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Complexation of Polyfunctional Organic Guest Molecules by Macrocyclic Polyethers. Complexes of *S-tert*-Butylisothiuronium Salts with 18-Crown-6 and 1,3-Xylyl-18-crown-5

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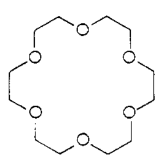
Crystalline complexes of *S-tert*-butylisothiuronium perchlorate (t-BuSC$(\mathrm{NH_2})_2$ClO$_4$) and 18-crown-6 (18C6) and 1,3-xylyl-18-crown-5 (1,3X18C5) with a 1:1 stoichiometry were obtained via extraction. X-ray diffraction analysis showed that in the solid state the guest molecule is coordinated via one of the two NH$_2$ groups to the crown ether. The second NH$_2$ group is bound to the anion. ^{1}H NMR spectroscopy of solutions of these complexes has been interpreted in a similar way. The relative association constant of t-BuSC$(\mathrm{NH_2})_2$ClO$_4$ with 18C6 compared to 1,3X18C5 in CDCl$_3$ at $T = 293$ K is $K_{\mathrm{rel}} = 9.5 \pm 0.5$. Lowering the temperature shows two different resonances for the NH$_2$ hydrogen atoms; the low-field signal corresponds to the NH$_2$ group coordinated to the crown ether and the high-field signal to the NH$_2$ group bound to the anion. The change of free energy of activation for the mutual exchange of NH$_2$ groups in CDCl$_3$ at the coalescence temperature T_c ranges from $\Delta G = 13$–16 kcal·mol^{-1} for the studied complexes. Since the rates of complexation–decomplexation of the NH$_2^+$–anion and NH$_2$–crown ether are fast, the observed slow mutual exchange of NH$_2$ groups between an anion and crown ether site is interpreted by the presence of contact NH$_2^+$–anion ion pairs. Within such an ion pair the anion–NH$_2^+$ exchange may be fast, because it proceeds via a bimolecular reaction mechanism.

One objective of our work on macrocyclic polyethers is the design and synthesis of receptor molecules to be used in the selective removal of urea from aqueous solutions. Therefore, we are currently interested in the complexation of urea-type molecules by crown ethers.[1] Previously, we have shown that 18-crown-6 (18C6; **1**) forms a complex with urea in the solid state having a molar 1:5 (18C6:urea) stoichiometry.[2] In this complex two urea molecules are hydrogen bonded to 18C6, the remaining urea molecules form hydrogen-bonded layers with a clathrate structure.

In contrast to the interaction with charged molecules crown ethers do form rather weak complexes with neutral molecules, e.g., with nitromethane.[3] We concluded, therefore, that protonation of the weak base urea, followed by crown ether complexation, might give more stable complexes. For this reason we have focused our attention on the complexation of crown ethers with charged urea-like molecules like guanidinium[1] and uronium salts.[4] We have shown before that 18C6 forms crystalline complexes with uronium nitrate (1:1),[4] uronium picrate (1:1), and uronium *p*-toluenesulfonate (1:2).[5] We also observed that benzo-27-crown-9 is able to carry uronium perchlorate from an aqueous to a chloroform phase as a 1:1 complex.[4]

In this study we describe the complexation of *S-tert*-butylisothiuronium salts (t-BuSC$(\mathrm{NH_2})_2$X) with 18C6 and 1,3-xylyl-18-crown-5 (1,3X18C5; **2**). These salts resemble urea in that they have two amino groups in close proximity with four hydrogen atoms that are able to form hydrogen bonds. We can define the t-BuSC$(\mathrm{NH_2})_2^+$ cation as a *polyfunctional* cation, because it has two conjugated functional groups that share one positive charge. The t-BuSC$(\mathrm{NH_2})_2$X salts have the advantage over guanidinium and uronium salts that they are more hydrophobic and that they have a convenient ^{1}H NMR probe, viz., the *tert*-butyl group.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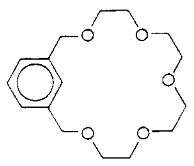
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We emphasize that these salts differ fundamentally from α,ω-diammonium alkyl salts ($\mathrm{H_3N^+(CH_2)_n{}^+NH_3 \cdot 2X^-}$) that may form complexes with cylindrical macrotricyclic polyethers[6–13] or with binaphthyl bis(crown ethers).[14] In these salts the two ammonium groups are separated by several methylene groups enabling both functions to complex independently with different parts of the host molecule.

