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Cyclopropylbenzene ring opening by chlorine atom: radicals or radical ions?†

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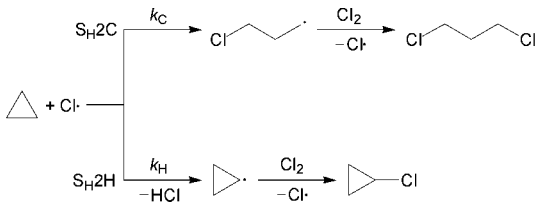
ABSTRACT: Cyclopropylbenzene radical chlorination leads to hydrogen atom abstraction and to ring opening. The contribution of the last process is increased in the presence of acids and in polar solvents. It is suggested that the ring opening process proceeds via radical cation formation by single electron transfer from cyclopropylbenzene to the chlorine atom in the first stage of reaction. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: mechanism; ring opening; free radical chlorination; radical cations

INTRODUCTION

The free radical halogenation of cyclopropanes produces halogen-substituted cyclopropanes and dihalosubstituted propanes (Scheme 1).

The ring opening reaction is usually described in the literature as a bimolecular radical substitution on a carbon atom (S_H2C)‡ and involves the backside attack of a chlorine atom on the least-hindered position of cyclopropane, resulting in the formation of the most stable ring-opened radical. Free radical processes have been thoroughly investigated in the bromination of arylcyclopropanes[1,2] and chlorination of cyclopropane;[3] however, little is known about the chlorination of cyclopropylbenzene.[4] This reaction is of considerable interest because arylcyclopropanes can be easily oxidized to form radical cations,[5,6] which may form ring opening products upon nucleophilic attack (Scheme 2). Moreover, such a radical cation pathway has been proposed for the side-chain photochlorination of polyalkylbenzenes.[7]



Scheme 1

RESULTS AND DISCUSSION

Free radical chlorination of cyclopropylbenzene (CPB) leads to 1-chloro-1-phenylcyclopropane, 1,3-dichloro-1-phenylpropane and products of aromatic electrophilic substitution (2- and 4-chlorophenylcyclopropanes) (Scheme 3). The yield of electrophilic substitution products is solvent dependent and ranges from 5 to 70 mol%.

The observed ratio of 1-chloro-1-phenylcyclopropane to 1,3-dichloro-1-phenylpropane [$(k_C/k_H)_{obs}$, chemoselectivity] is a convenient parameter for describing the reaction system:

$$\left(\frac{k_C}{k_H}\right)_{obs} = \frac{[1]}{[2] \times 2} \qquad (1)$$

The chemoselectivity is statistically corrected by a factor of two, because ring opening in cyclopropylbenzene can proceed by cleavage of two identical carbon–carbon bonds. We found that in polar solvents $(k_C/k_H)_{obs}$ is not constant, but becomes larger with higher conversion of cyclopropylbenzene. Addition of gaseous hydrogen chloride to the initial reaction mixture increases the chemoselectivity. However, addition of an acid scavenger (K_2CO_3) decreases $(k_C/k_H)_{obs}$ (Table 1).

The increase in chemoselectivity in the presence of

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‡The usual abbreviation for free radical hydrogen substitution is S_R or S_R2 and for free radical substitution on a carbon atom it is S_H2. We use S_H2H (homolytic bimolecular substitution on hydrogen atom) and S_H2C (homolytic bimolecular substitution on carbon atom) in this paper for the purpose of unification.
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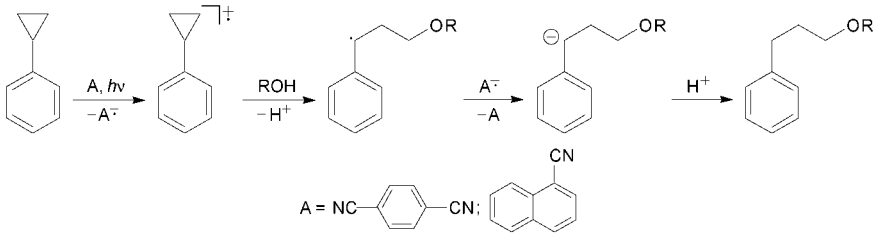
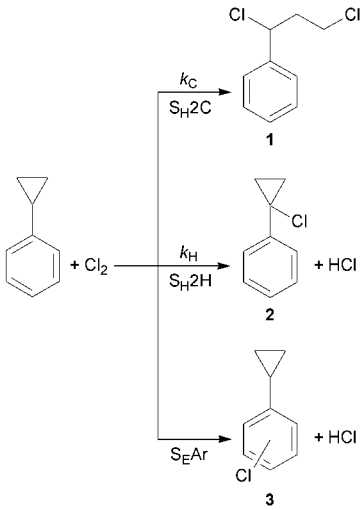


