principle, one could expect that the experimentally observed value of KIE, measured as the ratio of light and heavy ketones formed, would be the net result of two consecutive C-H bonds cleavages However, under certain kinetic conditions[15] the KIE for the cleavage of the first C-H bond is numerically equal to that ratio. The addition of PPh_3 to Gif^{IV} systems changes the distribution of the products, the major product in this case is alcohol instead of ketone due to the reduction of the intermediate hydroperoxide[16]. However, the value of KIE obtained is the same as in the absence of triphenylphosphine (Table). Thus, our systems display those kinetic characteristics, and the KIE can be derived from the ratio of the reaction products.

The KIE for selenylation reactions in all the systems examined is the same, its value being lower than for the oxidation and bromination and higher than for the formation of *cyclo*hexyl-pyridines in Fenton's system. The similarity between these values needs to be investigated further.

The values obtained for the partial relative reactivity of *cyclo*pentane and *cyclo*hexane (C_5/C_6) in oxidation under Gif^{IV}, GoAgg^{III} or GoChAgg conditions are different from most of the values in the other systems; C_5/C_6 values being smaller than in a hydrogen abstraction by hydroxyl radicals in water and higher than in the reaction with NO_2^+ in H_2SO_4 (Table). Although the system $HMnO_4$ in H_2O shows a value of C_5/C_6 similar to those for Gif-type reactions, the reported KIE is far from being comparable to those found in our systems. The value for radical bromination is 1.3[12].

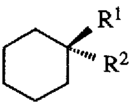
The values of KIE and C_5/C_6 obtained in our experiments are considered together, show clearly that for all the systems examined belonging to the Gif-family the first reaction step is similar and involves the cleavage of a C-H bond in the rate determining reaction step The reactive species is not a strong electrophile, in agreement with previous data deduced from its chemical reactivity[17], and the mechanism of C-H bond activation differs from hydrogen atom abstraction by hydroxyl radicals.

ACKNOWLEDGMENTS: One of us (Yu V.G.) is grateful to the Institute of Chemical Physics of the USSR Academy of Sciences for support of this work. We are also indebted to Merck Sharp & Dohme for a postdoctoral fellowship (D.D.) and to the N.S.F., B.P. and Quest Intl. for financial support.

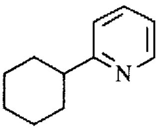
Table. Kinetic Isotopic Effect and Partial Relative Selectivity (C_5/C_6) [a].

System	Gif^{IV}	GoAgg^{II}	GoAgg^{III}	GoChAgg	Fenton	1 + $h\nu$	Fenton[e]	HMnO$_4$ [f]	NO$_2^+$ [g]
Solvent	Pyridine						Water		H$_2$SO$_4$
Additional Reagents, Major Products[a]	Kinetic Isotopic Effect (KIE) [h]								
none; **3,3***	2.3	2.2	2.1	2.3			1.1	5.0	2.2
PPh$_3$[b]; **2,2***	2.0	---- [k]	---- [k]	---- [k]	---- [k]				
Ph$_2$Se$_2$[c]; **5,5***	1.7	---- [k]	---- [k]	---- [k]	1.7	1.7			
N$_2$; **6, 6*,7,7***	---- [l]	---- [m]	---- [m]	---- [m]	1.5				
CBrCl$_3$[d]; **4,4***	---- [n]	2.4	2.1	2 4	1.5				
	Partial Relative Selectivity (C_5/C_6) [i]								
8 / 3	0.60 [j]		0.85	0.80			1.14	0.88	0.25

