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Kinetic study of trifluoromethylation with *S*-(trifluoromethyl)dibenzothiophenium salts

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Abstract

The kinetic parameters were determined for *C*-trifluoromethylation of aniline with *S*-(trifluoromethyl)dibenzothiophenium triflate (**1**), its 3,7-dinitro derivative (**2**) and *S*-(trifluoromethyl)diphenylsulfonium triflate (**3**) in DMF-d_7. The higher reactivity of heterocyclic **1** compared with non-heterocyclic **3** could be explained on the basis of its greatly enhanced activation entropy ($\Delta S^{\neq}$: -11.2 cal mol^{-1} K^{-1} for **1**; -47.1 for **3**), but not its enhanced activation enthalpy ($\Delta H^{\neq}$: 21.2 kcal mol^{-1} for **1**; 12.1 for **3**). The aromatic delocalization of the heterocyclic ring may thus be only slightly disturbed by the *S*-trifluoromethyl substituent. The high reactivity of **2** was attributed to the great electron deficiency caused by two nitro groups in addition to the heterocyclic salt system ($\Delta H^{\neq}$ 17.0 kcal mol^{-1}, $\Delta S^{\neq}$ -9.1 cal mol^{-1} K^{-1} for **2**). The reaction mechanism is discussed; the conventional S_N2 attack mechanism was ruled out and a mechanism for a side-on attack to the CF_3–S bond may possibly be applicable.

Keywords: Trifluoromethylation; *S*-(trifluoromethyl)dibenzothiophenium; Heterocyclic

1. Introduction

The importance of the trifluoromethyl functional group is widely recognized in basic and applied chemistries because of its unique properties such as high electronegativity, stability and lipophilicity [1–3]. Recently, one of the authors and his coworkers developed a new system of trifluoromethylating agents, *S*-, *Se*-, and *Te*-(trifluorometyl)-dibenzothio-, -seleno-, and -tellurophenium salts with high reactivity and varying degrees of trifluoromethylating power, which made possible for the first time the electrophilic trifluoromethylation of a wide range of substrates differing in reactivity [4–7]. This dibenzoheterocyclic chalcogen salt system is more reactive than the corresponding non-heterocyclic salt system, and its trifluoromethylating power varies greatly depending on the electronegativity of the chalcogen atoms and ring substituents. This power increases in the order Te < Se < S, and an electron-donating substituent < -withdrawing substituent. A kinetic study of trifluoromethylation by an *S*-(trifluoromethyl)dibenzothiophenium salt, its dinitro derivative and the non-heterocyclic salt is now reported and the reaction mechanism is discussed.

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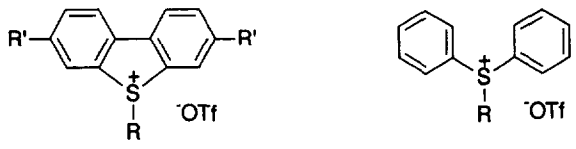
2. Results and discussion

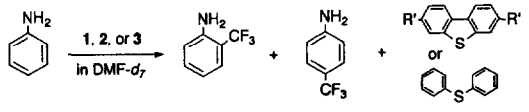
The kinetic parameters of *C*-trifluoromethylation of aniline with *S*-(trifluoromethyl)-dibenzothiophenium triflate (**1**), its dinitro derivative (**2**), and *S*-(trifluoromethyl)-diphenylsulfonium triflate (**3**) (Fig. 1 and Scheme 1) are summarized in Table 1.

Activation free energies $\Delta G^{\neq}$ showed the following quantitative power order, non-heterocyclic salt **3** < heterocyclic salt **1** < its dinitro salt **2**. As seen from Table 1, the reaction



1 R=CF_3, R'=H
2 R=CF_3, R'=NO_2
3 R=CF_3
4 R=CH_3, R'=H
5 R=CH_3

Fig. 1.



Scheme 1.

