



# 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].

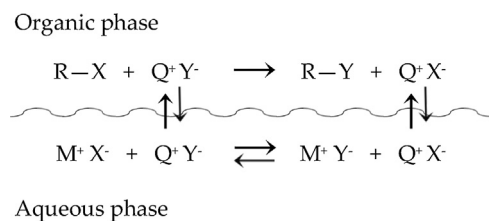
The simplest case of a phase-transfer catalytic mechanism is the Starks' transfer mechanism, depicted in Fig. 1 [2]. The catalyst in

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.

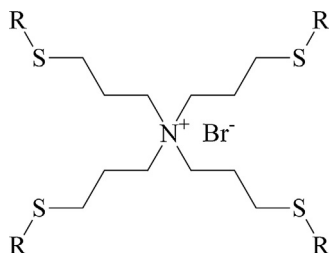
Due to their ionic yet lipophilic nature, the most common classes of phase-transfer catalysts are the quaternary tetraalkylammonium or tetraalkylphosphonium salts, called "quat salts" [4]. In these, the alkyl chains in the cations promote solubility in organic solvents. The anion for reaction is exchanged 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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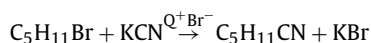
**Fig. 1.** Starks' transfer mechanism for a phase-transfer catalyzed nucleophilic substitution reaction:  $R-X + M^+Y^- \rightarrow R-Y + M^+X^-$ .  $M^+$  = metal cation,  $Q^+$  = quaternary ammonium ion.  $Q^+X^-$  is the phase-transfer catalyst.



**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.

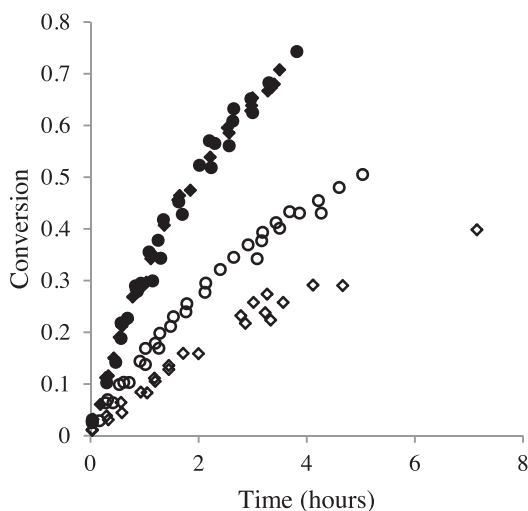
Reactions were conducted at 40 °C, 50 °C, 60 °C, and 80 °C. In each case, the catalyst was first dissolved in the organic reactant solution, and both solutions were brought to temperature before being combined. Samples of 1 μL of the organic phase were taken periodically throughout the reaction time 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].



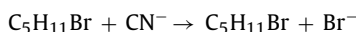
**Fig. 3.** Fractional conversion of 1-bromopentane to hexanenitrile at 60 °C using analogous tetraalkylammonium and tetra(4-thiaalkylammonium) bromides as phase-transfer catalysts. ● TDAB, ○ SC<sub>8</sub>, ◆ THAB, ◇ S(n-C<sub>3</sub>).

### 3. Results and discussion

#### 3.1. Comparison of alkyl and thiaalkyl catalyst activities

To evaluate the influence that the presence of a sulfur atom in the alkyl chains has on the effectiveness of a tetraalkylammonium salt as a phase-transfer catalyst, we compared tetraalkylammonium and tetra(4-thiaalkylammonium) bromides having chain lengths of twelve units and seven units. These salts are tetradodecylammonium bromide (TDAB) and tetraheptylammonium bromide (THAB) and their respective thiaquat analogs tetra(4-thiadodecylammonium) and (SC<sub>8</sub>) and tetra(4-thiaheptyl) ammonium bromide (S(n-C<sub>3</sub>)). Results of these reactions at 60 °C are shown in Fig. 3, which shows the conversion of 1-bromopentane to hexanenitrile over time for catalysts of both classes and chain lengths. The two tetraalkylammonium catalysts result in similar reaction rates, with slower rates for the sulfur-containing catalysts.

