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NUCLEOPHILICITY vs. BASICITY OF THE HYDROXIDE ION UNDER EXTRACTIVE PHASE TRANSFER CATALYSIS CONDITIONS.

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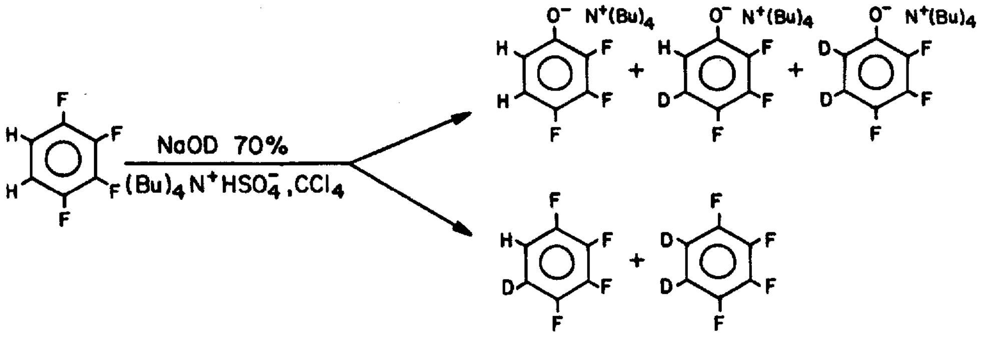
Abstract: Extraction of hydroxide ion under phase transfer catalysis conditions (PTC) affords an extremely strong base and nucleophile. The competition between H/D exchange and nucleophilic aromatic substitution on 1,2,3,4-Tetrafluorobenzene (1) shows that under extractive phase transfer catalysis conditions the hydroxide ion is more effective as a base than as a nucleophile.

Despite the well documented low extractability of the hydroxide ion by quaternary ammonium salts, a growing number of reports have appeared in which synthetic achievements have been attributed to OH^- extraction[1]. It seems that hydroxide extraction into a non-polar organic medium can be achieved under the right choice of phase transfer catalysis conditions. The hydroxide ion is extracted into the organic phase with a limited number of water molecules in its hydration sphere and proved to be a very strong base indeed[2]. This enhanced basicity has been applied for oxidation[3], isomerization[4] and H/D exchange of very weak carbon acids, as weak as those of pKa 38[3]·.

The extracted hydroxide ion can act as a nucleophile as well as a base. However, the question of the ability of basicity vs. nucleophilicity in the organic phase has received very little attention in the phase transfer catalysis literature. This phenomenon can be explained by the skepticism regarding the possibility of OH^- extraction and the fact that reactions such as deuteration, isomerization and oxidation have been applied on substrates that cannot react in a nucleophilic substitution reaction. On the other hand, when such a reaction does take place, the reaction mixture included minor amounts of substitution products[6-7]. The ratio of basicity vs. nucleophilicity of OH^- in the organic phase was examined by Herriott and Picker in elimination reactions[8] but the picture was not clear since different alkylhalides gave opposite results.

In order to clarify this question we examined the competition reaction between H/D exchange and nucleophilic aromatic substitution on 1,2,3,4-tetrafluorobenzene (1) under extractive phase transfer catalysis conditions. (Scheme 1).



Scheme 1: The competition between H/D exchange and nucleophilic aromatic substitution of 1,2,3,4-tetrafluorobenzene (1).

The basicity of the hydroxide ion was examined by the H/D exchange of the aromatic protons. This reaction, which demonstrates the basicity of OH^- under the reaction conditions, was monitored by proton NMR spectroscopy and the decrease of the aromatic proton band relative to an internal standard (mesitylene) was attributed to the H/D exchange process.

The nucleophilicity of the hydroxide ion as examined by the aromatic nucleophilic substitution of the fluorine atom was followed by UV spectroscopy. The decrease of the absorption of the 259 nm band was attributed to the nucleophilic displacement. Under these basic conditions, the product, i.e., the fluorophenolate ion precipitates from the organic phase (CCl_4) and therefore cannot be detected by UV spectroscopy.

Figure 1 shows the kinetics of the deuteration and the nucleophilic aromatic substitution reactions. It can be seen clearly that the deuteration reaction is faster than the nucleophilic aromatic substitution, a fact that illustrates that under these kinetic conditions the ability of the OH^- to behave as a base is greater than its ability to act as a nucleophile. This phenomenon is even more pronounced since part of the substrate (1) which participates in the aromatic nucleophilic reaction was first deuterated. This process was taken into account by a mathematical iteration process. The result is shown on graph C.

Aromatic nucleophilic substitutions have been applied under phase transfer catalysis conditions, but the role of the hydroxide ion was to create the active nucleophile: alkoxide, thiolate, etc.[8]. The results which were presented in this work are the first example of a direct aromatic nucleophilic substitution of OH^- under PTC conditions and formation of a phenol[9] derivative. The phenolic product was isolated and identified by standard methods[10]. Further studies on the properties of the hydroxide ion as a nucleophile under PTC conditions are in progress. A representative experiment on (1) was carried out in cyclohexane as the organic solvent (24°C, 50% NaOH and $Bu_4N^+HSO_4^-$ as PTC catalyst). The results of this experiment are depicted in Figure 2. In this case the conversion was rather high (45%).