Table 1
Kinetic parameters on trifluoromethylation of aniline

Salt	Temp. (°C)	Reaction rate k (s^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} K^{-1})	$\Delta G^{\neq}$ [a] (kcal mol^{-1})
1	62.0	3.64×10^{-4}	21.2	−11.2	24.5
	69.9	7.73×10^{-4}			
	81.4	2.18×10^{-3}			
2	−10.0	4.33×10^{-4}	17.0	−9.1	19.7
	−15.0	2.00×10^{-4}			
	−20.0	1.13×10^{-4}			
3	81.4	1.33×10^{-5}	12.1	−47.1	26.1
	103.6	3.19×10^{-5}			
	113.5	6.32×10^{-5}			

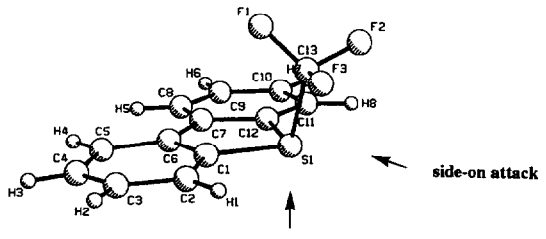
[a] At 25 °C.

rate of salt **1** was about 160 times that of salt **3** at 81.4 °C. The greatly enhanced activation entropy $\Delta S^{\neq}$ of **1** compared with **3**, but not the enhanced activation enthalpy $\Delta H^{\neq}$ of **1**, would be an explanation for this. The entropy term obviously overcomes deactivation caused by the enthalpy term. Our initial hypothesis for the reactivity of heterocyclic salt **1** suggested that it should have an additional driving force caused by the restoration of lost aromaticity by transformation of the central 5-membered heterocyclic ring regarded as 4 π anti-aromaticity, to a 6 π aromatic heterocycle [5], as discussed by Kevill et al. [8] and Horak et. al. [9]. For non-heterocyclic salt **3**, such a driving force would not be expected. However, the present kinetic study indicates the higher reactivity of **1** to be caused by a steric factor (entropy term). This suggests that aromatic delocalization of the heterocyclic ring is only slightly disturbed by trifluoromethyl substitution at the S-site. The unexpectedly enhanced activation enthalpy of **1** suggests that this trifluoromethylation should proceed via an intermediate thermodynamically much less stable than that of **3**. The highest reactivity of **2** was attributed to the reduced activation enthalpy $\Delta H^{\neq}$ caused by two strongly electron-withdrawing nitro groups in addition to the heterocyclic salt system. As expected, the entropy term $\Delta S^{\neq}$ of **2** remained essentially the same as that of **1**.

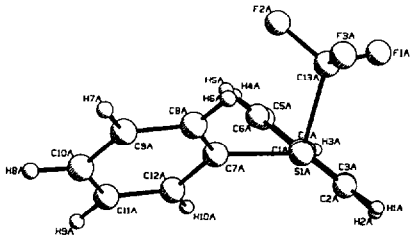
Kinetic studies on *S*-methyl analogues, *S*-methyldibenzothiophenium teterafluoroborate [8] and *S*-methyldiphenylsulfonium tetrafluoroborate [10] have been reported. The difference in $\Delta S^{\neq}$ between the former heterocyclic salt ($\Delta S^{\neq} = -13.4$ cal mol^{-1} K^{-1} at 14.9 °C for ethanolysis) and the latter non-heterocyclic salt ($\Delta S^{\neq} = -10.3$ cal mol^{-1} K^{-1} at 25 °C for *N*-methylation of pyridine-d_5) is small. Kinetic data on similar alkylations of various nucleophiles with several *S*-alkylsulfonium salts show similar $\Delta S^{\neq}$ values near -10 cal mol^{-1} K^{-1} [11,12]. This is consistent with the conventional S_N2 attack mechanism of a nucleophile on the CH_3 or alkyl carbon along the CH_3–S or alkyl-S bond, because nucleophile attacks should be insensitive to steric changes in the departing sulfur groups. Thus, the observed outstanding difference in $\Delta S^{\neq}$ between heterocyclic S–CF_3 salt **1** and non-heterocyclic salt **3** may be taken as an indication of a different type of reaction mechanism.