Based on the molecularity of a rate-limiting elementary step taking place in the organic phase:



second-order kinetics are implied, but the concentration of the catalyst complex is assumed constant, giving the rate law

$$r = k'[\text{C}_5\text{H}_{11}\text{Br}]_{\text{org}} \quad (1)$$

where

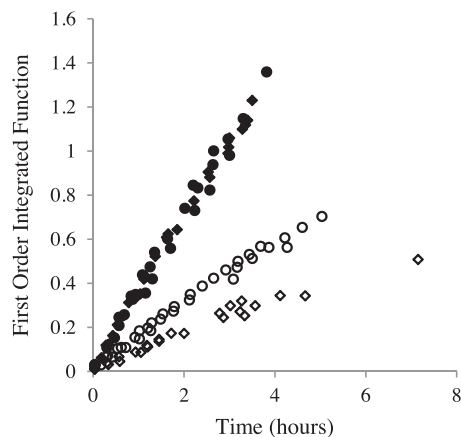
$$k' = k[\text{Q}^+\text{CN}^-]_{\text{org}} \quad (2)$$

Integration of the rate law yields the pseudo-first-order integrated rate expression:

$$\ln\left(\frac{1}{1-X}\right) = k't \quad (3)$$

where X is conversion of 1-bromopentane. The data from Fig. 3 are plotted according to this expression in Fig. 4.

The linearity of the data in Fig. 4 suggests that the reaction kinetics are indeed pseudo-first-order with respect to the concentration of 1-bromopentane, and the slopes of the lines represent the rate constants. This kinetic behavior is consistent with a constant amount of the reactive complex between the quaternary cation in the phase-transfer catalyst and the cyanide ion in the organic phase. The apparently constant concentration of the catalyst complex indicates that the reaction is rate-limited rather than transfer-limited



**Fig. 4.** Pseudo-first-order integrated rate expression for reaction of 1-bromopentane to hexanenitrile at 60 °C using analogous tetraalkylammonium and tetra(4-thiaalkylammonium) bromides as phase-transfer catalysts. The legend is the same as in Fig. 3.

under these conditions. The regenerated  $\text{Q}^+\text{Br}^-$  is able to partition between phases and undergo exchange for  $\text{CN}^-$  more rapidly than the intrinsic reaction occurs in the organic phase, and thus equilibrium levels of the  $\text{Q}^+\text{CN}^-$  are maintained in the organic phase.

Reaction data analysis for experiments with all of the other catalysts evaluated in this study also indicates pseudo-first-order kinetics. This consistency points to analogous mechanisms with the same rate determining step for all catalysts studied. Upon comparing the data in Figs. 3 and 4 with all of the later reaction systems described, we see no indication that there are differing reaction mechanisms occurring. Rate constants for all reactions described in this paper are included in Table 1, along with the abbreviations used for each salt. The abbreviated naming system used to distinguish between the thiaquat salts is based on the identification of the alkyl groups attached to the sulfur.

For the reactions represented in Fig. 3, rate constants for TDAB and THAB are equal, but those for SC<sub>8</sub> and S(n-C<sub>3</sub>) are lower. The similarity of the rates for the two reactions with traditional catalysts despite different chain lengths is consistent with other

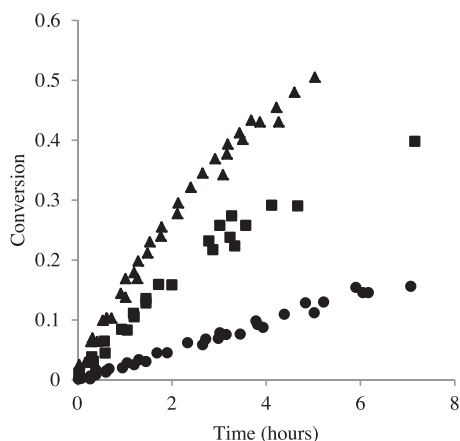
**Table 1**

Pseudo-first order rate constants for reaction of 1-bromopentane to hexanenitrile using various quaternary ammonium salts as phase-transfer catalysts. In all cases, aqueous phase is saturated KCN solution, and catalyst concentration is 0.010 M unless otherwise noted.