Results and Discussion

The complexes of crown ethers with t-BuSC$(\mathrm{NH_2})_2$ClO$_4$ were prepared by equilibration of an aqueous solution of t-BuSC$(\mathrm{NH_2})_2$Cl and LiClO$_4$ with a chloroform solution of the crown ether. The complexes were precipitated by addition of diethyl ether to the separated chloroform layer. Details are given in the Experimental Section.

X-ray Diffraction. The crystal structure of t-BuSC$(\mathrm{NH_2})_2$ClO$_4$·1,3X18C5 (1:1) is shown in Figure 1. One of

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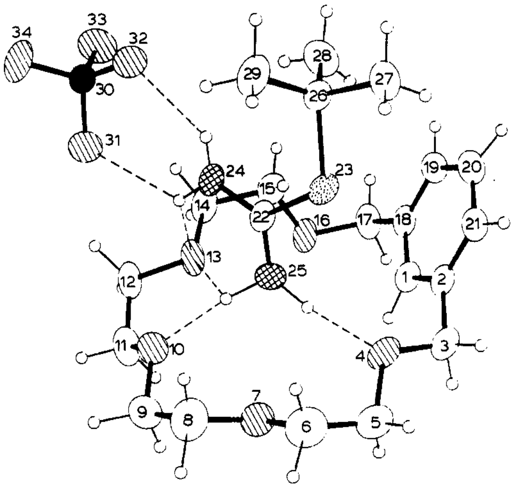

Figure 1. Solid-state structure of 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ (1:1) complex from X-ray diffraction analysis.

the two NH_2 groups of the t-BuSC$(NH_2)_2^+$ cation is hydrogen bonded to the crown ether molecule, forming two strong linear hydrogen bonds (N25···O4, 2.817 (4) Å, N25–H···O4, 171 (5)°, and N25···O10, 2.929 (4) Å, N25–H···O10, 153 (5)°) and a third weaker "hydrogen bond", which is strongly nonlinear (N25···O13, 3.027 (4) Å, N25–H···O13, 126 (4)°). The second NH_2 group does not form linear hydrogen bonds. The shortest nonbonded NH···O distances and the associated N–H···O angles are as follows: N24···O13, 3.087 (5) Å, with N24–H···O13, 139 (5)°; N24···O31, 2.956 (4) Å, with N24–H···O31, 120 (4)°; N24···O32, 2.918 (5) Å, with N24–H···O32, 138 (4)°.

From these data can be concluded that both NH_2 groups are differently bound. One group interacts with the crown ether, the other to the anion and the crown ether. The mean plane of the crown ether is approximately perpendicular to the plane of the aromatic ring. The t-BuSC$(NH_2)_2^+$ cation and the aromatic ring are on the same side of the crown ether. The macroring adopts the rather unusual $ag^+g^+\ ag^+a\ ag^+a\ ag^-a\ ag^+a\ ag^-a$ conformation.

The structure of the t-BuSC$(NH_2)_2ClO_4$·18C6 (2:1) complex has been published previously.[15] The crown ether ring has approximately D_{3d} symmetry; one of the NH_2 groups is hydrogen bonded to the crown ether, and the other forms hydrogen bonds to two perchlorate anions.

The determination of the crystal structure of t-BuSC$(NH_2)_2ClO_4$·18C6 (1:1) was hampered by disorder in one of the two crystallographically independent macrorings in the lattice at T = 150 K.

Static ^{1}H NMR Spectroscopy. The complexation of t-BuSC$(NH_2)_2ClO_4$ with 18C6 and 1,3X18C5 in solution was studied with ^{1}H NMR spectroscopy. The chemical shift of the t-Bu protons is δ 1.61 for the complex with 18C6 in $CDCl_3$. The corresponding 1,3X18C5 complex showed a resonance of the t-Bu protons at δ 1.38. This upfield shift originates from the shielding effect by the aromatic nucleus.[16-19] Therefore, the t-Bu group and xylyl moiety are on the same face of the crown ether in solution, similar to the observed structure in the solid state. The observed chemical shift difference has been used to determine the relative association constant (K_{rel}) of t-BuSC$(NH_2)_2ClO_4$ with 18C6 and 1,3X18C5. This has been done before[16] for the corresponding t-$BuNH_3PF_6$ complexes in chloroform. If the free salt concentration is neglected, the observed chemical shift of the t-Bu protons (δ_{obsd}) is the weighted average of the chemical shift in the 1,3X18C5 complex ($\delta_{c,1}$ 1.38) and the 18C6 complex ($\delta_{c,2}$ 1.61).