A radical chain mechanism was excluded, since no substantial suppression of the rate constant occurred in the presence of a radical scavenger, *p*-dinitrobenzene ($k = 9.95\times10^{-4}$, 8.27×10^{-4} and 7.76×10^{-4} s^{-1} at 80 °C in the presence of 0.0, 0.2 and 1.0 eq of *p*-dinitrobenzene, respectively). Further evidence for this is that salt **1** trifluoromethylated the strong radical scavenger, hydroquinone, in the presence of pyridine as a base. More reactive **2** readily reacted with hydroquinone to give trifluoromethyl- and bis(trifluoromethyl)-hydroquinone in 61 and 11% yield, respectively [5]. This may also suggest that a simple one-electron transfer mechanism which gives a CF_3 radical and a radical-cation of the substrate would not take place because the CF_3 radical should abstract a H radical from the radical-cation of hydroquinone to produce CF_3H and *p*-quinone. An aromatic hydrogen atom-abstraction reaction as the rate-determining step may be excluded by the absence of any substantial isotope effect in reactions of **1** with aniline-d_5 in DMF-d_7 ($k_D = 1.67\times10^{-7}$ s^{-1} at 80.6 °C; $k_H/k_D = 1.17$ at 80.6 °C). Thus, a bimolecular ionic substitution mechanism would appear applicable for trifluoromethylation. Such an ionic mechanism is supported by the fact that trifluoromethylation occurred faster in polar DMF than in acetonitrile (reaction rate $k = 2.18\times10^{-3}$ s^{-1} at 81.4 °C in DMF-d_7; $k = 7.31\times10^{-4}$ s^{-1} at 80.6 °C in CD_3CN).

As shown in Fig. 2, X-ray structural analysis [13] of **1** and **3** indicated both salts to possess a pseudo-trigonal bipyramidal structure around the sulfur atom. Crystal structures of salts **4** and **5** were also analyzed by X-ray and they both were found to have a tetrahedral structure around the sulfur atom. Salt **1** may be attacked by a nucleophile from either of the two directions indicated with arrows in Fig. 2 (hereafter called side-on or bottom-side attack) with the least loss of freedom, because the two phenyl rings, at an angle of C1 − S1 − C12 = 91.1°, are fixed in the same plane, as would be indicated by the small negative $\Delta S^{\neq}$. In non-heterocyclic **3**, side-on or bottom-side attack cannot occur without greatly lessening rotational freedom of the two phenyl groups, because the two rings at a wide angle (C1A − S1A − C7A = 107.8°) are not fixed, as would be indicated by the large negative $\Delta S^{\neq}$. If S_N2 attack on the CF_3 carbon along



1



3

Fig. 2. PLUTO drawings of cation parts of **1** and **3**.

the CF_3–S bond occurs, a small or no difference in $\Delta S^{\neq}$ between **1** and **3** should be expected, as in the case of methylation mentioned above. The great difference in $\Delta S^{\neq}$ as demonstrated by the present study strongly suggests the side-on or bottom-side attack mechanism for trifluoromethylation but not the S_N2 mechanism.

As discussed in our previous article [5], a sulfurane mechanism (formation of σ-sulfurane followed by ligand coupling) starting from the bottom-side attack (apical attack) to the sulfur atom would appear to be unlikely since **1** did not trifluoromethylate alkyl- or aryllithium and magnesium halides, which would lead to the formation of sulfuranes as intermediates followed by ligand coupling [14–16]. This may be further supported by the fact that **1** reacted with benzylamine to produce dibenzothiophene in almost quantative yield and a large amount of trifluoromethane, but neither the *N*-benzylsulfoximine of dibenzothiophene nor its hydrolysis product, dibenzothiophene S-oxide, were obtained.

