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Solvent network at the transition state in the solvolysis of hindered sulfonyl compounds

Mykyta Iazykov[a,b]*, Ludmila Rublova[a], Moisés Canle L.[b] and J. Arturo Santaballa[b]

Alcoholysis rates of unhindered benzenesulfonyl chlorides (X-ArSO$_2$Cl, X = H-; 4-Br-; 4-Me-) are similar in methanol; the same behavior is also observed in ethanol, whereas the reactivity order in *iso*-propanol is 4 Me- < H- < 4-Br-. On the other hand, alcoholysis of sterically hindered arenesulfonyl chlorides (X-ArSO$_2$Cl) (X = 2,4,6-Me$_3$-3-NO$_2$-; 2,6-Me$_2$-4-*t*Bu-; 2,4,6-Me$_3$-; 2,3,5,6-Me$_4$-; 2,4,6-*i*Pr$_3$-; 2,4-Me$_2$-; 2,4,6-(OMe)$_3$-) in all studied alcohols show a significant increase in reactivity, the so-called positive steric effect.

Most of the substrates showed a reaction order $b \sim 2$ with respect to the nucleophile in methanol and ethanol, and $b \sim 3$ in *iso*-propanol. The correlation between reactivity and the Kirkwood function ($1/\xi$) gives negative sensitivity (*U*) for all systems. All substrates showed high sensitivity to media nucleophilicity that depends on $\Sigma\sigma_X$.

Obtained results suggest the alcoholysis of benzenesulfonyl chlorides proceeds through S$_N$2 mechanism where the transition state (TS) involves the participation of 2–3 alcohol molecules; such a TS can be cyclic, in the case of unbranched alcohols, or linear, for alcohols with bulkier hydrocarbon groups like *iso*-propanol. To include the number of alcohol molecules playing such a role in the TS, the following terminology is proposed: cS$_N$2s$_n$ for S$_N$2 reactions involving n solvent molecules in a cyclic (c) TS, where "s" stands for the solvent and "n" is either the closest integer or half-integer to the reaction order relative to the solvent or, in computational studies, the proposed number of solvent molecules taking part in the TS, whereas S$_N$2s$_n$ is proposed when the TS is not cyclic. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: alcoholysis; cS$_N$2s$_n$; kirkwood function; media nucleophilicity; nucleophilic substitution; reaction mechanisms; S$_N$2 mechanism; S$_N$2s$_n$; solvent networks; solvolysis; sulfonyl chlorides

INTRODUCTION

Nucleophilic substitution at sulfur of the sulfonyl group has been a frequent matter of debate[1–5] because of the ambiguity of the solvolysis mechanism, often considered as bimolecular, with different transition state (TS) symmetries,[6,7] involving catalytic assistance of the solvent,[4,5,8,9] a possible molecular rearrangement during the nucleophilic attack,[10] and so on. A number of common mechanistic criteria for solvolytic processes of arenesulfonyl chlorides points to a typical S$_N$2-nucleophilic substitution mechanism: similar secondary and solvent isotope effect,[11,12] effect of the change of nucleophile,[3,13,14] and solvent effect.[3,14,15]

In recent years, the problem became more complicated with the study of sterically hindered arenesulfonyl compounds in which the attack on the S atom is apparently inhibited by the presence of *ortho*-alkyl groups.[16] On the other hand, hindered structures based on derivatives of benzene sulfonyl chloride have shown a significant increase in reactivity, the so-called positive steric effect,[6,16] which is in disagreement with the classical interpretation of the electronic effect of substituents on the rate of S$_N$2 processes.[10,13,15,17–19] Based on the described observations, and others already available in the literature, deviations of the TS structure are expected for a number of hindered substrates.[1,2,4,5,17,18,20–27]

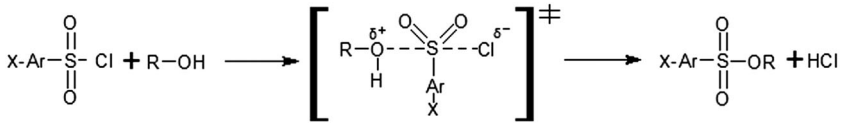
When studying the alcoholysis of deuterated 2,4,6-trimethylbenzenesulfonyl chloride,[28] we obtained kinetic data and activation parameters comparable with those for undeuterated 2,4,6-trimethylbenzenesulfonyl chloride, such evidence lets us neglect σ-π-hyperconjugation as a possible reason of the "positive steric effect" in this particular case.[10,28] The observation of small kinetic solvent isotope effects is an evidence against the catalytic effect of a second nucleophile molecule present in the TS[4,5,11] and supports the participation of a network of alcohol molecules in the TS, even as a cyclic chain.[28]