Scheme 2



Scheme 3

hydrogen chloride can be a consequence either of an increase in the rate of the ring opening reaction or of a decrease in the rate of radical abstraction. To understand what reaction is affected by the presence of acid we have studied the free radical chlorination of CPB–2-chlorobenzyl chloride and CPB–ethylbenzene substrate mixtures (Schemes 3 and 4).

The regioselectivity of ethylbenzene chlorination, $(k_\alpha/k_\beta)_{obs}$, and the relative reactivities of benzylic hydrogens $(k_H/k_\alpha)_{obs}$, $(k_H/k_{H'})_{obs}$, were not affected by the addition of acids or acid scavengers, implying that the presence of acids has little effect on the rate of hydrogen abstraction. In sharp contrast, the yield of ring-opened products and the relative rate constants $(k_C/k_\alpha)_{obs}$ and $(k_C/k_{H'})_{obs}$ were greatly affected by the presence of acids (Table 2).

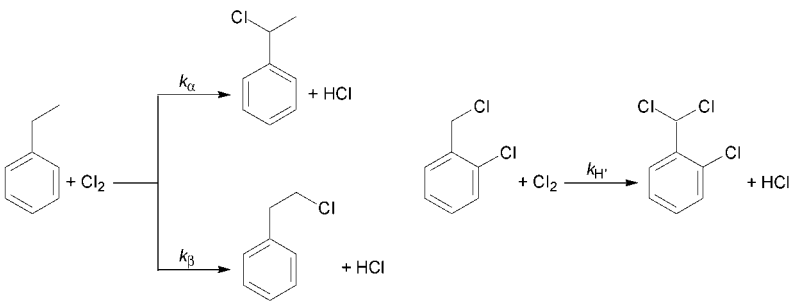
Table 1. Chemoselectivity of CPB chlorination[a]

	$(k_C/k_H)_{obs}$		
Solvent	Without additive	With HCl[b]	With K_2CO_3[c]
CCl_4	1.3 ± 0.2	1.5 ± 0.2	1.0 ± 0.2
$CHCl_3$	5.5 ± 1	25 ± 2	3.2 ± 0.3
CH_2Cl_2	12 ± 1	40 ± 7	4.5 ± 0.5

[a] [CPB] = 0.40 M, $[Cl_2]$ = 0.16–0.19 M, T = 36 ± 1 °C, *hv*.
[b] Hydrogen chloride was bubbled into the reaction mixture for 1 min before irradiation.
[c] 200–1000 mol% relative to Cl_2 concentration.

It should be noted that the chemoselectivity values of CPB in the two substrate mixtures are very different from that of CPB alone. This is due to the fact that in the substrate mixtures, the co-substrates generate additional quantities of HCl (Scheme 4) and thus accelerate the ring opening. The higher the reactivity of the benzylic hydrogen atom of the co-substrate, the faster the rates of CPB ring opening will be, since the yield of hydrogen chloride increases. Accordingly, $(k_C/k_H)_{obs}$ for the CPB–ethylbenzene mixture is greater than that for the CPB–2-chlorobenzylchloride mixture.

In support of our conclusion that HCl influences the ring-opening step exclusively, we carried out CPB free radical chlorination with reagents, such as *tert*-butyl hypochlorite and especially *N,N*-dichlorophenylsulfonamide, which do not produce HCl as reaction product[8] (Table 3). As expected, the ring opening process was essentially absent in the latter case.



