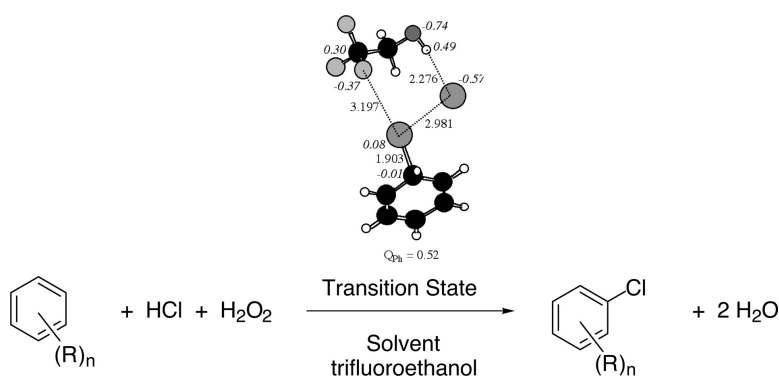


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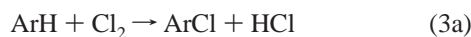
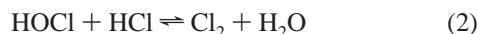
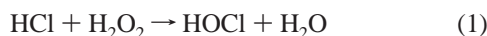
Electrophilic Aromatic Chlorination and Haloperoxidation of Chloride Catalyzed by Polyfluorinated Alcohols: A New Manifestation of Template Catalysis

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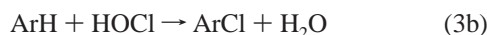
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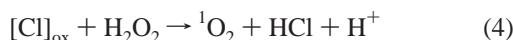
The use of hydrohalic acids as green halogenating agents has been inspired by the activity of haloperoxidase enzymes that catalyze halogenation reactions by oxidizing halides with hydrogen peroxide.¹ This has also led to extensive research activity in the area of functional and structural mimics of these enzymes, with emphasis on bromoperoxidase models.² Haloperoxidase reactions are based on the concomitant oxidation of a halide (e.g., Cl⁻) with H₂O₂ and halogenation of substrates (e.g., arenes), eqs 1–3.



and/or



For oxychlorination, it is possible to oxidize chloride under acidic conditions in the absence of a catalyst³ to obtain HOCl and/or Cl₂;⁴ these oxidized species can then be reacted in situ with substrates such as arenes to yield chlorinated products. It is, however, normally essential for the substrate to be highly active in the chlorination reaction to avoid competitive fast reduction of the oxidized chlorine species, eq 4.⁵



The synthetic utility of HCl/H₂O₂ as a general and “green” (no halide waste) chlorination method is limited by the facts that (a) only very reactive substrates can be used (rate eq 3 > rate eq 4) and (b) a large excess of HCl is needed for complete conversion of the organic substrate,³ vide infra. Recently, it has been found that polyfluorinated alcohol solvents can activate H₂O₂ and facilitate epoxidation reactions.⁶ Notable rate enhancements were also observed in other oxidation reactions with H₂O₂ upon addition of typical catalysts.⁷ Theoretical calculations showed that the catalytic effect of the polyfluorinated alcohol in epoxidation with H₂O₂ is a result of its action as a complementary charge template that stabilizes the transition state (TS) of the reaction by 5–8 kcal mol⁻¹.⁸ Now we report that trifluoroethanol as solvent catalyzes chlorination of arenes by a similar complementary charge template stabilization of the TS. This allows the extension of the use of HCl/H₂O₂ as a high yield chlorinating agent for arene substrates that do not undergo oxychlorination in other solvents.

The catalytic effect of trifluoroethanol (TFE) as solvent as compared to its nonfluorinated analogue, ethanol, in the oxychlorination of two representative arenes, anisole and toluene, with HCl/H₂O₂ is presented in Figure 1.