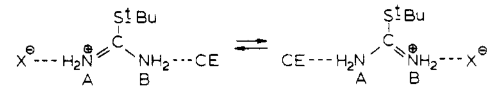

Figure 2. Exchange of amino groups in CE·t-BuSC$(NH_2)_2$X complexes. CE is crown ether and X^- is the anion.

Table I. Chemical Shifts of *tert*-Butyl Hydrogen Atoms and Intraannular Aromatic Hydrogen Atoms in *t*-BuSC$(NH_2)_2ClO_4$•1,3X18C5•18C6 Mixtures at T = 293 K[a]

[1,3X18C5]/[18C6]	$\delta_{t\text{-Bu}}$	δ_H
0	1.61	
0.90	1.564	7.684
1.23	1.537	7.663
1.55	1.514	7.644
2.34	1.474	7.621
∞	1.38	7.579

[a] [1,3X18C5] = [t-BuSC$(NH_2)_2ClO_4$] = 0.1245 mol·L^{-1}. Solvent: $CDCl_3$. Shifts are relative to internal tetramethylsilane.

$$\delta_{obsd} = X\delta_{c,1} + (1 - X)\delta_{c,2} \tag{1}$$

where X = mole fraction of t-BuSC$(NH_2)_2ClO_4$ complexed with 1,3X18C5.

Increasing the 18C6 concentration at constant 1,3X18C5 and t-BuSC$(NH_2)_2ClO_4$ concentrations shows a downfield shift of the t-Bu hydrogen atoms (Table I). With eq 1 and the mass balance equations, K_{rel}, as defined in eq 2, was calculated to be K_{rel} = 9.5 ± 0.5. Comparison of K_{rel} with

$$K_{rel} = \frac{K_{18C6}}{K_{1,3X18C5}} = \frac{[18C6\cdot t\text{-BuSC}(NH_2)_2ClO_4][1,3X18C5]}{[1,3X18C5\cdot t\text{-BuSC}(NH_2)_2ClO_4][18C6]} \tag{2}$$

K_{rel} = 100 found for the complexation of t-$BuNH_3PF_6$ with the corresponding two crown ethers[17] (under similar experimental conditions) shows that the two crown ethers discriminate less for the thiuronium salts than for the ammonium salts.

Upon decreasing the ratio [1,3X18C5]/[18C6], t-BuSC$(NH_2)_2ClO_4$ is displaced from the 1,3X18C5 molecule as monitored by the shift of the intraannular aromatic hydrogen atom (Table I, δ_H). This probe might be useful for the determination of the *absolute* association constant with 1,3X18C5. Two different series of experiments were performed in order to obtain the association constant. In one series of experiments the chemical shift of this probe varied by the addition of different amounts 1,3X18C5 to a chloroform solution containing the 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ complex. With the method described before,[16,17] an association constant of $K_{1,3X18C5}$ = 185 ± 20 L·mol^{-1} was calculated. In a second series of experiments a chloroform solution containing 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ was diluted from 50 to 2.5 mmol·L^{-1} successively. However, the observed chemical shifts δ_H remained almost constant. This makes the determination of an association constant impossible. Probably, the expected chemical shift change due to decomplexation is compensated by chemical shift changes originating from diluting

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Table II. Chemical Shifts of Amino Protons of t-BuSC$(NH_2)_2$•X-CE Complexes at Different Temperatures, Their Coalescence Temperature, and Change of Free Energy of Activation[a]

complex					
X	CE	T, K	δ_{NH_2}	T_c, K[b]	ΔG, kcal·mol^{-1}
ClO_4	18C6	246	8.22, 7.87		
		309	8.04	265	13
ClO_4	1,3X18C5	231	8.06, 7.55	307	15
		309	7.82		
PF_6	1,3X18C5	231	8.06, 7.26	323	16
ClO_4, PF_6	1,3X18C5		8.06, 7.39		

[a] X is the counterion; CE means crown ether, 18C6 = 18-crown-6, and 1,3X18C5 = 1,3-xylyl-18-crown-5. Solvent is $CDCl_3$. Shifts are relative to internal tetramethylsilane. [b] Coalescence temperature.

the solution. This effect has not been studied in more detail. It indicates that association constants determined by this method may be dependent on the concentration scale.

