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### **Graphical Abstract**



## Mechanistic studies and quantification of the Electrophilicity of Aromatic Triflones in $\sigma$ complexation and S<sub>N</sub>Ar reactions

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**Abstract:** The reactions of anilines (N–nucleophiles) and enamines (C–nucleophiles) with NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> substituted aromatic triflones were investigated spectrophotometrically in acetonitrile at 20 °C. We found that the second-order rate constants  $k_1$  related to the C–N and C–C bond forming step of these nucleophilic aromatic substitution reactions (S<sub>N</sub>Ar) and  $\sigma$ -complexation reactions follow the three-parameter equation log  $k_{(20 \circ C)} = s_N (N + E)$ , allowing the determination of the electrophilicity *E* of such aromatic triflones for the first time. The ranking of these neutral electron-deficient compounds on the comprehensive electrophilicity scale defined by Mayr *et al.* reveals that the most electrophilic triflone, the 1,3,5-tris(trifluoromethanesulfonyl)benzene (TTSB), has an electrophilic in anionic  $\sigma$ -complexation chemistry, by roughly 6 units of *E*. This finding holds promise for expanding the range of coupling reactions which can be envisioned between this series of electron-deficient neutral aromatics and nucleophiles.

#### **Keywords** :

Aromatic triflones, Trifluoromethanesulfonyl group, S<sub>N</sub>Ar reactions, Electrophilicity, Kinetics.

#### 1. Introduction

The reactions of electron-deficient arenes and heteroarenes substituted by very strong electron-withdrawing substituents such as  $SO_2CF_3$  with O–, N– and C–nucleophiles are of great interest from a synthetic and mechanistic point of view. [1-7] Indeed the anionic Meisenheimer  $\sigma$ –complex intermediates are highly stabilized by the  $SO_2CF_3$  substitutents and can be characterized or isolated, and the resulting products are highly valuable aromatic compounds [8-12].

Discussions of the substituent effects and of the mechanisms of these  $S_NAr$  type reactions through the use of empirical linear free–energy relationships is one of the preferred approach in the literature. Indeed, since the introduction of the electrophilicity and nucleophilicity concepts to describe the reactivity of electron–deficient (electrophile) and electron–rich (nucleophile) species by Ingold in the 1930s [13], there has been a growing interest in classifying molecules within scales of electrophilicity/nucleophilicity. From that time, the classification and the quantification of the reactivity organic molecules within empirical and hopefully unique scales of electrophilicity and nucleophilicity have been attempted. For instance, several linear free-energy relationships (LFERs) such as the well–known Hammett equation [14] and other relationships involving kinetic parameters instead of equilibrium constants have been proposed in the literature [15-19]. The main objective of such correlations was the development of absolute reactivity scales that could be independent on the reactivity of the nucleophile/electrophile partners. This objective is ambitious if one considers that a universal scale should accommodate a wide diversity of chemical species presenting quite different structural and bonding properties.

Mayr and co-workers have, however, recently defined nucleophilicity and electrophilicity parameters that are independent of the reaction partners and that describe the rates of many reactions in organic and organometallic chemistry [20-23]. It has been well established, in contrast to the accepted opinion about the relative character of the experimental electrophilicity/nucleophilicity scales, that the rates of reactions of hundreds of carbenium ions, Michael acceptors and other electrophiles with charged and uncharged  $\sigma$ -,  $\pi$ - and n-nucleophiles obey the linear free-energy relationship given by:

$$\log k_{(20\,^{\circ}\text{C})} = s_{\text{N}} (N + E) \tag{1}$$

where  $k_{(20 \circ C)}$  is the second-order constant in mol<sup>-1</sup> dm<sup>3</sup> s<sup>-1</sup>,  $s_N$  is the nucleophile sensitivity parameter, *N* is the nucleophilicity parameter, and *E* is the electrophilicity parameter. Based on Eq. (1), general electrophilicity (*E*) and nucleophilicity (*N*) scales, each covering a

reactivity range of more than 30 orders of magnitude have been defined and successfully used to predict the feasibility and rate of many interactions [24-27].

Interestingly, it has recently been shown that the electrophilicity of an extended series of neutral electron-deficient nitroaromatics and heteroaromatics of widely differing reactivity and structure is appropriately described by this equation [28].