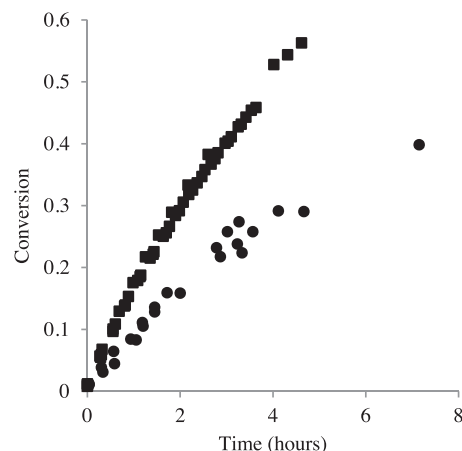
Quaternary cation in catalysts <sup>a</sup>	Abbreviation	Temperature (°C)	Rate constant, $k' \times 10^6$ (s <sup>-1</sup> )
Tetradodecylammonium	TDAB	40	22.0
		50	50.1
		60	95.4
		80	261
Tetra(4-thiadodecyl) ammonium	SC <sub>8</sub>	40	6.54
		50	17.8
		60	38.5
		80	142
Tetraheptylammonium	THAB	60	62.2 <sup>b</sup>
		40	20.0
		50	44.7
Tetra(4-thiaheptyl) ammonium	S(n-C <sub>3</sub> )	60	92.8
		40	3.18
		50	9.60
		60	20.7
Tetra(4-thiahexyl) ammonium	SC <sub>2</sub>	60	7.57
		40	9.48
Tetra(4-thia-5-methylhexyl) ammonium	S(i-C <sub>3</sub> )	50	21.6
		60	47.9

<sup>a</sup> Anion is bromide in each case.

<sup>b</sup> Amount of catalyst used is doubled.



**Fig. 5.** Effect of chain length in tetra(4-thiaalkyl) ammonium bromide catalysts on the rate of conversion of 1-bromopentane to hexanenitrile at 60 °C.  $\blacktriangle$  SC<sub>8</sub>,  $\blacksquare$  S(n-C<sub>3</sub>),  $\bullet$  SC<sub>2</sub>.



**Fig. 6.** Effect of S-substituent branching in tetra(4-thiaalkyl) ammonium bromide catalysts on the rate of conversion of 1-bromopentane to hexanenitrile at 60 °C.  $\blacksquare$  S(i-C<sub>3</sub>),  $\bullet$  S(n-C<sub>3</sub>).

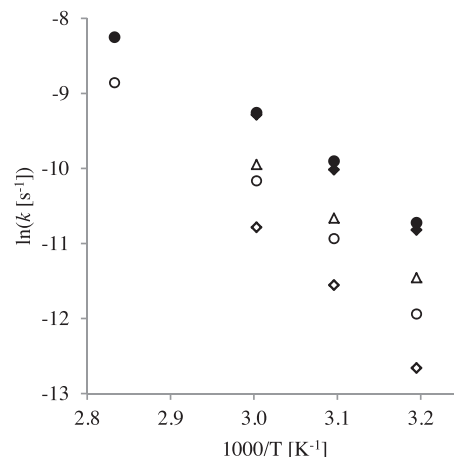
studies. The slower reaction rates for the thiaquat catalysts indicate additional factors introduced by the incorporation of sulfur in the chains. One interpretation of this result is that the sulfur atoms cause conformational and electronic changes in the chains that allow for tighter ion pairing with the cyanide ions, reducing their nucleophilicity and thus the rate of the substitution reaction. This explanation implies smaller intrinsic rate constant ( $k$ ) for the thiaquat-catalyzed reactions. Another possible explanation is that the sulfurs affect the partitioning of the catalyst between the organic and the aqueous phases. In this analysis, the apparent rate constant  $k'$  is lowered by a reduction in  $[Q^+CN^-]_{org}$ . Both of these possibilities will be addressed later in this paper.