Mulliken population calculations [13] on the *S*-(trifluoromethyl)dibenzothiophenium cation and the analogous *S*-methyl cation showed a sharp contrast in the electron distributions between the S–CF_3 and S–CH_3 parts: $S^{\delta+}$–$C^{\delta+}(-F^{\delta-})_3$ and $S^{\delta+}$–$C^{\delta-}(-H^{\delta+})_3$. The calculation was carried out using GAUSSIAN 90 (3-21G*//6-31G*). The other parts had almost the same electron distributions. Mulliken populations obtained for the S–CF_3 and S–CH_3 parts were as follows; $S^{+0.83}-C^{+0.96}(F^{-0.30})(F^{-0.32})(F^{-0.32})$ and $S^{+0.81}$–$C^{-0.51}(H^{+0.22})(H^{+0.21})(H^{+0.21})$. Thus, the electron population of CF_3 is opposite to that of CH_3, and the positive CF_3 carbon binds to the positive S atom. The side-on attack of aniline (ortho- or para-position) to the S–CF_3 bond would thus appear applicable since the doubly positive $S^{\delta+}$–$C^{\delta+}$ bond of S–CF_3 is expected to be the most electron-deficient (Fig. 3). Although the real mechanism for the

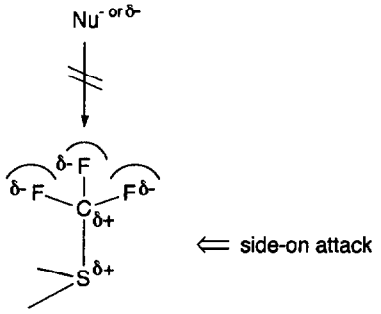
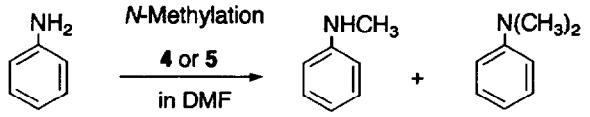


Fig. 3.



Scheme 2.

cleavage of the S–CF_3 bond is not clear at present, it appears to us that it may be a kind of insertion mechanism accompanied by an one-electron or two-electrons exchange, depending on the nature of the nucleophile.

The CF_3 electron distribution opposite to CH_3 may explain why the conventional S_N2 attack mechanism by a nucleophile is beset with such a great disadvantage for trifluoromethylation since the CF_3 carbon atom is covered by three negatively charged fluorine atoms somewhat larger in size than the hydrogen atoms, as shown in Fig. 3.

For comparison with the S–CF_3 salts **1** and **3**, reactions of *S*-methyl salts **4** and **5** with aniline were carried out. Both salts gave *N*-methylated products only. This is totally in contrast to the S–CF_3 salts which gave only *C*-trifluoromethylated products. Thus, the difference should arise from the fundamentally different mechanisms.

3. Conclusions

The present study provides kinetic data for the *C*-trifluoromethylation of aniline with dinitro-substituted and unsubstituted *S*-(trifluoromethyl)dibenzothiophenium salts and *S*-(trifluoromethyl)diphenylsulfonium salt, the quantitative trifluoromethylating powers of which differ. The data demonstrate the origin of the high reactivity of the dibenzoheterocyclic salt system and the novelty of the trifluoromethylation mechanism which differs distinctly from the conventional S_N2 mechanism of methylation (Scheme 2).

4. Experimental

4.1. Materials

S-(Trifluoromethyl)dibenzothiophenium triflate (**1**), *S*-(trifluoromethyl)-3,7-dinitrodibenzothiophenium triflate (**2**), and *S*-(trifluoromethyl)diphenylsulfonium triflate (**3**)

were prepared by the methods reported [4,5]. Aniline was passed through an alumina column and distilled. Reaction solvents were used as purchased. Salts **1** and **2** are commercially available from Daikin Chemicals Sales, Tokyo.