In this paper, we report on the determination of the electrophilicity of the four aromatic triflones **1-4** shown in Scheme 1. Electrophilicity parameters *E* of **1-4** were determined from the kinetics of their reactions with various anilines and enamines **A-G** of known nucleophilicity parameters *N* and which are defined as reference nucleophiles (Table 1). This extension of the applicability of Eq. (1) to  $S_NAr$  and  $\sigma$ -complexation processes further demonstrates the general utility of this relationship and the new kinetic data might allow synthetic chemists to design new addition reactions of nucleophiles to NO<sub>2</sub> and SO<sub>2</sub>CF<sub>3</sub> substituted arenes.



Scheme 1. Structures and numbering of the aromatic triflones

< Table 1 >

#### 2. Results and Discussion

The kinetic study was performed under pseudo-first-order conditions with the concentration of anilines or enamines in excess over the substrates concentration. All of the reactions obeyed first-order kinetics. Pseudo-first-order rate constants ( $k_{obs}$ ) were calculated from the equation  $\ln (A_{\infty} - A_t) = -k_{obs} t + C$ . The  $k_{obs}$  values with the reaction conditions are summarized in Tables S1-S7 in the Supporting Information.

For anilines reactions, all pseudo-first-order rate constants  $k_{obs}$  obey Eq. (2) with negligible  $k_0$  as illustrated in the plots of  $k_{obs}$  vs. aniline concentration in the case of the

reaction of the *p*-methoxyaniline **A** with the triflones **1**, **2** and **3** (Fig. 1). The second-order rate constants  $k_1$  were determined from the slopes of theses linear plots, based on Eq. (2).

$$k_{\rm obs} = k_{\rm o} + k_1 [{\rm An}] \tag{2}$$

Furthermore, no higher–order terms were detected and no complications were found in the determination of  $k_1$ .

This suggests that there is no base catalysis or noticeable side reactions, and that the overall reaction follows the mechanism described in Scheme 2. This is also in agreement with the traditional interpretation of nucleophilic aromatic substitution by amines, and in agreement with the S<sub>N</sub>Ar–Ad.E mechanism, where the rate–limiting formation of the zwitterionic  $\sigma$ – complex intermediate **ZW**<sup>±</sup> is followed by the fast expulsion of the methoxy leaving group [31, 32].



The second-order rate constants  $k_1$  of the S<sub>N</sub>Ar reactions of anilines A-C (*p*-methoxyaniline A, *p*-methylaniline B and aniline C) with aromatic triflones 1-3 at 20 °C in MeCN are summarized in Table 2. The substitution of one nitro group of 2,6-bis(SO<sub>2</sub>CF<sub>3</sub>)-4-nitroanisole 2 and 2,4-bis(SO<sub>2</sub>CF<sub>3</sub>)-6-nitroanisole 3 by a SO<sub>2</sub>CF<sub>3</sub> group to give the 2,4,6-tris(SO<sub>2</sub>CF<sub>3</sub>)anisole 1 increases the rate of reactions with anilines by 15 and 40–fold, respectively. These results emphasize that the SO<sub>2</sub>CF<sub>3</sub> group has a stronger electron-withdrawing character than a NO<sub>2</sub> group, both in the *ortho*– and *para*–positions of a reactive center in an aromatic ring. This behavior is consistent with the higher values of the Hammett

constants of the SO<sub>2</sub>CF<sub>3</sub> substituent ( $\sigma_m = 0.76$ ,  $\sigma_p = 0.96$ ,  $\sigma_{p-} = 1.65$ ) obtained from studies of the ionization of various AH-type acids (benzoic acids, anilinium ions and phenols) [6, 33, 34] than the Hammett constants of the NO<sub>2</sub> substituent ( $\sigma_m = 0.71$ ,  $\sigma_p = 0.78$ ,  $\sigma_{p-} = 1.27$ ). Obviously, these substituent constants fit well the finding that the SO<sub>2</sub>CF<sub>3</sub> group is markedly more activating than a NO<sub>2</sub> group on *para* than on *ortho*-position.