Here, we present a mechanistic study of the alcoholysis (Scheme 1) of different sterically hindered arenesulfonyl chlorides (X-ArSO$_2$Cl) at 323 K (X = 2,4,6-Me$_3$-3-NO$_2$-; 2,6-Me$_2$-4*t*Bu-; 2,4,6-Me$_3$-; 2,3,5,6-Me$_4$-; 2,4,6-*i*Pr$_3$-; 2,4-Me$_2$-; 2,4,6-(OMe)$_3$-; H-; 4-Me-; 4-Br-) in methanol, ethanol, and *iso*-propanol to elucidate the structure of the TS and looking for a better understanding of the solvolytic process.

* *Correspondence to: Mykyta Iazykov, Chemical Reactivity and Photoreactivity Group, Department of Physical Chemistry and Chemical Engineering, Faculty of Sciences and CICA, University of A Coruña, E-15071 A Coruña, Spain. E-mail: nikitich205@gmail.com*

a *M. Iazykov, L. Rublova*
Department of General Chemistry, Faculty of Ecology and Chemical Technology, Donetsk National Technical University, ave Bogdana Khmelnitskogo 106, 83015, Donetsk, Ukraine

b *M. Iazykov, M. Canle L., J. A. Santaballa*
Chemical Reactivity and Photoreactivity Group, Department of Physical Chemistry and Chemical Engineering, Faculty of Sciences and CICA, University of A Coruña, E-15071, A Coruña, Spain



Scheme 1. Classical S_N2 mechanism in the alcoholysis of arenesulfonyl chlorides

RESULTS AND DISCUSSION

First-order kinetic model adequately fits to chemical kinetic data of alcoholysis. Reaction rates are scarcely affected in the case of unhindered benzenesulfonyl chlorides (X-$ArSO_2Cl$, X = H-; 4-Br-; 4-Me-) when solvolysis takes place in methanol and ethanol as shown in Figs. 1 and 2. Hereafter we will call those three compounds "model series", and the term "hindered" will refer to the presence of two alkyl *ortho* substituents.

Hammett plots for methanolysis and ethanolysis (Figs. 1 and 2), with all the difficulties derived from assigning values to the effects of substituents in different positions,[29] show a general tendency to an increased reactivity as the combination of substituent's effects becomes more electron releasing. For *iso*-propanolysis (Fig. 3), the tendency is less clear. Here, in contrast with the similar reactivity in methanolysis and ethanolysis, the reactivity order within the model series is 4-Me- < H- < 4-Br-. Different correlations might be possible for different combinations of hindered and unhindered substrates; therefore, we have not drawn any tendency line, but just keep a qualitative analysis. The tendency shown in Figs. 1 and 2 implies a non-negligible decrease in electron density at the reaction site. This may be indicative of a "loosening" of the S-Cl bond and subsequent displacement of the TS toward a more "cationic"-like TS structure.[30]

2,4-Me_2-benzenesulfonyl chloride shows higher reactivity than the model series, lesser in *iso*-propanol than in unbranched alcohols (Figs. 1–3).

Sulfonyl chlorides X-$ArSO_2Cl$ with methyl/methoxy substituents in both *ortho*- positions (X = 2,4,6-Me_3-, 2,6-Me_2,4-*t*-Bu-; 2,3,5,6-Me_4-; 2,4,6-Me_3,3-NO_2-; 2,4,6-OMe_3-,) show a noticeable higher reactivity for all the three alcohols (Figs. 1–3). The accelerating effect of alkyl *ortho* substituents also operates with the bulkier compound 2,4,6-*i*-Pr_3-benzenesulfonyl chloride; it reacts faster than model series and 2,4-Me_2-benzenesulfonyl chloride in methanol and ethanol.