Dynamic ^1H NMR Spectroscopy. In all our studied t-BuSC$(NH_2)_2$X crown ether complexes line broadening and subsequent line splitting of the NH_2 resonance upon lowering the temperature was observed. The complexes studied and the relevant data are given in Table II. The observed line splitting reflects a slow mutual exchange process of the NH_2 groups of the t-BuSC$(NH_2)_2^+$ cation (Figure 2). The change of free energy of activation (ΔG) of this exchange process is similar for the different complexes and amounts ΔG = 13–16 kcal·mol^{-1}. The two resonances observed show that both amino groups are not equivalent. This may originate from strong interactions with the anion and/or the crown ether. Inspection of the chemical shift data presented in Table II shows that the low-field NH_2 resonance can be assigned most probably to the amino group interacting with the crown ether. The high-field NH_2 resonance is assigned to the amino group associated with the anion. This picture of the complex structure in solution also emerged from the X-ray diffraction analysis of the solid-state complex (vide supra).

In a mixture of t-BuSC$(NH_2)_2ClO_4$:t-BuSC$(NH_2)_2PF_6$:1,3X18C5 = 1:1:2 (molar), under conditions of slow exchange, the δ 8.06 resonance is assigned to the amino group interacting with the crown ether and the δ 7.39 resonance is the weighted average of the chemical shift of the NH_2 group interacting with ClO_4^- (δ 7.55) and PF_6^- (δ 7.26) anion (Table II). Therefore, it is concluded that the anion–NH_2^+ exchange is still fast on the ^1H NMR time scale in this experiment.

In a mixture of t-BuSC$(NH_2)_2ClO_4$:18C6:1,3X18C5 = 2:1:1 (molar), under conditions of slow exchange, a similar observation was made. The chemical shift of the t-Bu hydrogen atoms (δ 1.51), which is very sensitive to the type of crown ether complexed (vide supra), is the weighted average of the chemical shift in the 18C6 complex (δ 1.61), and the 1,3X18C5 complex (δ 1.38) over the temperature range 220–309 K. The T_c value for the mutual exchange of the NH_2 groups was found to be 280 K which corresponds to a ΔG = 14 kcal·mol^{-1}. From this experiment, it is concluded that also the crown ether–NH_2 exchange is fast on the ^1H NMR time scale. Additional evidence for this conclusion comes from 500-MHz ^1H NMR spectroscopy on t-BuSC$(NH_2)_2ClO_4$·1,3X18C5 in CD_2Cl_2. Upon lowering the temperature from 297 to 193 K the part of the spectrum assigned to crown ether methylene groups does not change significantly. This contrasts our observation in an earlier study[18] on t-BuNH_3X·1,3X18C5 in CD_2Cl_2. Then the observation of splitting of the resonance of the benzylic hydrogen atoms into a double doublet and also line broadening of the other methylene hydrogen resonances followed by line splitting at T = 238 K led to the conclusion of a slow back-to-face interchange process.

Returning to the observation of two noninterchangeable NH_2 groups, in combination with the observations of fast anion–NH_2^+ as well as fast crown ether–NH_2^+ exchange processes, we suggest that the anion–NH_2^+ exchange is fast because it proceeds via a bimolecular mechanism.[19] Therefore, the amino group is interacting continuously with an anion forming a contact ion pair and making mutual interchange of both amino groups unlikely. For steric reasons, such a mechanism seems improbable for the crown ether–NH_2^+ exchange.

Conclusions. The structures of the complexes between t-BuSC$(NH_2)_2ClO_4$ and 18C6 or 1,3X18C5 in the solid state and in solution are similar. One NH_2 group interacts with the crown ether and the other interacts with the anion. The t-BuSC$(NH_2)_2ClO_4$ is more tightly bound to 18C6 than to 1,3X18C5 (K_{rel} = 9.5 ± 5). The observed slow exchange of NH_2 groups in a series of t-BuSC$(NH_2)_2$X·CE complexes in solution is interpreted by the presence of a contact NH_2^+·X^- ion pair. It is suggested that the mutual anion exchange at the NH_2^+ site is fast (as is the mutual CE–NH_2 exchange), since it proceeds via a bimolecular mechanism.