Scheme 4

Table 2. Influence of additives on the selectivity of chlorination in two-substrate systems

Additive	$(k_C/k_H)_{obs}$ [a]	$(k_\alpha/k_\beta)_{obs}$ [a]	$(k_H/k_\alpha)_{obs}$ [a]	$(k_C/k_\alpha)_{obs}$ [a]	$(k_C/k_H)_{obs}$ [b]	$(k_H/k_{H'})_{obs}$ [b]	$(k_C/k_{H'})_{obs}$ [b]
—	22 ± 2	7.5 ± 0.5	0.20 ± 0.06	4.5 ± 0.2	14 ± 2	10 ± 1	140 ± 18
HCl	34 ± 3	8.3 ± 0.5	0.17 ± 0.05	5.9 ± 0.2	40 ± 10	10 ± 1	400 ± 98
CH_3COOH	40 ± 2	7.0 ± 0.6	0.28 ± 0.05	11.0 ± 0.7	32 ± 3	14 ± 2	450 ± 43
K_2CO_3	17 ± 2	10.3 ± 0.5	0.23 ± 0.04	3.9 ± 0.1	6 ± 1	9 ± 1	49 ± 9

[a] [CPB] = 0.40 M; [$PhCH_2CH_3$] = 0.82 M; [Cl_2] = 0.16–0.19 M; solvent CH_2Cl_2; $T = 36 \pm 1$ °C; *hv*.
[b] [CPB] = 0.40 M; [2-$ClC_6H_4CH_2Cl$] = 3.9 M; [Cl_2] = 0.16–0.19 M; solvent CH_2Cl_2; $T = 36 \pm 1$ °C; *hv*.

Table 3. Chemoselectivity of CPB chlorination by various reagents[a]

Reagent	Conditions	$(k_C/k_H)_{obs}$
Cl_2	*hv*, 36 °C	1.2
$(CH_3)_3COCl$	*hv*, 36 °C	0.2–0.3
$C_6H_5SO_2NCl_2$	AIBN[b], 80 °C	<0.05

[a] [CPB] = 0.40 M, [reagent] = 0.08–0.16 M, solvent CCl_4.
[b] Azobisisobutyronitrile (5 mol%).

We investigated the influence of the acid concentration on the chemoselectivity to obtain additional kinetic data, which might help to understand better the mechanism of ring opening of CPB. Acetic and trifluoroacetic acid were used, because their concentration can be measured more accurately than that of gaseous HCl.

We found that the ring opening reaction was accelerated on addition of acids (Fig. 1). The curvatures of the plots corresponding to acetic and trifluoroacetic acid are the reverse of each other. We assume that chlorination of CPB in trifluoroacetic acid is a complex reaction. Cyclopropanes can react with trifluoroacetic acid via an electrophilic mechanism[9] and such process distorted the results of the gas chromatographic analysis of our reaction mixtures. In the case of the highest investigated concentration of trifluoroacetic acid, the chromatographic peaks of unidentified products overlap the peaks of the studied products. In contrast, acetic acid reacts with cyclopropanes very slowly. In control experiments we checked that there are no side-reactions during chlorination of CPB in this solvent. Finally, CPB was chlorinated in different solvents and the chemoselectivity was studied as a function of the solvent. It was found earlier that regioselectivity of free radical chlorination (e.g. of ethylbenzene or 2,3-dimethylbutane) depends on the solvent owing to chlorine atom complexation ($Cl^{\cdot}$/Solv, where Solv = benzene, pyridine, carbon disulfide, alkyl bromides, etc).[10,11] No relationship was found between the regioselectivity of ethylbenzene, $(k_\alpha/k_\beta)_{obs}$, and the chemoselectivity of CPB, $(k_C/k_H)_{obs}$. Therefore, the difference in chemoselectivities in various solvents could not be explained by chlorine atom complexation. The chemoselectivity values were correlated with a variety of solvent parameters (Kirkwood function, internal pressure, viscosity, E_T and others), but a satisfactory correlation was found only with Dimroth's E_T scale ($R^2 = 0.97$) (Fig. 2).

According to our data (Table 2) for $(k_H/k_\alpha)_{obs}$ and $(k_H/k_{H'})_{obs}$, hydrogen substitution from the benzylic position of CPB proceeds by the classical S_H2H mechanism. However, it is unlikely that ring opening proceeds by S_H2C, because such a reaction should be not affected by addition of acids. We propose that this reaction occurs by a radical cation process (Scheme 5).