Correlation between reactivity and the Kirkwood function ($1/\xi$) takes into account exclusively nonspecific solvation, that is, the ability of the solvent to promote charge transfer, as well as to polarize substrate molecules.[31] The permittivity of the mixture (ξ_{mix}) was calculated according to the Lichtenecker–Rother Eqn 1,:[32]

$$\log \xi_{mix} = f_{alc} \times \log \xi_{alc} + f_{hex} \times \log \xi_{hex}, \quad (1)$$

where f_{alc} and f_{hex} are the volume fractions, and ξ_{alc} and ξ_{hex} are the permittivities of alcohol and hexane, respectively. Equation 2 was used to build the corresponding correlations:

$$\log k_{obs} = U\frac{1}{\xi} + \log k_0. \quad (2)$$

When solvent polarity is considered, the sensitivity (U) is negative for all systems (Table 1).

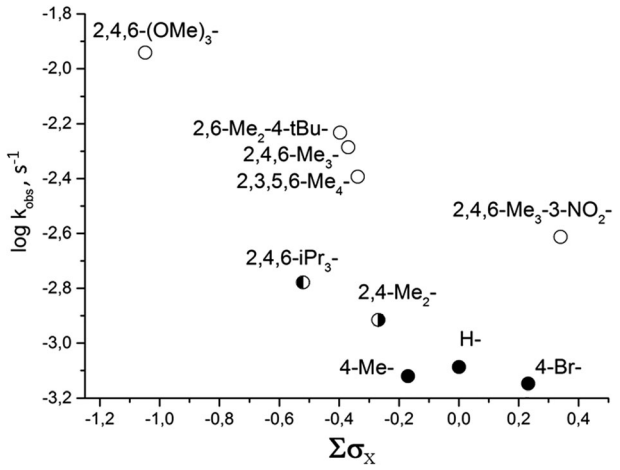


Figure 1. Hammett plot for X-$ArSO_2Cl$ methanolysis (T = 323 K): ●, unhindered compounds; ○, compounds with enhanced reactivity

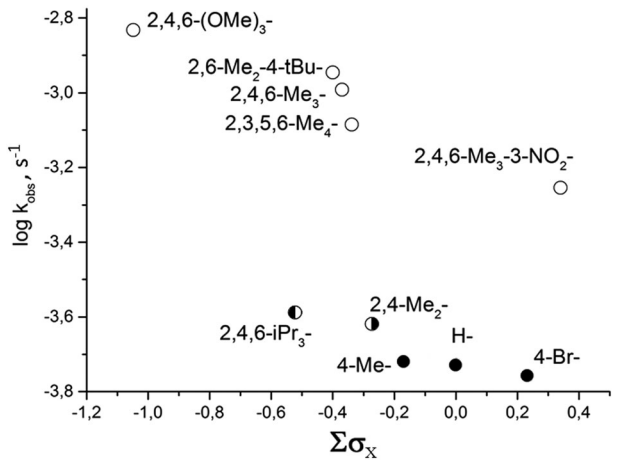


Figure 2. Hammett plot for X-$ArSO_2Cl$ ethanolysis (T = 323 K): ●, unhindered compounds; ○, compounds with enhanced reactivity

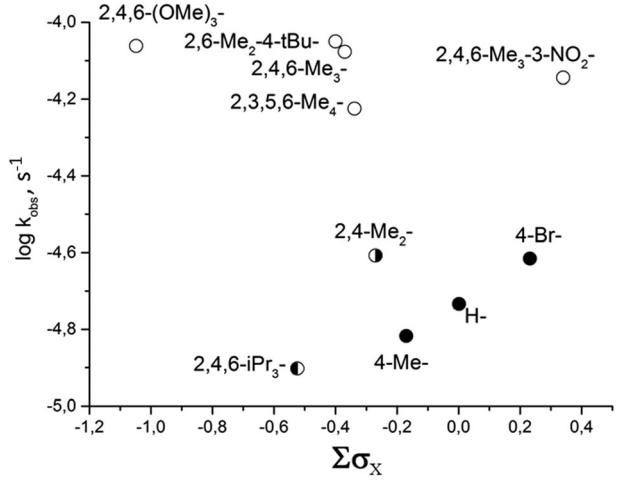


Figure 3. Hammett plot for X-$ArSO_2Cl$ *iso*-propanolysis (T = 323 K): ●, unhindered compounds; ○, compounds with enhanced reactivity

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Table 1. Fitted parameters for *log* k_{obs} *versus* $1/\xi$ dependences (Eqn 2) for X-$ArSO_2Cl$ solvolysis in alcohol-hexane (43–100% MeOH, 36–100% EtOH, 29–100% *i*-PrOH; V/V) mixtures at 323 K