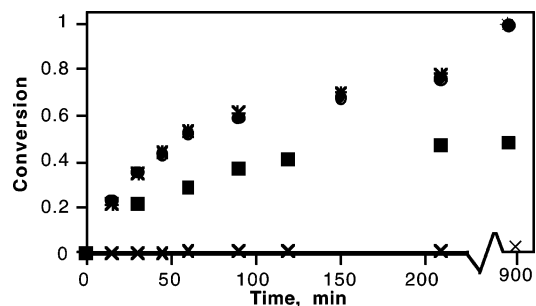


Figure 1. Oxychlorination of anisole and toluene with HCl/H₂O₂ in TFE and EtOH. Reaction conditions: 1 M ArH, 1 M HCl, 5 M H₂O₂, 10.6 M H₂O in TFE or EtOH, 25 °C. *, anisole (TFE), $k = 2.21 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ($r^2 = 0.98$); ●, toluene (TFE), $k = 2.09 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ($r^2 = 0.99$); ■, anisole (EtOH), $k = 9.43 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ($r^2 = 0.98$); ×, toluene (EtOH), $k = 1.83 \times 10^{-7} \text{ M}^{-1} \text{ s}^{-1}$ ($r^2 = 0.83$).

The reaction is initially cleanly second order (ArH and HCl) in the presence of excess H₂O₂ (second-order rate constants were calculated, Figure 1). One may note several key differences between the reactions in TFE and EtOH. First, the reaction rates are essentially the same for anisole and toluene in TFE. Second, anisole reacted only twice as fast in TFE versus EtOH, while for toluene the rate was accelerated by 3 orders of magnitude. Third, only anisole reacted in reactions where mixtures of anisole and toluene (0.5 M each) were used as substrates. Fourth, in EtOH, the chlorination of anisole considerably deviated from the second-order profile after 3.5 h, and the reaction did not proceed beyond ~60% even after 1 week; however, in TFE, the reactions were cleanly second order to completion. Fifth, there was no deuterium isotope effect for the oxychlorination of toluene/toluene-*d*₈ in TFE; however, there was an isotope effect, $k_{\text{H}}/k_{\text{D}} = 4.9 \pm 0.3$, for oxychlorination for HCl–H₂O/DCI–D₂O. Finally, by titration analysis, there appeared to be no significant nonproductive decomposition of H₂O₂.

The results obtained indicate the following: (a) anisole is inherently much more reactive than toluene in electrophilic aromatic chlorination ($\rho = \sim -9$);⁹ this difference was verified for oxychlorination by using anisole/toluene mixtures. Thus, TFE acts mainly to accelerate the chlorination of toluene to a very significant extent ($\times 1000$), and, as such, the rate-determining step in TFE becomes the formation of the active chlorinating species (eqs 1 and 2), precisely as for anisole. This conclusion is strongly supported by the $k_{\text{H}}/k_{\text{D}} = 4.9$ for HCl–H₂O/DCI–D₂O. (b) TFE has only a minor effect (a factor of 2) on the formation of the active chlorinating species as compared to EtOH. (c) TFE, however, supports the oxychlorination of arenes to completion of HCl, whereas in EtOH, the reaction stops at 50–60%. The cessation of the reaction in EtOH (anisole) is not related to nonproductive decomposition of the active chlorinating species (H₂O₂ is not lost),

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Table 1. Oxychlorination of Arene with HCl/H₂O₂ in Trifluoroethanol^a

substrate	yield, mol %	product
benzene	73	chlorobenzene (100)
toluene	>99	2-chlorotoluene (36) 4-chlorotoluene (64)
ethylbenzene	>99	2-chloroethylbenzene (33) 4-chloroethylbenzene (67)
cumene	>99	2-chlorocumene (21) 4-chlorocumene (79)
<i>i</i> -butylbenzene	98	2-chloro- <i>iso</i> -butylbenzene (25) 4-chloro- <i>iso</i> -butylbenzene (75)
<i>t</i> -butylbenzene	>99	2-chloro- <i>tert</i> -butylbenzene (15) 4-chloro- <i>tert</i> -butylbenzene (85)
<i>p</i> -xylene	98	2-chloro- <i>p</i> -xylene (100)
mesitylene	>99	chloromesitylene
chlorobenzene	23	1,4-dichlorobenzene (67) 1,2-dichlorobenzene (33)

^a Reaction conditions: 1 M ArH, 1.5 M HCl, 3 M H₂O₂, 8.1 M H₂O in TFE, 25 °C, 15 h.

but rather it is because of low H⁺ concentrations. Therefore, the polyfluorinated alcohol has a dual function in the nonmetal-catalyzed oxychlorination of arenes; it catalyzes electrophilic chlorination of less reactive arenes and oxidation of chloride at lower H⁺ concentrations. In practice, TFE can be used as solvent to oxychlorinate a series of normally nonreactive arenes, Table 1. It may be observed that benzene and its alkylated derivatives react in high yields at room temperature. Even deactivated substrates such as chlorobenzene were somewhat reactive, although nitrobenzene did not react.¹⁰