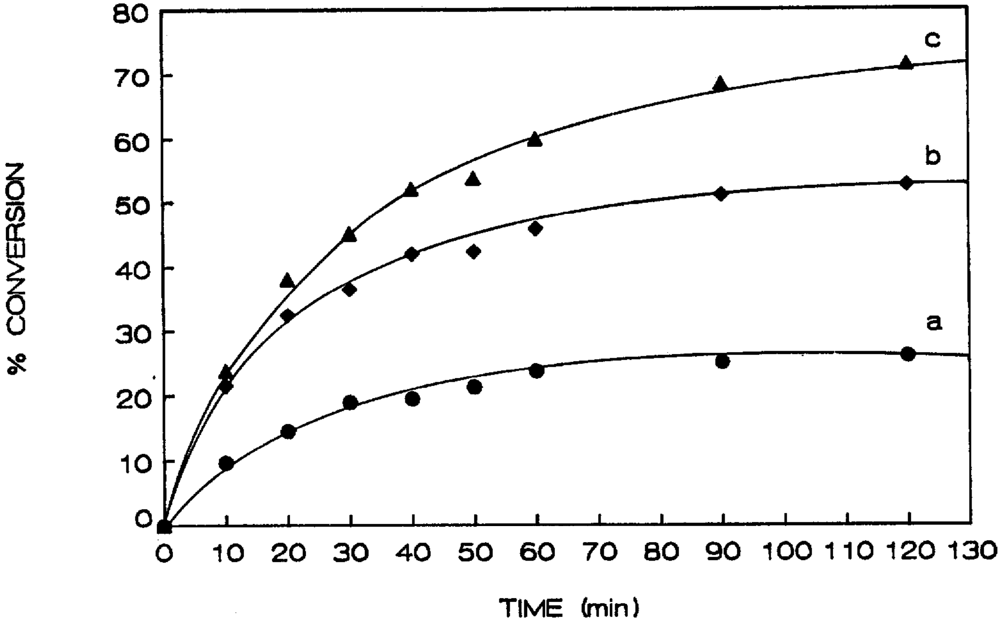


Figure 1: Deuteration vs. nucleophilic aromatic substitution of 1,2,3,4-tetrafluorobenzene (1). (a) Nucleophilic aromatic substitution; (b) H/D exchange as derived from ^1H NMR; (c) H/D exchange after mathematical iteration process.

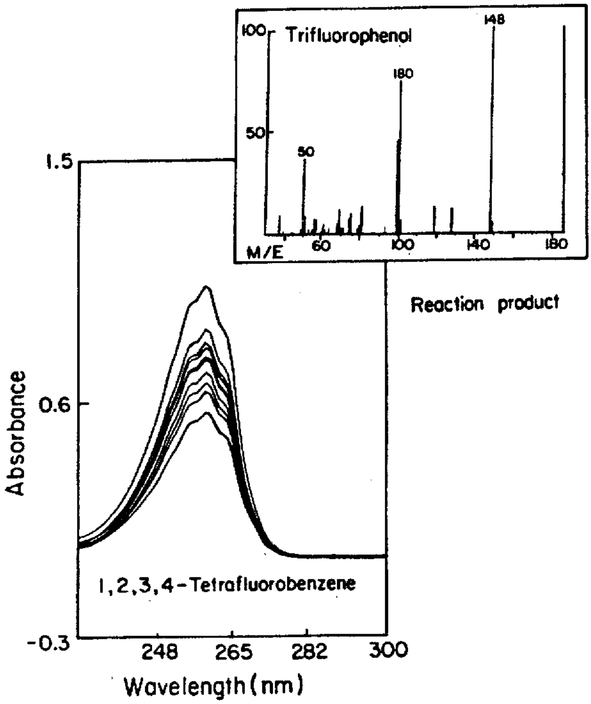


Figure 2: Progress of the nucleophilic aromatic substitution reaction and the product identification by GC/MS analysis.

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9. Standard reaction conditions are: (a) Competition experiment - 300 mg (2 mmole) of (1), 600 mg, 70% $NaOD/D_2O$, 680 mg (2 mmole) $Bu_4N^+HSO_4^-$, 5cc CCl_4, 120 mg (1 mmole) of mesitylene (only for the H/D exchange experiment). (b) Nucelophilic aromatic substitution - 300 mg (2 mmole) of (1), 800 mg 50% NaOH, 680 mg (2 mmole) $Bu_4N^+HSO_4^-$, 5 cc cyclohexane, 3h, 24°C.
10. Standard methods of structure elucidation of the phenol: GC/MS; ^1H NMR, ^{19}F NMR and IR spectroscopy.

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