The first step of the proposed mechanism is a single

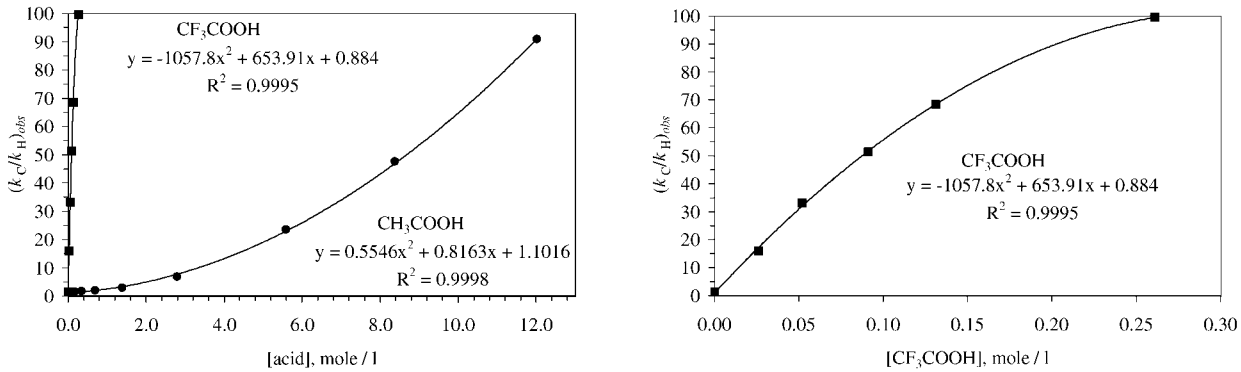


Figure 1. The influence of acetic and trifluoroacetic acids on the chemoselectivity of CPB photochlorination

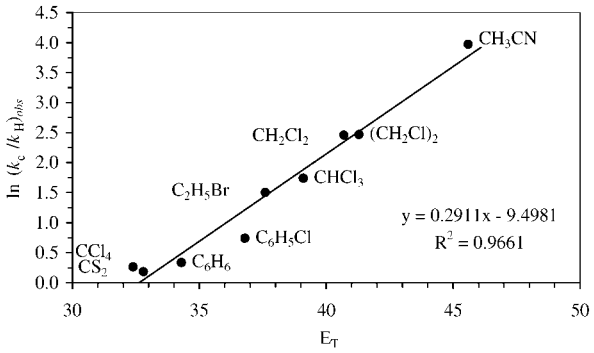


Figure 2. The correlation of the chemoselectivity of CPB photochlorination with Dimroth's E_T scale

electron transfer from the CPB molecule to a chlorine atom, which usually is rate determining in an overall irreversible transformation. This assumption is supported by the values of the one-electron oxidation potentials of CPB ($E°_{ox}$ vs SCE = 1.94 V)[6] and chlorine atom ($E°_{ox}$ vs NHE = 2.1 V,[12] which corresponds approximately to 1.83 V vs SCE) in acetonitrile, if one considers that acids shift the oxidation potential of chlorine atom in a positive direction. In other words, acids can accelerate an electron transfer step because of hydrogen bond formation with a radical ion pair. The non-linear (parabolic) dependence of chemoselectivity on the concentration of acetic acid may be explained by assuming that two molecules of acid are involved in the electron transfer reaction.[13]

The correlation of chemoselectivity with E_T scale may be explained by better stabilization of the radical ion pair in polar solvents.

EXPERIMENTAL

General considerations. Reaction systems were analysed by gas chromatography on a Tsvet-104 instrument equipped with a flame-ionization detector. Analyses were carried out using a 3 m × 3 mm i.d. SE-30 column. Cyclopropylbenzene and its derivatives, *tert*-butyl hypochlorite and *N*,*N*-dichlorophenylsulfonamide were synthesized by the usual methods. Ethylbenzene, 2-chlorobenzyl chloride and solvents were commercially available. All solvents were distilled prior use. The solvents such as chlorinated hydrocarbons were purified by passing through a column packed with potassium permanganate on aluminium oxide before distillation with the purpose of eliminating the inhibitors of free radical reactions (these inhibitors are standard additives to commercially available chlorinated hydrocarbons which prevent its light-induced decomposition).