a Reactions were carried out at room temperature and atmospheric pressure *Gif*^{IV} 28 0 ml of pyridine, 5 0 ml of acetic acid, 0 2 mmol of FeCl$_3$ 6H$_2$O, 7 0 mmol of Zn powder, under air. *GoAgg*^{II} same as Gif^{IV} but using 13 0 mmol of H$_2$O$_2$ instead of Zn *GoAgg*^{III} same as GoAgg^{II} with additional 0 6 mmol of picolinic acid *GoChAgg* 33.0 ml of pyridine, 3 0 mmol of Py HClO$_4$, 0.3 mmol of Cu(ClO$_4$)$_2$ 6H$_2$O *Fenton*· 28 0 ml of pyridine, 5 0 of acetic acid, 12 0 mmol of Fe(ClO$_4$)$_2$ 6H$_2$O, 8 0 mmol of H$_2$O$_2$ *Photolysis of 1* 6.0 mmol of **1** in 28 0 ml of pyridine and 5 0 ml of acetic acid were irradiated (W lamp, 150 W) in the presence of Ph$_2$Se$_2$ An equimolar ratio of C$_6$H$_{12}$ and C$_6$D$_{12}$ (10.0 mmol each) was used in every case. The asterisk indicates the corresponding *per*-deuterated cyclohexyl-derivative *b*.16 0 mmol *c* 28 0 mmol *d* 15 0 mmol *e* From from reference 6 *f* From reference 10 *g* From reference 11 *h* For detailed experimental details, see reference 9 *i* Yields of ketones normalised *per* C-H bond *j* From reference 12 *k* H$_2$O$_2$ reacts very rapidly with the additional reagent (PPh$_3$ or Ph$_2$Se$_2$), therefore no further reaction is observed *l*. Reaction requires O$_2$ *m* O$_2$ does not not have any effect on this reaction (see reference 14) *n* CBrCl$_3$ reacts with Zn, therefore this reaction is studied in H$_2$O$_2$-based systems only



2. R^1=H; R^2=OH
3. R^1,R^2=O
4. R^1=H; R^2=Br
5. R^1=H; R^2=SePh



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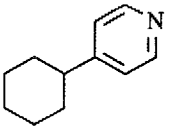

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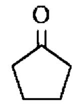

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V. *Tetrahedron*, in press. For the nomenclature of Gif-type systems see: *c*. Barton, D. H. R.; Halley, F.; Ozbalik, N.; Schmitt, M.; Young, E. and Balavoine, G. *J. Am. Chem Soc.* **1989**, *111*, 7144 .

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9. Experimental details and work-up procedures are as reported elsewhere[3b]. The end of the reactions were determined by hydrogen peroxide consumption (I_2/starch test) or by the complete dissolution of the Zn powder. The reaction mixtures were analyzed by GC-MS. The average mass spectra of each major product was obtained. The KIE was calculated as the ratio of the heights of the following peaks: 98/108 for *cyclo*hexanones; 82/92 for *cyclo*hexanols; 83/94 for *cyclo*hexylbromides; 161/172 for *cyclo*hexylpyridines; (83+240)/(94+251) for *cyclo*hexylphenylselenides.
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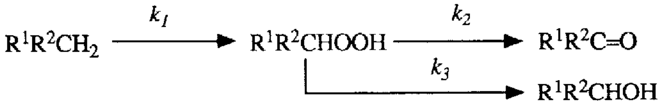
15. It can be demonstrated that for a reaction scheme like the one shown below, if



$$\begin{tikzcd}
R^1R^2CH_2 \arrow[r, "k_1"] & R^1R^2CHOOH \arrow[r, "k_2"] \arrow[dr, "k_3"'] & R^1R^2C{=}O \\
& & R^1R^2CHOH
\end{tikzcd}$$

$d[R^1R^2C{=}O]/dt{=}k_2[R^1R^2CHOOH]^n$ and $d[R^1R^2CHOH]/dt{=}k_3[R^1R^2CHOOH]^n$, the ratio of unlabelled and deuterated products will be equal to the KIE of the rate determining step if there is one major reaction product, e.g $k_2 \gg k_3$ or $k_2 \ll k_3$ Then the decomposition of the intermediate *cyclo*alkyl hydroperoxide will not influence the value of KIE. Under appropriate conditions ketone and alcohol are formed in comparable yields[16], from these data the KIE for the hydroperoxide fragmentation to ketone was estimated to be about 2. This was done considering that in the reduction of the former to the alcohol there is not hydrogen isotopic effect (breakage of an O-O bond).

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(Received in USA 19 March 1991)