X	Alcohol	log k_0	*U*	R^2	*n**
2,4,6-Me_3-3-NO_2-	MeOH	−2.86 ± 0.03	−2.7 ± 0.2	0.988	5
	EtOH	−3.32 ± 0.05	−3.2 ± 0.3	0.982	4
	i-PrOH	−3.68 ± 0.05	−6.1 ± 0.4	0.989	5
2,6-Me_2-4-*t*-Bu-	MeOH	−2.50 ± 0.04	−3.2 ± 0.3	0.978	5
	EtOH	−3.04 ± 0.05	−3.7 ± 0.3	0.985	5
	i-PrOH	−3.77 ± 0.06	−5.9 ± 0.5	0.982	5
2,4,6-Me_3-	MeOH	−2.45 ± 0.04	−3.5 ± 0.3	0.981	4
	EtOH	−3.07 ± 0.03	−3.4 ± 0.2	0.994	5
	i-PrOH	−3.70 ± 0.02	−6.9 ± 0.1	0.999	5
2,3,5,6-Me_4-	MeOH	−2.63 ± 0.05	−3.1 ± 0.4	0.962	5
	EtOH	−3.23 ± 0.04	−3.6 ± 0.2	0.988	5
	i-PrOH	−3.92 ± 0.04	−5.8 ± 0.3	0.993	5
2,4,6-*i*-Pr_3-	MeOH	−2.89 ± 0.03	−5.1 ± 0.3	0.994	4
	EtOH	−3.59 ± 0.01	−4.6 ± 0.1	0.999	4
	i-PrOH	−4.62 ± 0.06	−5.4 ± 0.4	0.982	5
2,4-Me_2-	MeOH	−3.12 ± 0.03	−3.0 ± 0.2	0.986	5
	EtOH	−3.64 ± 0.01	−4.0 ± 0.1	0.999	3
	i-PrOH	−4.29 ± 0.05	−6.2 ± 0.4	0.989	5
2,4,6-$(OMe)_3$-	MeOH	−2.14 ± 0.04	−2.3 ± 0.4	0.956	4
	EtOH	−3.13 ± 0.02	−1.9 ± 0.1	0.992	4
	i-PrOH	−3.72 ± 0.08	−5.0 ± 0.6	0.957	5
H-	MeOH	−3.31 ± 0.02	−2.6 ± 0.1	0.995	5
	EtOH	−3.82 ± 0.05	−3.2 ± 0.3	0.977	4
	i-PrOH	−4.50 ± 0.04	−4.7 ± 0.3	0.990	5
4-Me-	MeOH	−3.32 ± 0.05	−2.5 ± 0.3	0.953	5
	EtOH	−3.89 ± 0.06	−3.0 ± 0.4	0.962	4
	i-PrOH	−4.51 ± 0.03	−4.8 ± 0.2	0.996	4
4-Br-	MeOH	−3.48 ± 0.02	−3.1 ± 0.1	0.994	5
	EtOH	−3.83 ± 0.04	−2.6 ± 0.2	0.980	5
	i-PrOH	−4.16 ± 0.04	−5.8 ± 0.3	0.991	5

**n*, sample size.

For methanol-hexane and ethanol-hexane mixtures, *U* values are closer and even approximately the same (Table 1), while they almost doubles for *iso*-propanol-hexane mixtures. It is also remarkable that *U* grows inversely with the polarity of the alcohol, in accordance with the Reactivity Selectivity Principle,[33] and according to Hughes–Ingold rule;[31] increase in reactivity with solvent polarity indicates the TS is more solvated than the reactants. From these results, it follows that the TS's for methanolysis and ethanolysis of sulfonyl chlorides are similar and much less polar than for *iso*-propanolysis, which is in agreement with the observed reactivity tendency. Thus, more polar TS's occur in less polar media, with decrease of reactivity. Such tendency is quite unusual for S_N2 processes. The different behavior of *iso*-propanolysis cannot be explained by the difference in media polarity because the experiments were carried out in media of similar polarity.