Experimental Section

NMR Spectroscopy. All ^1H NMR spectra were recorded on a Bruker WP 80-MHz apparatus or a Bruker WM 500-MHz apparatus, both equipped with a B-VT-1000 temperature accessor. The temperature was verified with a thermocouple. Me_4Si was used as the internal standard.

Elemental Analysis. Elemental analyses were carried out by the Elemental Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buis and G. J. Rotscheid.

Determination of the Relative Association Constant. For a series of $CDCl_3$ samples containing 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ (1:1) (0.1245 M) and 18C6 (0.0533–0.1369 M) the chemical shifts of the t-Bu group were determined at 293 K. According to eq 1 and 2 the relative association constants of 18C6·t-BuSC$(NH_2)_2ClO_4$ and 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ complexes have been determined.

Determination of the Association Constant of the 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ Complex. (a) Excess Crown Ether Method. For a series of $CDCl_3$ samples containing the same amount of t-BuSC$(NH_2)_2ClO_4$ (0.05 M) and different amounts of 1,3X18C5 (0.05–0.172 M) the chemical shifts of the intraannular hydrogen atom of 1,3X18C5 were determined at T = 309 K. The observed chemical shift (δ_{obsd}) is given by eq 3. The association constant was calculated by minimization of the function F (eq 4) as described previously.[3]

$$\delta_{obsd} = X_f\delta_f + (1 - X_f)\delta_c \qquad (3)$$

$$F = \sum_i[\delta_{obsd,i} - X_{f,i}\delta_f - (1 - X_{f,i})\delta_c]^2 \qquad (4)$$

δ_c = the chemical shift at complete complexation

δ_f = the chemical shift in the absence of complexation

$X_{f,i}$ = the mole fraction of uncomplexed crown ether

(b) Dilution Method. For a series of $CDCl_3$ samples containing 1,3X18C5 and t-BuSC$(NH_2)_2ClO_4$ in a 1:1 ratio at different concentrations (0.05–0.0025 M) the chemical shifts of the intraannular hydrogen atom of 1,3X18C5 were determined at T = 309 K. The association constant was calculated by minimization of the function F (eq 4).

X-ray Diffraction. X-ray diffraction measurements on 1,3X18C5·t-BuSC$(NH_2)_2ClO_4$ (1:1) were made at T = 147 K on a Philips PW 1100 diffractometer using graphite monochromated Cu Kα radiation (λ = 1.5418 Å). Crystal data: monoclinic, space group $P2_1/n$, a = 14.082 (5) Å, b = 17.049 (4) Å, c = 11.058 (5)

Å, $\beta = 90.99$ (3)°, $Z = 4$, $d_c = 1.329$ g·cm^{-3}. Measurement: ω–2θ scan mode, $3° < \omega < 74°$; scan speed, $(\omega)0.03°$ s^{-1}; scan width, $(\omega)(2.0 + 0.5 \tan \theta)°$; number of reflections measured, 4875.

Solution[20] and refinement[21] of the structure are based on 4153 reflections with $I > \sigma(I)$. Hydrogen atoms were found in difference Fourier syntheses. The number of parameters refined was 456: scale factor, extinction parameter, positional parameters of all atoms, and thermal parameters (isotropic for hydrogen atoms, anisotropic for others). The final R factor was 7.8%. The drawings have been made by ORTEP.[22]

Materials. 18C6·*t*-BuSC(NH$_2$)$_2$ClO$_4$ (1:1) was prepared by extraction of an aqueous solution of t-BuSC(NH$_2$)$_2$Cl (4 mmol/mL) and LiClO$_4$ (1 mmol/mL) with a solution of 18C6 in chloroform. The compound was precipitated by addition of diethyl ether to the chloroform layer and recrystallized from ethanol/petroleum ether: mp 136–137 °C; 80-MHz ^{1}H NMR (CDCl$_3$) δ 8 (br s, 4 H, NH), 3.64 (s, 24 H, CH$_2$), 1.60 (s, 9 H, CH$_3$). Anal. Calcd for C$_{17}$H$_{37}$ClN$_2$O$_{10}$S (M_r = 497.004): C, 41.08; H, 7.50; Cl, 7.13; N, 5.64; S, 6.45. Found: C, 41.15; H, 7.64; Cl, 7.00; N, 5.54; S, 6.36.