### 3.2. Effect of chain length for thiaalkyl catalysts

In addition to the twelve- and seven-unit chains used for comparison to traditional catalysts, a six-unit salt, tetra(4-thiahexyl) ammonium bromide (SC<sub>2</sub>), was employed. Results for all three straight-chain thiaquat salts are shown in Fig. 5. The data indicate that increasing the length of the carbon chain beyond the sulfur atom increases the rate of reaction. At these total chain lengths, the overall chain length did not affect rates for traditional quats, as noted previously. This is consistent with the interpretation that the sulfur atoms have induced alterations in the geometry and electron density in the chains that result in a tighter association between the catalyst cation and nucleophilic anion. Shorter chains beyond the sulfur augment its effects by making the region around the sulfur more accessible to the anions.

### 3.3. Effect of branching for thiaalkyl catalysts

To explore the hypothesis that a more accessible region adjacent to the sulfur slows the rate of reaction, we investigated the effect of branching on the alkyl chain beyond the sulfur. Using isopropyl chains beyond the sulfur rather than ethyl or *n*-propyl chains, reaction rates were again evaluated, and results are compared in Fig. 6. The rate with the isopropyl group is markedly faster than that with the straight chains, and is in fact the fastest rate measured with thiaquat catalysts. Like the effect of chain length discussed above, this observation supports the explanation that reaction rates are lowered as a result of stronger ion association when the sulfur is present and the adjacent methylene units are accessible to the nucleophilic anion.



**Fig. 7.** Arrhenius plot for evaluation of activation energies for phase-transfer catalyzed reaction of 1-bromopentane to hexanenitrile with various catalysts.  $\bullet$  TDAB,  $\circ$  SC<sub>8</sub>,  $\blacklozenge$  THAB,  $\diamond$  S(n-C<sub>3</sub>),  $\triangle$  S(i-C<sub>3</sub>).

### 3.4. Effect of temperature

The effect of temperature on the rates of reaction using linear catalysts with 7- and 12-unit chains both with and without sulfur was evaluated by performing reactions at 40, 50, 60, and 80 °C. The branched thiaquat, S(i-C<sub>3</sub>) is also shown. As expected, the rate of reaction increased with temperature in all cases. Using rate constants obtained by plotting pseudo-first-order integrated expressions, the Arrhenius plots shown in Fig. 7 were constructed. Activation energies were calculated using the slopes from linear fits of the data in Fig. 7, and are reported in Table 2.

For the traditional quat salts, the activation energy for the quat with the longer chains is lower. This can be explained in that the longer chains make the positive center less accessible to

**Table 2**  
Activation energies for phase-transfer catalyzed substitution of cyanide on 1-bromopentane.

Catalyst	$E_A$ (kJ/mol)
TDAB	56
THAB	66
SC <sub>8</sub>	70
S(n-C <sub>3</sub> )	81
S(i-C <sub>3</sub> )	70

**Table 3**  
Experimental distribution ratios of  $Q^+Br^-$  between toluene and water at 60 °C, and the percent of the total catalyst amount that is present in the organic phase.