Interestingly, Table 2 shows that contrasting trends govern the reactivity of 2,4bis(trifluoromethanesulfonyl)-6-nitroanisole **3**. This contrasting behavior is readily understood in terms of steric effects. As revealed by X-ray crystallography, the NO<sub>2</sub> groups in the 2-and 6-positions are strongly twisted from the plane of the ring [35, 36].

For enamines reactions, Figures S1-S4 in the Supporting Information show the oscilloscope traces illustrating the unique relaxation process corresponding to the formation of the  $\sigma$ -adducts representative of the various electrophile 4 – enamines **D-G** (morpholinoisobutylene D, 1-(phenylmethylamino)cyclohexene Е, 1-(Nand F 1-(N-morpholino)cyclopentene **G**) morpholino)cyclohexene combinations investigated. The observed pseudo first-order rate constant for the approach to equilibrium, as illustrated in Scheme 3, is simply given by

 $k_{\rm obs} = k_1 [\text{Enamine}] + k_{-1} \tag{3}$ 

Figure 2 shows for a representative example that plots of  $k_{obs}$  vs. enamine concentration were also linear with negligible intercepts ( $k_{-1} \approx 0$ ), indicating that the resulting  $\sigma$ -adducts have a high thermodynamic stability in acetonitrile solution and that the reverse reaction is not observed.



Scheme 3

Determination of the second-order rate constants  $k_1$  from the slopes of the  $k_{obs}$  vs [enamine] plots was straightforward for all reactions studied, and the data are summarized in Table 2 together with the  $k_1$  values for the structurally analogue 1,3,5-trinitrobenzene (TNB) **5** [28]. A significant result is that the replacement of three NO<sub>2</sub> groups of the TNB **5** by three SO<sub>2</sub>CF<sub>3</sub> groups to give the 1,3,5-tris-(trifluoromethanesulfonyl)benzene **4** results in an enormous increase in reactivity, as reflected by the ratios  $k_1^4/k_1^5$  in the order of ~ 10<sup>4</sup> for the reactions with the enamines **D**-**G**. This huge reactivity differences emphasize again the much greater activating effect exerted by the SO<sub>2</sub>CF<sub>3</sub> groups relative to the NO<sub>2</sub> groups in anionic  $\sigma$ complex formation and related S<sub>N</sub>Ar processes. This effect is fully consistent with previous observations, showing that the rate-constants of the formation of the adducts are strongly influenced by the variation in the substitution pattern of the aromatic or heteroaromatic ring [6, 7, 35-38].

< Fig. 2 >

< Table 2 >

#### **Determination of the electrophilicity parameters of 1-4**

In the recent years, much interest has been paid to the design of electron-deficient aromatics and heteroaromatics exhibiting a high reactivity in  $\sigma$ -complex formation [8, 9, 41-44]. Although the electrophilicity of various aromatic substrates have been already measured by studying the kinetics of attack of nucleophiles at unsubstituted CH positions of their  $\pi$ -system, kinetics of the reactions of nucleophiles at a substituted position, for instance by a chloride, fluoride or a methoxy substituent, have been less studied [45, 46].

The addition of nucleophiles at positions bearing a leaving group such as OMe is even of higher synthetic potential because the leaving group facilitates the subsequent rearomatizationa step by its expulsion, and hence facile achievement of the overall  $S_NAr$  substitution.

We have found that these  $\sigma$ -complexation and S<sub>N</sub>Ar reactions described above follow the three-parameters equation log  $k_{(20 \ ^{\circ}C)} = s_N (N + E)$  developed by Mayr and co-workers. Assuming that the rate determining step of these reactions is the C-C or C-N bond formation, the  $k_I$  values given in Table 2 have been used for the determination of the *E* parameters for **1**-**4**. The obtained *E* values and the derived standard deviations are given in Table 3. The

resulting electrophilicity parameters *E* are, respectively, for each 2-Y-4-Z-6-(trifluoromethanesulfonyl)anisole: E = -14.98 for **1** (Y = Z= SO<sub>2</sub>CF<sub>3</sub>), E = -16.69 for **2** (Y = SO<sub>2</sub>CF<sub>3</sub>; Z = NO<sub>2</sub>), E = -17.34 for **3** (Y = NO<sub>2</sub>; Z = SO<sub>2</sub>CF<sub>3</sub>) and E = -7.98 for the 1,3,5tris(SO<sub>2</sub>CF<sub>3</sub>)benzene **4**.