Kinetic data allow us to compare the reactivity of arenesulfonyl chlorides in different media of equal polarity ($\varepsilon_{mix} \approx 10$) that simultaneously vary by the nucleophile type (MeOH, EtOH, and *i*-PrOH). The ratios of rate constants k_{MeOH}/k_{EtOH}, $k_{MeOH}/k_{i\text{-}PrOH}$, and $k_{EtOH}/k_{i\text{-}PrOH}$ measure the sensitivity of the X-substituted substrate to the nucleophilicity of medium. The obtained results show higher sensitivity coefficients for all sterically hindered substrates with $\Sigma\sigma_X < 0$ (Table 2) relative to unhindered benzenesulfonyl chloride. In contrast with Bentley's results,[27] sensitivity coefficients increase as $\Sigma\sigma_X$ decreases, which may be explained by the different nucleophile type (97% TFE and 40% ethanol) used by him and the corresponding polarities.

The high sensitivity coefficients to solvent nucleophility for hindered arenesulfonyl chlorides once again suggests an S_N2-like mechanism.

Effective rate constants of solvolysis, k_{obs}, were determined by varying the nucleophile (alcohol) concentration, C_N, using constant initial concentration of sulfonyl chloride in alcohol-hexane mixtures at 323 K (Supporting Information). Alcoholysis rate varies linearly with alcohol concentration (Fig. 4). When a specific sulfonyl chloride is considered, the reaction rate varies in the order: methanolysis > ethanolysis > *iso*-propanolysis. The presence of *ortho*-methyl groups accelerates the process in agreement with earlier observations.[3–5,16,19,28,34]

The slope, *b,* of the observed dependences gives the reaction order with respect to the nucleophile, that is, the corresponding reaction order, according to Eqn 3:[21]

$$\ln k_{obs} = A + b \cdot \ln C_N \quad (3)$$

The so-obtained reaction orders are compiled in Table 3 (see also Tables S9, S11, and S13 at the Supporting Information).

Table 2. Observed rate constants and their ratios for solvolysis of X-$ArSO_2Cl$ in MeOH-hexane, EtOH-hexane, and *i*-PrOH-hexane mixtures at 323 K

X	$k_{MeOH}\cdot10^4$, s^{-1} $\varepsilon_{Mix}=9.4$	$k_{EtOH}\cdot10^4$, s^{-1} $\varepsilon_{Mix}=10.0$	$k_{i\text{-}PrOH}\cdot10^4$, s^{-1} $\varepsilon_{Mix}=9.8$	$\frac{k_{MeOH}}{k_{EtOH}}$	$\frac{k_{MeOH}}{k_{i\text{-}PrOH}}$	$\frac{k_{EtOH}}{k_{i\text{-}PrOH}}$
2,4,6-Me_3-3-NO_2-	7.27 ± 0.01	2.37 ± 0.01	0.466 ± 0.001	3.06	15.6	5.10
2,6-Me_2-4-*t*-Bu-	13.6 ± 0.1	4.11 ± 0.01	0.374 ± 0.001	3.31	36.4	11.0
2,4,6-Me_3-	14.8 ± 0.1	4.06 ± 0.01	0.416 ± 0.001	3.65	35.7	9.77
2,3,5,6-Me_4-	11.0 ± 0.1	2.74 ± 0.01	0.315 ± 0.001	4.02	34.9	8.68
2,4,6-*i*-Pr_3-	3.48 ± 0.01	0.895 ± 0.001	0.072 ± 0.001	3.89	48.4	12.4
2,4-Me_2-	3.45 ± 0.01	0.933 ± 0.01	0.125 ± 0.001	3.69	27.6	7.47
2,4,6-$(OMe)_3$-	40.8 ± 0.01	4.79 ± 0.01	0.517 ± 0.001	8.51	78.9	9.27
H-	2.55 ± 0.01	0.757 ± 0.001	0.102 ± 0.001	3.37	25.1	7.46
4-Me-	2.56 ± 0.01	0.673 ± 0.001	0.104 ± 0.001	3.80	24.6	6.46
4-Br-	2.14 ± 0.01	0.872 ± 0.001	0.174 ± 0.001	2.46	12.3	5.00

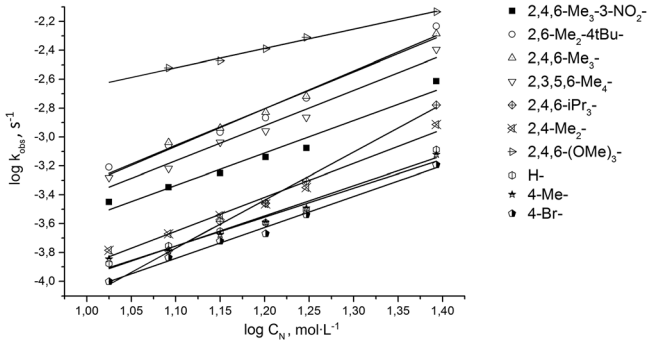

Figure 4. *log* k_{obs} *vs. log* C_N for X-$ArSO_2Cl$ methanolysis in methanol-hexane (43–100%, V/V), T = 323 K