Salt	$\alpha$	% $Q^+_{org}$
TDAB	$1.1 \times 10^2$	99%
THAB	$1.0 \times 10^2$	99%
SC <sub>8</sub>	$4.0 \times 10^1$	98%
S(n-C <sub>3</sub> )	$1.1 \times 10^{-2}$	1.1%
S(i-C <sub>3</sub> )	$1.8 \times 10^{-2}$	1.8%

the anion, thus weakening the ion pairing and making the ion a stronger nucleophile. The activation energies for the thiaquat salts are higher than those for their analogous alkyl quats. The higher activation energy for the sulfur-containing salts is consistent with our interpretation that the thiaalkylammonium cations associate more strongly with the reactant anions, as more energy is necessary to weaken that association for reaction to occur. The data for the branched thiaquat supports this reasoning, showing that with hindered access to the sulfur region, the activation energy is similar to that with a longer chain. This effect is discussed further below in terms of computational results.

### 3.5. Effect of catalyst amount

The effect of changing the amount of catalyst in the system was investigated by doubling the amount of SC<sub>8</sub> for a reaction at 60 °C. As can be seen in the data in Table 1, the increase in the apparent rate constant is less than a factor of 2. One possible explanation for this behavior is that the solubility of the catalyst in toluene was exceeded in this case. If so, then  $[Q^+CN^-]$  in Eq. (2) is not actually doubled as intended, resulting in a lessened rate enhancement. An additional possibility for consideration is that the rate of reaction at the higher catalyst concentration is sufficiently fast that mass transfer limitations at the phase boundary begin to affect the apparent rate.

### 3.6. Mass-transfer limitations

Based on the activation energies shown in Table 2, we conclude that the stirring rate of 1400 rpm is sufficiently high that the rate of mass transfer does not limit the rate of reaction for most of the experiments performed. Temperature dependence would be significantly reduced if mass transfer were the rate-limiting step. The one case where that may present an exception is the reaction with doubled catalyst amount, addressed above.

### 3.7. Distribution ratios

The measured distribution ratios, defined:

$$\alpha = \frac{[Q^+Br^-]_{org}}{[Q^+Br^-]_{aq}} \quad (4)$$

for selected quaternary ammonium salts between toluene and water at 60 °C are displayed in Table 3.

A pronounced difference is observed between the behavior of the traditional quats and the thiaquats, indicating a significant increase in hydrophilicity resulting from the presence of the sulfurs. This can be attributed to interaction between the lone pairs on the sulfur atoms and the hydrogens in the water molecules. Further evidence supporting this explanation can be found in comparing the distribution ratios for the three thiaquats in the table. The salt with the octyl chain beyond this sulfur favors the organic phase, while both salts with terminal propyl groups favor the aqueous phase.

Note that these values were measured using a bromide anion rather than the cyanide anion in the reacting complex. It is possible

that hydration of the cyanide ions will cause an increase in aqueous phase concentrations for the cyanide salts over the bromide salts measured. However, while the values are for the bromide salts, the trends for the cyanide salts should be similar. Another notable difference between these values and those in the actual reacting system may result from the ionic strength of the solution in the reaction experiments. Here we have no added salt, and the aqueous phase during reaction is saturated with KCN. While the degree to which this will affect distribution is not quantified, its effect on the hydration and distribution of the two thiaquat salts with terminal propyl groups should be similar. We predict that the increased ionic strength in the aqueous phase will increase the amount of catalyst complex in the organic phase. In summary, while the values in Table 3 do not represent the distribution ratios for the specific reactive complex in this study, the trend in values should be similar for our reactive system.

