

# Impact of sulfur heteroatoms on the activity of quaternary ammonium salts as phase transfer catalysts for nucleophilic displacement reactions



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## ABSTRACT

The application of a new class of alkylammonium salts as phase-transfer catalysts was investigated. These salts are tetra(4-thiaalkyl) ammonium bromides, and the key questions of the study focus on how the incorporation of a sulfur atom in the alkyl chains affects the efficacy of the salts as phase-transfer catalysts. Employing the nucleophilic substitution of cyanide for bromide on 1-bromopentane as a model reaction, reaction rate constants and activation energies are evaluated. The kinetic parameters obtained using the tetrathiaalkylammonium salts are compared to those obtained using their tetraalkylammonium analogs. The general trend is that the presence of sulfur in the alkyl chains reduces the reaction rates and increases activation energies. This trend is analyzed both in terms of computational modeling and experimental distribution coefficients to determine the cause of the slower reaction rates. Thiaquats are shown to distribute more into the aqueous phase than traditional quat salts of similar chain length, resulting in lower organic phase concentrations. Quantum calculations indicate stronger ion pairing for the thiaquats, increasing activation energies and slowing reaction rates. Thus, differences in rate enhancements are attributable both to phase distribution and ion pairing effects.

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## 1. Introduction

A common challenge encountered in organic synthesis is the need to bring about reaction between two reagents that are present in immiscible phases. For example, a reaction might require an anion that is available in a water-soluble salt to displace a leaving group on a compound present in an organic solvent. One means of addressing this issue is the use of a phase-transfer agent that acts to bring one reactant across a phase boundary and into contact with the other reactant. As the reaction takes place, the phase-transfer agent is regenerated and available for another cycle. Because of this regeneration, the phase-transfer agents are necessary only in catalytic amounts, and thus the process is termed phase-transfer catalysis (PTC) [1].

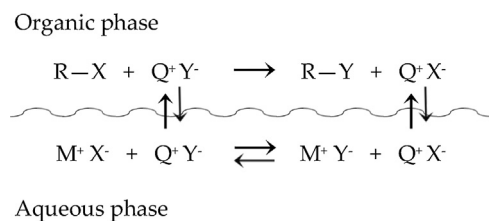
The simplest case of a phase-transfer catalytic mechanism is the Starks' transfer mechanism, depicted in Fig. 1 [2]. The catalyst in

this case is represented by  $Q^+X^-$ , and the desired intrinsic reaction is the one that takes place in the organic phase. For more complex interfacial reactions, an alternate mechanism was proposed by Makosza [3]. Whether a transfer or interfacial mechanism predominates depends on numerous factors, including the organophilicity of the catalyst and the degree of hydration of ionic reactants.

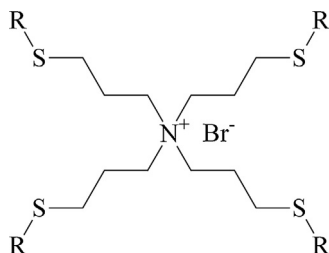
Due to their ionic yet lipophilic nature, the most common classes of phase-transfer catalysts are the quaternary tetraalkylammonium or tetraalkylphosphonium salts, called "quat salts" [4]. In these, the alkyl chains in the cations promote solubility in organic solvents. The anion for reaction is exchanged between the reactant cation and the catalyst cation either in the aqueous phase or at the interface between the phases, and carried into the organic phase for reaction as part of an ion pair with the quaternary cation. Most of the literature on PTC argues that not only does the phase-transfer catalyst act to bring the anion into contact with the organic reagent, but also that the anion is activated for reaction, having stronger nucleophilicity as a result of looser pairing with the quaternary cation than with its original cation, often  $Na^+$  or  $K^+$ . Evidence for this argument has been found in the trends with respect to alkyl

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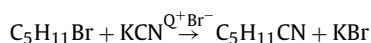
**Fig. 1.** Starks' transfer mechanism for a phase-transfer catalyzed nucleophilic substitution reaction:  $R-X + M^+Y^- \rightarrow R-Y + M^+X^-$ .  $M^+$  = metal cation,  $Q^+$  = quaternary ammonium ion.  $Q^+X^-$  is the phase-transfer catalyst.



**Fig. 2.** A tetra(4-thiaalkyl) ammonium salt. The structure may be varied by altering the nature of the R- group. Traditional quat salts have a methylene group in place of the sulfur atoms.

chain lengths: looser pairing is associated with longer chains, which yield faster reaction rates [5,6]. This idea was challenged in a recent paper which argued that the effect was solely due to distribution between the phases, with longer chains resulting in higher catalyst complex concentrations in the organic phase [7].