Sterically unhindered substrates (**8–10**, Table 3, see also Table S9 at the Supporting information) and also all hindered *ortho*-methylated compounds showed a reaction order $b \sim 2$ with respect to the nucleophile (methanol) but 2,4,6-*i*Pr_3-benzenesulfonyl chloride (**5**) and 2,4,6-$(OMe)_3$-benzenesulfonyl chloride (**6**) (Table 3), for which reaction orders are 3 and 1.3, respectively.

Solvolysis in ethanol (Fig. 5) shows reaction orders $2 < b < 3$ with respect to the nucleophile (ethanol) for all *ortho*-methylated substrates (**1–4** and **7** in Table 3, see also Table S11 in the Supporting Information). Unhindered substrates (**8** and **10** in Table 3) show $b \sim 2$, but 4-Me-benzenesulfonyl chloride (**9**) ($b \sim 2{,}8$). 2,4,6-*i*Pr_3-benzenesulfonyl chloride (**5**) and 2,4,6-$(OMe)_3$-benzenesulfonyl chloride (**6**) (Table 3) also have a particular behavior, as for methanolysis, with slope 3.0 and 1.5, respectively.

In the case of *iso*-propanolysis (Fig. 6), the reaction order with respect to the nucleophile (*iso*-propanol) is ~ 3, except for 2,4,6-$(OMe)_3$-benzenesulfonyl chloride (**6**) and benzenesulfonyl chloride (**8**) for which is slightly higher than 2 (Table 3; see also Table S13 at the Supporting Information).

The reactivity of sulfonyl chlorides significantly depends on the nucleophile concentration (Figs. 4–6), as predicted for S_N2 processes.[1–7] Assuming the reaction order on the nucleophile relates to the number of solvent molecules participating in the TS, our results suggest the TS involves two nucleophile molecules in methanolysis and three for *iso*-propanolysis (Table 3). The change in space requirements at the TS as the steric hindrance of the nucleophile increases may explain the increase in the number of nucleophile molecules for *iso*-propanolysis TS. The intermediate values obtained for ethanolysis can be

Table 3. Reaction order relative to the nucleophile, *b* of Eqn 3, for X-$ArSO_2Cl$ solvolysis in alcohol-hexane mixtures, T = 323 K

№	X	Reaction order relative to the nucleophile (*b* of Eqn 3)		
		MeOH-hexane 43–100%, V/V	*EtOH-hexane* 36–100%, V/V	*Iso-propanol-hexane* 29–100%, V/V
1	2,4,6-Me_3-3-NO_2-	2.3 ± 0.2	2.3 ± 0.1	3.2 ± 0.1
2	2,3,5,6-Me_4-	2.0 ± 0.2	2.8 ± 0.1	3.04 ± 0.08
3	2,4,6-Me_3-	2.1 ± 0.1	2.66 ± 0.03	3.0 ± 0.2
4	2,6-Me_2-4tBu-	2.1 ± 0.1	2.6 ± 0.1	3.2 ± 0.2
5	2,4,6-*i*-Pr_3-	3.1 ± 0.1	3.04 ± 0.04	3.0 ± 0.2
6	2,4,6-$(OMe)_3$-	1.31 ± 0.05	1.52 ± 0.09	2.25 ± 0.05
7	2,4 Me_2-	1.95 ± 0.07	2.65 ± 0.08	3.5 ± 0.2
8	H-	2.1 ± 0.1	2.1 ± 0.2	2.35 ± 0.08
9	4-Me-	1.90 ± 0.06	2.8 ± 0.2	3.1 ± 0.1
10	4-Br-	2.0 ± 0.1	2.01 ± 0.04	3.3 ± 0.2