The quantitative ranking of the electrophiles **1-4** on the electrophilicity scale (Figure 3) make possible a comparison of their electrophilic reactivity with that of related compounds previously classified in the scale. The experimental *E* values of **1-3** show that the substitution of one nitro group of 2,6-bis(SO<sub>2</sub>CF<sub>3</sub>)-4-nitroanisole **2** and 2,4-bis(SO<sub>2</sub>CF<sub>3</sub>)-6-nitroanisole **3** by a SO<sub>2</sub>CF<sub>3</sub> group to give **1** increases their electrophilic strength by approx. 3 orders of magnitude. Interestingly, The *E* values of **1-3** determined are comparable to those of other electron-deficient aromatics, such as 1-Hal-2,4-dinitrobenzene: E = -14.1 for Hal = F, E = -17.6 for Hal = Cl and Br, and E = -18.3 for Hal = I [46], that also engage in S<sub>N</sub>Ar displacement reactions.

# < Table 3 >

Most importantly, the reactivity domain of neutral electrophilic aromatic substrates is greatly expanded by the 1,3,5-tris(trifloromethanesulfonyl) benzene **4** which has an *E* values of -7.98, *i.e.* almost 6 orders of magnitude more electrophilic than the trinitrobenzene **5** (E = -13.19), however, considerably more electrophilic that the most reactive neutral substrate studied by Mayr namely benzylidenemalonitrile (E = -9.42). The electrophilicity of **4** compares well with that of the 6-cyano-4-nitrobenzofuroxan (E = -7.01) and found to approach that of 4-nitrobenzodifuroxan NBDF (E = -6.25), an activated nitroolefin with a superelectrophilic behavior. Anchoring to carbocationic reactivity, the electrophilicity of **4** is of the same order of reactivity as that of a stabilized benzhydrylium cation such as Michler's hydrol blue (E = -7.02), but higher than that of other positively charged species such as triallyl cations or arylallylpalladium complexes as shown in Figure 3.

The determination of the electrophilicity of the triflones **1-4** represents an extension of the previously reported electrophilicities of neutral electron-deficient aromatics and heteroaromatics of widely different reactivity and structure which were also appropriately

described by Eq (1) [28, 42-46]. Our data furthermore increase the scope and the applications of this equation which was originally mostly developed by modulating the strength of the electrophilic partner through variations of the substituents and structural variations of carbocationic structures.

Thus, TTSB **4** represents a departure from the classical electrophilicity domain and an entry to the superelectrophilic domain of reactivity ( $E \sim < -8$ ) in  $\sigma$ -complex formation and related reactivities of aromatic substrates. The *E* value that we correctly predicted earlier for **4**, based on an empirical correlation between *E* and pK<sub>a</sub> (eq. 4) was E = -7.56 from the value  $pK_{\alpha}^{MeOH} = 9.12$  [9].

$$E = -0.662 \ pK_{a}^{MeOH} - 1.53 \quad (4)$$

A similar approach has been used earlier in order to estimate the *E* values of the aromatic triflones **1-3**, where the nucleophilic attack occurs at a substituted position of the aromatic ring, in contrast to **4**. The predicted *E* values were E = -6.37 ( $pR_{\alpha}^{MeOH} = 7.32$ ) for **1**[8], E = -8.47 ( $pR_{\alpha}^{MeOH} = 10.48$ ) for **2** [9], E = -7.76 ( $pR_{\alpha}^{MeOH} = 9.42$ ) for **3** [47], suggesting that **1-3** are very strong electrophiles.

These predicted *E* values were very far from the experimental values (Table 3) because eq.4. refers to the methoxylation reaction at unsubstituted positions, *i.e.* reactions with negligible steric effects, or it refers to the methoxylation reaction at substituted position (OMe sustitutent) to give 1,1-dimethoxy adducts through  $\sigma$ -complexation reaction, *i.e.* reactions with nucleophile of small sizes. The reactions of aromatic triflones 1-3 with anilines A-C, nucleophiles of larger size attacking at a position substituted by OMe, gave experimental *E* values of approx. 9 units of electrophilicity less than predicted earlier, illustrating in the strong effect of substituent and of nature of nucleophile partner on the attacked position of the aromatic ring.