Kinetic measurements. Selectivities were calculated using the following equations:

$$\left(\frac{k_\alpha}{k_\beta}\right)_{obs} = \frac{[PhCHClCH_3] \times 3}{[PhCH_2CH_2Cl] \times 2} \quad (2)$$

$$\left(\frac{k_H}{k_\alpha}\right)_{obs} = \frac{[\alpha\text{-ClCPB}] \times [PhCH_2CH_3]_0 \times 2}{[PhCHClCH_3] \times [CPB]_0} \quad (3)$$

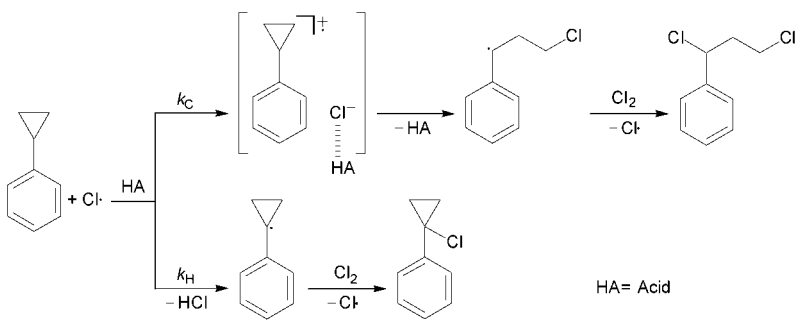
$$\left(\frac{k_H}{k_{H'}}\right)_{obs} = \frac{[\alpha\text{-ClCPB}] \times [2\text{-}ClC_6H_4CH_2Cl]_0 \times 2}{[2\text{-}ClC_6H_4CHCl_2] \times [CPB]_0} \quad (4)$$

$$\left(\frac{k_C}{k_\alpha}\right)_{obs} = \frac{[PhCHClCH_2CH_2Cl] \times [PhCH_2CH_3]_0}{[PhCHClCH_3] \times [CPB]_0} \quad (5)$$

$$\left(\frac{k_C}{k_{H'}}\right)_{obs} = \frac{[PhCHClCH_2CH_2Cl] \times [2\text{-}ClC_6H_4CH_2Cl]_0}{[2\text{-}ClC_6H_4CHCl_2] \times [CPB]_0} \quad (6)$$

Although the relative constants were obtained at considerably high conversion of substrates (30–40%), no further chlorination of the primary reaction products was observed. In the case of two substrate systems, the assumption that the initial and final concentrations of two competitors are equal resulted in an error no larger than 10%.

We mentioned above that the chemoselectivity depends on the conversion of CPB in polar solvents. This is connected with by-product hydrogen chloride, that is produced in S_H2H and S_EAr processes. In order to fix the reaction conditions we carried out experiments with a constant concentration of molecular chlorine (0.16–0.19 mol l^{-1}). However, it should be noted that the



Scheme 5

portion of CPB spent on the radical pathways (S_H2H and S_H2C) is different in various solvents and in the presence of additives. This is due to the different ratio of the radical and the electrophilic processes in various media.

Kinetic experiments were carried out in 1 ml open glass tubes thermostated by a water flow from an ultrathermostat (VEB MLW U15^C) with stirring by a magnetic microstirrer.

For chlorination with molecular chlorine, a solution of substrate was thermostated for 10 min, then irradiation with a 400 W medium-pressure mercury arc lamp at a distance of 30 cm was turned on and a titrated solution of chlorine in carbon tetrachloride (1.0–1.2 M) was added to the substrate (e.g. the resulting concentration of CPB was 0.4 M), then irradiation was continued for 10 min. Such a method of chlorine solution addition is used to prevent the electrophilic aromatic substitution which otherwise proceeds to a great extent. Chlorination with *tert*-butyl hypochlorite was carried out in the same manner, but the chlorinating agent was added to the substrate before irradiation. There was no residual reagent in the above reactions (KI probe) at the end of these experiments (conversion of reagent was 100%), therefore the samples were analysed by gas chromatography without additional treatment. For chlorination with *N*,*N*-dichlorophenylsulfonamide, a solution of the substrate, the chlorinating agent and azobisisobutyronitrile (5 mol%) was heated on water-bath (80 °C) with stirring for 3–5 h. Residual reagent was removed by shaking the reaction mixture with aqueous KI and the organic layer was dried and analysed by gas chromatography.

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