Also included in Table 3 are values for the percent of the total quat salt in the system that is present in the organic phase. Based on those distribution ratios and the relative volumes of the toluene and aqueous phases, this percent was calculated:

$$\%Q^+_{org} = \left(1 + \frac{1}{\alpha}\right)^{-1} \times 100\% \quad (5)$$

If the difference in apparent rate constants is solely due to the difference in distribution between the phases, then the ratios of the rate constants using two different catalysts should be equal to the ratio of the percent of total catalyst present in the organic phase:

$$\frac{k_1}{k_2} = \frac{\%Q^+_{org,1}}{\%Q^+_{org,2}} \quad (6)$$

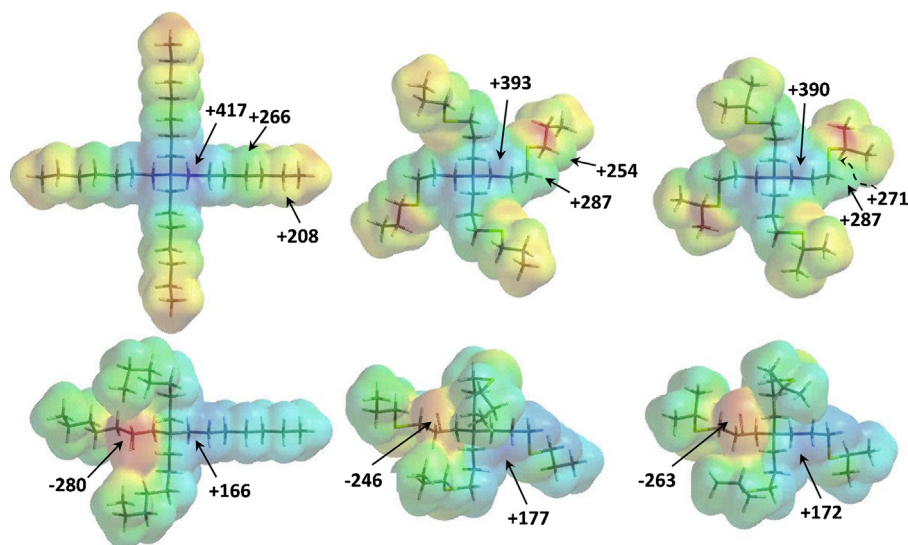
This relationship is based upon the assumption that the rate limiting step is the second-order elementary step in the organic phase, shown in Fig. 1.

Comparing the thiaalkyl salts in Table 3 to the TDAB and THAB, the relationship between the rate constants shown in Eq. (6) does not appear to hold true. For the longer salts, TDAB and SC<sub>8</sub>, there is not a significant difference in organic phase concentration, but the rate constant for SC<sub>8</sub> is less than half of that for TDAB at 60 °C. For the smaller salts, the rate constants are of the same order of magnitude, while the distribution ratios differ by almost four orders of magnitude. If the difference in rates resulted from distribution only, the rate constant for the thiaalkyl salts should be approximately 50 times smaller than that for the THAB. The fact that the thiaquat rates are much faster than predicted by the distribution ratio may indicate significant reaction occurring at the interface with the thiaquat catalysts.

The difference in reaction rates resulting from reactions using each of the two 7-unit thiaalkyl quats also does not appear attributable to distribution alone. The distribution ratios are similar, while the rate constant for the salt with the isopropyl group attached to the sulfur is more than twice that for the one with the *n*-propyl group. Even more significant, the rate for the branched thiaquat S(i-C<sub>3</sub>) is greater than that for the longer-chain thiaquat SC<sub>8</sub>, despite the much greater concentration of the SC<sub>8</sub> complex in the organic phase. A likely explanation for this behavior is that in addition to distribution effects, the strength of ion pairing has a critical effect on reaction rates. This is further explored below using molecular modeling.

### 3.8. Quantum-based modeling

Computational molecular models were generated for the set of seven-unit-chain quat salts, which includes the linear traditional and thiaquat analogs and one branched thiaquat. The lowest-energy conformations of these model cations and their cyanide