#### 3. Conclusions

Our study has established that the  $SO_2CF_3$  group is markedly more activating than a  $NO_2$  group in  $\sigma$ -complex formation and therefore in related nucleophilic aromatic displacement processes. Importantly, our results provide a quantitative demonstration that the tris- $SO_2CF_3$  benzene **4** exhibits a reactivity which surpasses that of conventional electron-deficient aromatics, e.g. TNB, by several orders of magnitude.

Applying the general approach to nucleophilicity/electrophilicity developed by Mayr et al, the E parameters, quantifying the electrophilic reactivity of the triflones **1-4**, have been

determined in acetonitrile, through kinetic investigations of  $\sigma$ -complexation and S<sub>N</sub>Ar substitution reactions involving anilines and enamines as N- and C-nucleophiles. It has been shown that this reactions form an integral part of electrophile-nucleophile interactions through the definition of general electrophilicity (E) and nucleophilicity (N) scales.

Overall, this relationship appears as being a nice probe to predict the feasibility of the reactions of  $S_NAr$  substitutions and related  $\sigma$ -complexation processes, which will be of real benefit for broadening the range of synthetic and analytical applications in this field.

#### 4. Experimental

**Materials.** 2,4,6-tris(trifluoromethanesulfonyl)anisole 1, 2,6-bis(trifluoromethanesulfonyl)-4nitroanisole 2, 2,4-bis(trifluoromethanesulfonyl)-6-nitroanisole 3, and 1,3,5-tris(trifluoromethanesulfonyl)benzene 4 was prepared as previously described by Yagupolskii et al. [48-50]. Anilines A-C were of the highest quality available (Aldrich products) and were recrystallized or distilled before use whenever necessary. Enamines D-G were prepared by condensation of the ketone or aldehyde with the corresponding secondary amine [51]. Acetonitrile was distilled over  $P_2O_5$  and stored under nitrogen.

**Kinetics.** Kinetic determinations were performed on an Applied Photophysics SX-18MV stopped-flow apparatus or a conventional Shimadzu (model 1650 PC) UV–Vis spectrophotometer, the cell compartments of which were maintained at  $20 \pm 0.1$  °C. All kinetic runs were carried out in triplicate under pseudo-first-order conditions with a triflone concentration of ~ 3 x 10<sup>-5</sup> mol dm<sup>-3</sup> and an concentration in the range of 5 x 10<sup>-3</sup> - 1 mol dm<sup>-3</sup> for anilines and an concentration in the range of 5 x 10<sup>-4</sup> – 0.1 mol dm<sup>-3</sup> for enamines. In a given experiment, the rates were found to be reproducible to 2–3 %.

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#### Table 1

Nucleophilicity N and nucleophile sensitivity parameter  $s_N$  of the anilines **A-C** and of the enamines **D-G** used as reference nucleophiles in this study.

	Nucleophiles	Ν	s <sub>N</sub>
A		13.42 <sup>a</sup>	0.73 <sup>a</sup>
В	H <sub>3</sub> C-NH <sub>2</sub>	13.19 <sup>a</sup>	0.69 <sup>a</sup>
С		12.64 <sup>a</sup>	0.68 <sup>a</sup>
D	O	10.04 <sup>b</sup>	0.82 <sup>b</sup>
E		10.73 <sup>b</sup>	0.81 <sup>b</sup>
F		11.40°	0.83 <sup>c</sup>
G		13.41 <sup>b</sup>	0.82 <sup>b</sup>
<sup>a</sup> From	n ref. [29]. <sup>b</sup> From ref. [3	0]. <sup>c</sup> From re	f. [22]

#### Table 2

Second–order rate constants  $k_1 \pmod{10^3 \text{ s}^{-1}}$  for coupling of the electrophiles **1-5** with the reference nucleophiles **A-G** in acetonitrile at 20 °C.