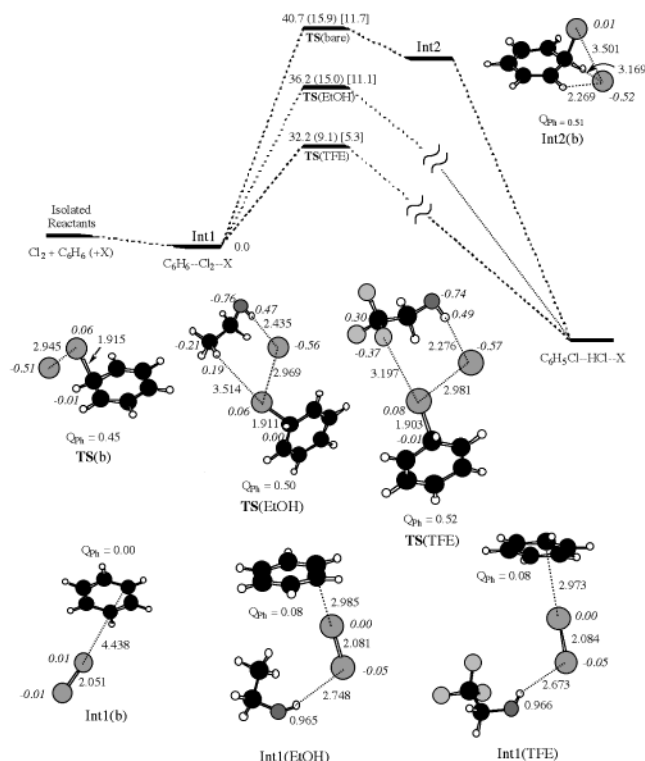


Figure 2. Bond activation barriers (kcal/mol) for the chlorination of benzene: out of parentheses, in the gas phase; in parentheses, a solvent with a dielectric constant $\epsilon = 10.65$; in square brackets, a solvent with $\epsilon = 33.65$. X is EtOH or TFE.

To understand the catalytic effect of TFE on the electrophilic chlorination of arenes, we used DFT¹¹ to study the chlorination of benzene by one of the conceivable active chlorinating species, Cl₂. Figure 2 shows the energy profiles for chlorination in the bare system, and with EtOH and TFE.¹² It is seen that, irrespective of the dielectric constant, TFE lowers the barrier relative to the bare

system or the one coordinated by EtOH by ~ 6 kcal/mol. The bottom geometries and charge distribution (NBO charges) in the three TS's show that TFE stabilizes the polar TS by acting as a charge template with charges complementary to those in the TS. Thus, the OH group stabilizes the departing Cl⁻ by an OH⁻...Cl⁻ hydrogen bond, while the negative fluorine stabilizes the positively charged Cl^{δ+} that attacks the benzene ring. This charge complementarity can be contrasted with the adverse effect of ethanol. Here, while EtOH can stabilize the departing Cl⁻, its interaction with the attacking Cl^{δ+} is repulsive due to the positive charges on the hydrogen atoms of the CH₃ group. Thus, TFE catalyzes the chlorination by providing a complementary charge template to the TS, thereby enabling oxychlorination of less activate arenes.¹³

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Supporting Information Available: Details of the B3LYP/6-311+G* results (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (12) To ascertain that the trends in the barriers do not arise from global solvent polarity effects, we calculated (Jaguar 4.1, Schrödinger, Inc., Portland, OR, 2001) all of the processes in two dielectric constants ($\epsilon = 10.65$, nonpolar solvent, and $\epsilon = 33.65$, methanol). We used RB3LYP hybrid functional and the 6-311+G* basis set after benchmarking (Table S1). The critical species passed the stability test and did not reveal a lower unrestricted solution. The bare system led to the expected cationic σ -complex coordinated to Cl⁻ (see Supporting Information). The surface around this intermediate is extremely flat, and our geometry scans show that it collapses either to the addition product or the substitution product. This collapse is not the rate determining step (verified experimentally – no deuterium isotope effect in the oxychlorination of toluene/*toluene-d₈*). Therefore, in all reactions, we focused on the bond activation step which is rate determining.
- (13) Similar effects on the TS and similar experimental rate constants were observed using hexafluoro-2-propanol instead of TFE as solvent.

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