1,3X18C5·*t*-BuSC(NH$_2$)$_2$ClO$_4$ (1:1) was prepared by extraction of an aqueous solution of t-BuSC(NH$_2$)$_2$Cl (4 mmol/mL) and LiClO$_4$ (4 mmol/mL) with a solution of 1,3X18C5 (4 mmol/mL) in chloroform. The compound was precipitated by addition of diethyl ether to the chloroform layer and recrystallized from ethanol: mp 106–108 °C; 80-MHz ^{1}H NMR (CDCl$_3$) δ 8.04 (br s, 2 H, NH), 7.57 (s, 1 H, Ar H), 7.50 (br s, 2 H, NH$_2$), 7.23 (m, 3 H, Ar H), 4.56 (s, 4 H, Ar CH$_2$), 3.73 (s, 8 H, OCH$_2$), 3.65 (s, 8 H, OCH$_2$), 1.40 (s, 9 H, CH$_3$). Anal. Calcd for C$_{21}$H$_{37}$ClN$_2$O$_9$S (M_r = 529.049): C, 47.68; H, 7.05; Cl, 6.70; N, 5.30; S, 6.06. Found: C, 47.51; H, 7.13; Cl, 6.60; N, 5.64; S, 5.96.

1,3X18C5·*t*-BuSC(NH$_2$)$_2$PF$_6$ (1:1) was prepared by extraction of an aqueous solution of t-BuSC(NH$_2$)$_2$Cl (4 mmol/mL) and LiPF$_6$ (4 mmol/mL) with a solution of 1,3X18C5 (4 mmol/mL) in chloroform. The compound was precipitated by addition of diethyl ether and was directly used: ^{1}H NMR (CDCl$_3$) δ 8.06 (br s, 2 H, NH), 7.57 (s, 1 H, Ar H), 7.26 (m, 5 H, Ar H′ and NH), 4.56 (s, 4 H, Ar CH$_2$), 3.76 (s, 8 H, OCH$_2$), 3.64 (s, 8 H, OCH$_2$), 1.38 (s, 9 H, CH$_3$). Elemental analyses were not performed because PF$_6$ salts are unstable.

Registry No. 18-C-6·t-BuSC(NH$_2$)$_2$ClO$_4$ (1:1), 98720-12-8; 1,3-X-18-C-5·t-BuSC(NH$_2$)$_2$ClO$_4$ (1:1), 98720-13-9; 1,3-X-18-C-5·t-BuSC(NH$_2$)$_2$PF$_6$ (1:1), 98720-15-1.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles (7 pages). Ordering information is given on any current masthead page.

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Substitution of Unactivated Aryl Halides by Thiolate Anions in Polyglymes

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Tetraglyme was found to be a suitable reaction medium to effect the substitution of hexa-, tetra-, tri-, di-, and monochlorobenzenes with sodium alkanethiolates. The substitution of hexa-, tetra-, and trichlorobenzenes by sodium benzenethiolate gave the corresponding (phenylthio)benzenes in tetraglyme, albeit in lower yield. The results of the substitution of chloro-, bromo-, and fluoro-substituted benzenes by an alkanethiolate suggest that an S$_N$Ar mechanism is operative. The effectiveness of the polyglyme as a reaction medium was shown to decrease in the order tetraglyme > triglyme > diglyme > monoglyme.

Introduction

The substitution of aryl halides by thiolate anions continues to be an active area of interest from both a synthetic[1] and mechanistic[2] point of view, since the substitution products are the subject of considerable theoretical study.[3] In particular, hexasubstituted arylthiobenzenes have been shown to function as inclusion hosts,[4] e.g., the adduct of carbon tetrachloride with hexakis(phenylthio)benzene has a true clathrate structure.[5]

Tiecco and co-workers have advocated the use of hexamethylphosphoric triamide (HMPT) as the solvent of choice for the substitution of activated and unactivated aryl halides by thiolate anions.[6] Both *N*,*N*-dimethylacetamide (DMAC)[7] and *N*,*N*-dimethylformamide (DMF)[8] have been advanced as suitable replacements for the potentially carcinogenic HMPT. Quite recently, our laboratory reported the substitution of activated aryl halides by thiolate anions in triethyleneglycol dimethyl ether (triglyme)[9,10] including a single example of the substitution

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