**Fig. 8.** Optimized structures of cations (top) and cyanide complexes (bottom) using B3LYP/6-31G(d,p) model: (a) Tetraheptylammonium cyanide (b) Tetra(4-thiaheptyl) ammonium cyanide ( $S(n-C_3)$ ) (c) Tetra(5-methyl-4-thiahexyl) ammonium cyanide. ( $S(i-C_3)$ ) Common elstat scale for cations: +98.0 (red) to +418.0 (blue). Common elstat scale for complexes:  $-292.3$  (red) to  $+162.0$  (blue). Elstat units are kJ/mol. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

complexes are shown in Fig. 8. At the left side of Fig. 8 are the tetraheptylammonium cation (top) and its cyanide complex (bottom). In the center and are the tetra(4-thiaheptyl) ammonium cation and its cyanide complex. This cation has a terminal *n*-propyl chain beyond the sulfur atom. On the right, the thiaquat terminating in an isopropyl group attached to the sulfur is shown.

The depictions of the isolated cations at the top of Fig. 8 show a quasi-tetrahedral arrangement of the chains about the nitrogen center. All three possess  $S_4$  symmetry. As expected, there is a gradual falling off of positive charge along the heptyl chains of the alkyl quat cation. In contrast, the electronegative sulfur atom of the 4-thiaheptyl chains causes the C3 and C5 methylene regions to be far more positive than their alkyl counterparts. This effect is somewhat less pronounced in the branched cation, likely due to the electron-donating inductive effect of the additional methyl group on C5.

As a result of the greater positive potential distributed down the thiaalkyl chains and the low barrier to rotation about the C–S bonds, comparatively stronger binding with greater delocalization of the anion's charge is achieved in the thiaquat-anion complexes. As can be seen at the bottom of Fig. 8, all three complexes have chains in partial contact with cyanide ion (red/orange). Some C–C bonds adopt gauche conformations to maximize anion–cation contacts. The behavior of the salts is in agreement with our findings reported previously [8]. The maximum negative elstat magnitudes in the cyanide complexes follow the trend: alkyl quat > branched thiaquat > linear thiaquat. This trend is consistent with the trend in reaction rates for the series, indicating that stronger ion pairing between the cation and cyanide results in a reduced nucleophilicity of the cyanide, slowing the intrinsic reaction rate.

To quantify this effect, we have evaluated the difference in binding energies by computing  $\Delta E$  for cyanide ion exchange between the cations. The question of interest is whether the difference in binding energy accounts for the difference in rates for the reactions with the three catalysts. For the linear quat cation and linear thiaquat  $S(n-C_3)$ , our computational model shows that cyanide binding in the thiaquat complex is greater by 16 kJ/mol. This value is similar to the difference in experimental activation energies between the two catalysts (15 kJ/mol). Between the two thiaquats, cyanide binding to the linear one is greater by 5.5 kJ/mol. Still, cyanide binding to the branched thiaquat is favored over binding to

the quat cation by 10.5 kJ/mol. These trends are consistent with the qualitative appearance of the elstat maps illustrated in Fig. 8. They also follow the trend in reaction rates, with lower cyanide binding energies resulting in faster reactions. The agreement between these trends leads to the conclusion that stronger ion pairing for the thiaquat salts compared to tradition salts does in fact play a role in the reducing the nucleophilicity of the cyanide ions, thus decreasing reaction rates.

#### 4. Conclusions

We have demonstrated that tetra(4-thiaalkyl) ammonium bromide salts are effective as phase-transfer catalysts for nucleophilic substitution reactions. While the sulfur atoms in the chain do reduce the activity as a PTC compared to analogous tetraalkylammonium salts, the reduction in rate can be overcome by a slight increase in temperature. Furthermore, branching on the catalyst chains beyond the sulfur atom reduces the effect of the sulfur, thus enhancing the reaction rate. Thus, opportunities exist to take advantage of the straightforward, versatile, and inexpensive catalyst synthesis method to prepare catalysts that are tailored for specific applications.

In addition to informing potential applications for the thiaquat catalysts, we have used these catalysts to show the effects of both phase distribution and ion pairing on rate enhancement under PTC conditions. Both factors were shown to have effects on rates, with increased partitioning in the organic phase and weaker ion pairing both resulting in faster reactions.

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