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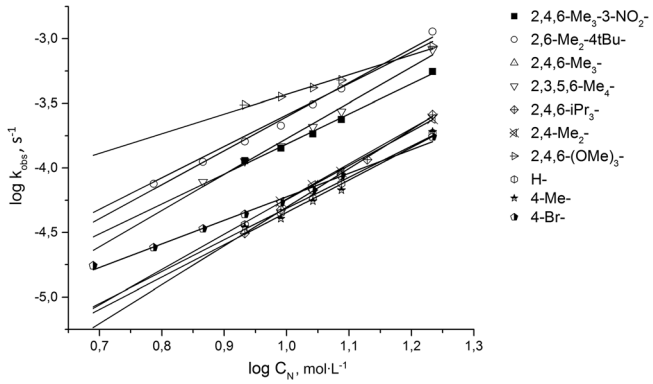


Figure 5. *log* k_{obs} *versus log* C_N for X-$ArSO_2Cl$ ethanolysis in ethanol-hexane (36–100%, V/V), T = 323 K

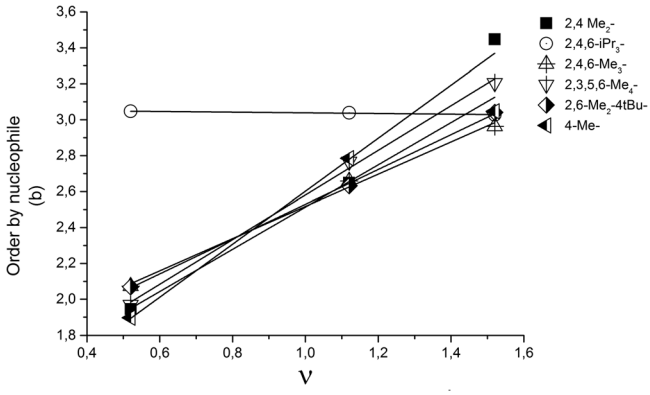


Figure 7. Reaction order with respect to the nucleophile (b) *versus* Charton's ν for X-$ArSO_2Cl$ solvolysis

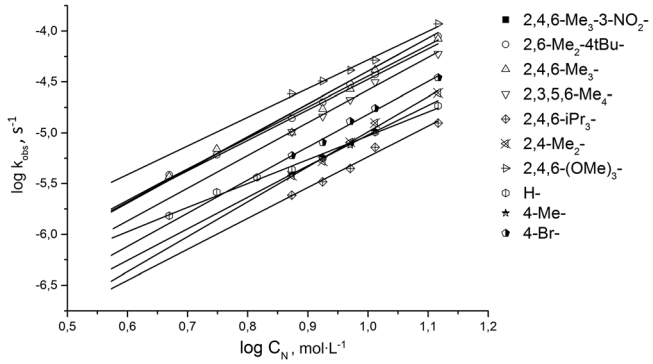


Figure 6. *log* k_{obs} *versus log* C_N for the *iso*-propanolysis of X$ArSO_2Cl$ in *iso*-propanol-hexane (29–100%, V/V), T = 323 K

Table 4. Fitted parameters of Eqn 4 for X-$ArSO_2Cl$ solvolysis in *iso*-propanol-hexane system at T = 323 K

X	$b = \delta \cdot \nu + c_1$		
	c_1	δ	R^2
2,6-Me_2-4tBu-	1.56 ± 0.03	0.97 ± 0.02	0.999
2,4,6-Me_3-	1.62 ± 0.07	0.90 ± 0.06	0.996
2,3,5,6-Me_4-	1.34 ± 0.07	1.24 ± 0.06	0.997
2,4 Me_2-	1.3 ± 0.3	1.5 ± 0.2	0.977
4-Me-	1.3 ± 0.3	1.2 ± 0.2	0.964

interpreted in terms of a change in the degree of solvation and the simultaneous participation of an alcohol molecule in interactions with other substrate and solvent molecules.

From our point of view in going to bulkier nucleophiles, the role of steric effects in TS increases including the positive steric effect, which is reflected on the specific kinetic behavior of hindered sulfonyl chlorides.

Obviously, TS space requirements must change with the length/size of the side chain of the alcohol. The reaction order with respect to the nucleophile, *b,* was plotted *versus* Charton's steric constants ν to estimate the steric effect of the alcohol (Fig. 7).[35] Most of the substrates show an increase in *b* with bulkier nucleophiles. Satisfactory correlations were obtained only for alkylated derivatives of benzenesulfonyl chloride with $\Sigma\sigma_X < 0$ (Table 4) in terms of the linear equation:

$$b = \delta \cdot \nu + c_1 \quad (4)$$

From there it follows that the reaction order with respect to the nucleophile, *b,* increases with the volume of alkyl *ortho* substituents and is not related uniquely to the electronic nature of the X substituent group.