Recent work in our group has addressed the synthesis of a novel class of quaternary ammonium salts, tetra(4-thiaalkyl) ammonium salts, represented in Fig. 2 [8]. These salts have a sulfur atom replacing the fourth methylene group from the nitrogen center on each chain. The sulfur in the chain is an artifact of a new versatile synthesis method employing thiol-ene click chemistry to synthesize these salts with a variety of functional groups beyond the sulfur [9]. This study investigates the use of these novel “thiaquat” salts as phase-transfer catalysts. As a model reaction, we have chosen one that has a well-characterized mechanism, the cyanide displacement on an alkyl halide. This irreversible, second-order nucleophilic substitution reaction is commonly used to evaluate the behavior of novel phase-transfer catalysts [10–18]. In this case, the substrate is 1-bromopentane:



By using an already well-understood reaction system, we are able to use PTC as a tool to elucidate information about the behavior of these compounds. Additionally, we are investigating the efficacy of these salts as phase-transfer catalysts and exploring their potential for industrial applications of PTC.

## 2. Experimental

### 2.1. Materials

For the catalysts syntheses, all of the starting organic thiols employed for our studies were commercially available in high purity and used without further purification. Octanethiol (>98.5% purity), ethanethiol (97% purity) and 2,2-dimethoxy-2-phenylacetophenone (99% purity, photoinitiator) were purchased from Aldrich Chemical Company. 1-Propanethiol (98% purity) and 2-propanethiol (isopropylthiol, 98% purity) were purchased from Acros Organics. Each salt was synthesized using tetraallylammonium bromide prepared from triallylamine (99% purity) and allyl

bromide (99% purity), both purchased from Aldrich Chemical Company and used without further purification.

Reactants for the phase-transfer reactions were obtained from Acros Organics. The 1-bromopentane was obtained in 99% purity and used as received. The potassium cyanide was purchased from Fisher Scientific and used as received.

### 2.2. Catalyst synthesis

The synthesis methods for the tetra(4-thiaalkyl) ammonium bromides employed as phase-transfer catalysts in this study are as described in a recent paper [8]. For these particular salts, the thiols used were ethanethiol, 1-propanethiol, 2-propanethiol, and octanethiol, resulting in the compounds tetra(4-thiahexyl) ammonium bromide, tetra(4-thiaheptyl) ammonium bromide, tetra(3-methyl-4-thiahexyl) ammonium bromide and tetra(4-thiadodecyl) ammonium bromide, respectively.

### 2.3. Phase transfer catalytic reactions

Experiments were conducted to evaluate the reaction kinetics parameters using both the tetra(4-thiaalkyl) ammonium bromide catalysts and the tetraalkylammonium bromides of analogous chain lengths. These reactions were carried out in a 50 mL round-bottom flask with stirring and temperature control. The organic phase was initially 10.0 mL of 0.200 M 1-bromopentane in toluene, and the aqueous phase was 2.0 mL of a saturated solution of potassium cyanide. The amount of potassium cyanide initially present was 20 times the stoichiometric amount, and solid was visible throughout the experiment. Catalyst amounts in all experiments were 5.0% of the molar amount of 1-bromopentane.

Reactions were conducted at 40 °C, 50 °C, 60 °C, and 80 °C. In each case, the catalyst was first dissolved in the organic reactant solution, and both solutions were brought to temperature before being combined. Samples of 1 μL of the organic phase were taken periodically throughout the reaction time and analyzed using a gas chromatograph (Agilent 7820A) equipped with a thermal conductivity detector. Stirring was maintained at 1400 rpm for all experiments.

### 2.4. Distribution ratios

The distribution of the quaternary salts between toluene and water was evaluated gravimetrically. A sample of the salt was first dissolved in toluene, and an equal volume of water was added. The flask was placed in a temperature-controlled bath and its contents were stirred slowly over a 24 h period (“slow-stir” method) [19]. The stirring was stopped, and the phases were allowed to separate completely, still at the desired temperature. Several samples of known volume were drawn from each phase. Sample volumes ranged from 1.000 mL to 4.000 mL. After complete evaporation of the solvent, the mass of salt remaining was measured, and the relative amounts from organic and aqueous phase samples were used to evaluate distribution ratios.

### 2.5. Quantum-based computational modeling

Preliminary optimizations and post-generation of electrostatic potential energy maps were performed using Spartan '08 (Wavefunction, Inc., Irvine, CA). The isolated cations and cation/bromide complexes were optimized in the gas phase using the B3LYP density functional method [20–23] and the 6-31G(d,p)\*\* basis set [24–26]. All structures were reoptimized and confirmed as stable by computing analytic vibrational frequencies using Gaussian 09 [27].

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