4.1.1. S-Methyldibenzothiophenium triflate (4)

Methyl triflate (1.64 g, 1 mmol) was added into a benzene solution (1 mL) of dibenzothiophene (1.84 g, 1 mmol) at room temperature. After being refluxed for 2 d, the reaction mixture was evaporated to dryness. Recrystallization of the residue from acetone-THF-Et_2O gave 2 g (57%) of **4**: mp 128.3–128.8 °C; ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) −78.6 ppm (s); ^1H NMR ($CDCl_3$) δ 8.50 (m, 2H), 8.10 (m, 2H), 7.99 (m, 4H), 3.56 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{11}F_3O_3S_2$: C,48.27; H, 3.18%. Found: C, 48.06; H, 2.97%.

4.1.2. S-Methyldiphenylsulfonium triflate (5)

A mixture of diphenyl sulfide (1.86 g, 1 mmol) and methyl triflate (1.64 g, 1 mmol) was stirred at room temperature for 30 min. The solidified mixture was recrystallized from CH_2Cl_2-hexane to give 3.3 g (95%) of **5**: mp 96.5–97.0 °C; ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) −78.7 ppm (s); ^1H NMR ($CDCl_3$) δ 7.93 (m, 4H), 7.67 (m, 6H), 3.70 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{13}F_3O_3S_2$: C, 47.99; H, 3.74%. Found: C, 47.70; H, 3.45%.

4.2. Kinetic study

The reaction of the salts **1**, **2** and **3** with aniline were conducted in a NMR tube under pseudo-first-order conditions using excess aniline (11.3 equiv.) in DMF-d_7 at various temperatures as shown in Table 1. The concentration of **1**, **2** and **3** in DMF-d_7 was about 0.2 mol L^{-1}. The temperatures for the kinetic experiments were determined based on the reflux temperatures of the bath liquids for **1** and **3** (chloroform around 62 °C, hexane 70 °C, benzene 81 °C, dioxane 103 °C, toluene 113 °C) and by the NMR temperature controller for **2**. The consumption of these salts and the formation of *o*- and *p*-(trifluoromethyl)aniline were monitored and analyzed by ^{19}F-NMR using counter triflate anions as the internal reference. ^{19}F-NMR measurements for the kinetics of **1** and **3** were conducted with a Varian Gemini NMR spectrometer at 188 MHz. A Bruker AMX500 spectrometer at 470.5 MHz, equipped with a variable-temperature controller, was used for the kinetics of **2**. ^{19}F chemical shifts from $CFCl_3$ as the internal standard were defined as being negative to the higher field. CF_3 ^{19}F chemical shifts (in DMF-d_7) were as follows; **1**, −54.0 ppm; **2**, −49.8; **3**, −50.4; *o*-(trifluoromethyl)-aniline, −61.7; *p*-(trifluoromethyl)aniline, −59.3; triflate anion, −77.5. Trifluoromethylation of aniline proceeded quantitatively based on **1**, **2** and **3**. The production ratio of *o*- and *p*-(trifluoromethyl)anilines was always constant at all temperatures [5]. Pseudo-first-order plots of salt concentration vs. time indicated the expected straight line up to three reaction half lives. Aniline-d_5 was used instead of aniline to determine isotope effects. All rate constants (k) were calculated by the least-squares method.

4.3. Reactions of aniline with S-methyl salts 4 and 5

A mixture of aniline (0.5 mmol) and **4** (0.2 mmol) in DMF (2 mL) was stirred at room temperature for 30 min. GC analysis of the reaction mixture showed that *N*-methyl- and *N,N*-dimethylanilines were produced in 67 and 26% yields, respectively. The reaction with **5** was accomplished by heating a mixture of aniline (1 mmol) and **5** (0.4 mmol) in DMF (3 mL) at 75 °C for 2 h. GC analysis showed that the same products were obtained in 48 and 15% yields. Both the GC analyses were carried out after acetylation (acetic anhydride/pyridine) by using naphthalene as an internal standard. In both cases, even a trace amount of the *C*-methylated products was not detected by mass fragmentography using authentic *o*- and *p*-methylanilines as standards.

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