Nucleophile	1	2	3	4	5 <sup>d</sup>
Α	8.73 x 10 <sup>-2</sup>	4.99 x 10 <sup>-3</sup>	1.72 x 10 <sup>-3</sup>		
В	5.42 x 10 <sup>-2</sup>	3.54 x 10 <sup>-3</sup>	1.31 x 10 <sup>-3</sup>		
С	2.21 x 10 <sup>-2</sup>	1.49 x 10 <sup>-3</sup>	5.32 x 10 <sup>-4</sup>		
D				9.11 x 10 <sup>1</sup>	3.8 x 10 <sup>-3</sup>
Ε				$1.65 \times 10^2$	6 x 10 <sup>-3</sup>
F				$6.53 \times 10^2$	1.14 x 10 <sup>-2</sup>
G				$1.61 \times 10^4$	5.0
<sup>d</sup> From ref. [2	28]				

#### Table 3

Electrophiles	Nucleophiles	N	s <sub>N</sub>	$\log k_1$	Ε
OCH3	Α	13.42	0.73	-1.06	-14.87
CF <sub>3</sub> O <sub>2</sub> S SO <sub>2</sub> CF <sub>3</sub>	В	13.19	0.69	-1.27	-15.03
	С	12.64	0.68	-1.65	-15.06
SO <sub>2</sub> CF <sub>3</sub>					$E(1) = -14.98 \pm 0.10^{e}$
1					
OCH3	Α	13.42	0.73	-2.30	-16.57
CF <sub>3</sub> O <sub>2</sub> S SO <sub>2</sub> CF <sub>3</sub>	В	13.19	0.69	-2.45	-16.74
	С	12.64	0.68	-2.82	-16.78
					$E(2) = -16.69 \pm 0.11^{e}$
2					
OCH <sub>3</sub>	Α	13.42	0.73	-2.76	-17.20
O <sub>2</sub> NSO <sub>2</sub> CF <sub>3</sub>	В	13.19	0.69	-2.88	-17.36
	С	12.64	0.68	-3.28	-17.46
$\stackrel{\restriction}{SO_2CF_3}{3}$					$E(3) = -17.34 \pm 0.13^{e}$
CF <sub>3</sub> O <sub>2</sub> S SO <sub>2</sub> CF <sub>3</sub>	D	10.04	0.82	1.96	-7.65
	Ε	10.73	0.81	2.22	-7.99
"\	F	11.40	0.83	2.81	-8.00
SO2CE3	G	13.41	0.82	4.21	-8.27
4	-				$E(4) = -7.98 \pm 0.36^{e}$

Determination of the electrophilicity parameters E of **1-4** from reactions with different reference nucleophiles **A-G** in acetonitrile at 20 °C.

<sup>e</sup> The *E* parameter is obtained by minimizing  $\Delta^2 = \sum [\log k_1 - s (E + N)]^2$  and deviates slightly from the arithmetic mean of *E* derived from the individual reactions [22].



**Fig. 1.** Influence of the concentration of *p*-methoxyaniline **A** on the observed first-order rate constant for addition to 2,4,6-tris(SO<sub>2</sub>CF<sub>3</sub>)anisole **1**, 2,6-bis(SO<sub>2</sub>CF<sub>3</sub>)-4-nitroanisole **2**, and 4,6-bis(SO<sub>2</sub>CF<sub>3</sub>)-2-nitroanisole **3** in MeCN at 20 °C



**Fig. 2.** Influence of the concentration of enamine **D** on the observed first-order rate constant for addition to 1,3,5-tris(trifluoromethanesulfonyl)benzene **4** in MeCN at 20 °C.



Fig. 3. The ranking of aromatic triflones 1-4 on the *E* scale, as defined by Mayr *et al*.

### **Graphical Abstract**

Applying the general approach to nucleophilicity/electrophilicity developed by Mayr et *al.*, the *E* parameters, quantifying the electrophilic reactivity of four aromatic triflones, have been determined in acetonitrile, through kinetic investigations of  $\sigma$ -complexation and S<sub>N</sub>Ar substitution reactions involving anilines and enamines as N- and C-nucleophiles.

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#### Highlights

We quantify the electrophilic reactivity for four aromatics triflones

We examine changes in the substitutent of aromatic ring about electrophilic strength

Ranking the neutral electro-deficient electrophiles in Mayr's scale

Increasing the scope and the applications of the Mayr equation

Expanding the range of coupling reactions