Recently, Yamabe *et al.* carried out a computational chemistry study of the hydrolysis of benzenesulfonyl chlorides using DFT, with explicit consideration of water molecules.[8] They assume a mechanistic change from S_N2 to S_N3 on going from electron donor to electron withdrawing substituents. This would probably not be the case in alcoholic solutions, because of higher steric requirements of the TSs, where all the studied substrates ($\Sigma\sigma_X < 0$ and $\Sigma\sigma_X > 0$) show a reaction order, relative to the nucleophile, higher than one. However, the importance of electronic effects should not be neglected, despite the poor sensitivity shown by all systems.

Space requirements are also supported by X-ray diffraction data. The highly sterically hindered 2,4,6-*i*Pr_3-benzenesulfonyl chloride[36] shows a slightly distorted benzene ring plane (±0.021 Å), which takes the form of a highly flattened "bath". Moreover, the relative orientation of the *ortho-iso*-propyl substituents facilitates intramolecular interaction between the oxygen atoms of the sulfo group and the hydrogens of the central carbon atoms of the *iso*-propyl *ortho*-groups (Fig. 8). Thus, bulky *iso*-propyl *ortho*-substituents impede the rotation around the C-S bond, limiting the approach of the nucleophile, which contributes to the formation of a TS with three solvent molecules. 2,4,6-$(OMe)_3$-benzenesulfonyl chloride exhibits lower reaction order with respect to the nucleophile but an increased reactivity, providing additional evidence that S_N2-type substitution at tetracoordinate hexavalent sulfur atom in arenesulfonic acids derivatives show an important variability of the TS structure.

Obtained results suggest the TS incorporates 2–3 alcohol molecules, possibly forming a cyclic solvent network, as shown in Scheme 2. Within this framework, the reaction proceeds as follows: (i) the sulfonyl chloride is attacked by an alcohol molecule linked to other alcohol molecules associated by hydrogen bonds; (ii) a cyclic TS is formed, with the charge redistributed along the whole network of forming/breaking bonds; and (iii) the nucleofuge leaves and the cyclic TS collapses. The main benefit of a cyclic TS is the extra stabilization obtained by charge

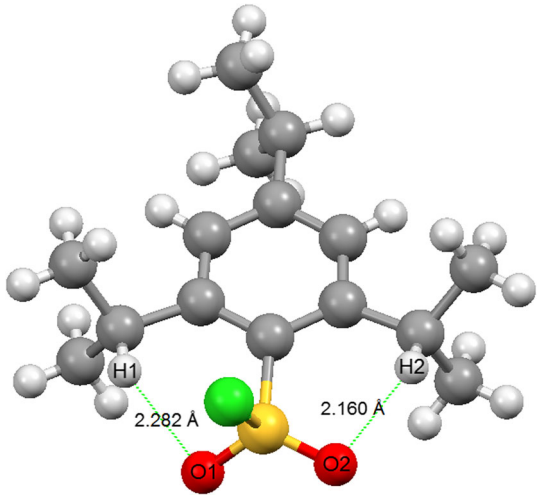
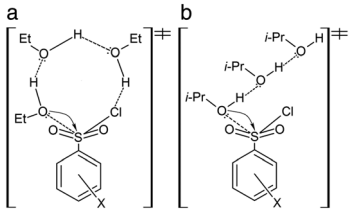


Figure 8. X-Ray diffraction structure of 2,4,6-tri(propan-2-yl) benzenesulfonyl chloride

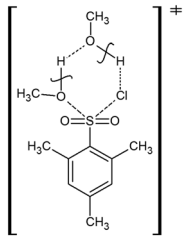


Scheme 2. TS involving three alcohol molecules. a. cS_N2s_3 TS; b. S_N2s_3 TS

dispersion and that proton transfer along the network is not necessarily the rate-limiting step. Such cyclic TS would contain at least three molecules, four in some cases, thus explaining the reaction order obtained with respect to alcohol (2–3). This kind of TS can be considered as the boundary between tri-molecular and bi-molecular processes, although formally it would correspond to an S_N2-process.

The influence of the electron nature of the substituent *X* on the TS and, therefore, on the reactivity is unambiguous. Electron-withdrawing substituents contribute to the bond-forming interaction S···O, while electron-donating substituents reduce the positive charge density on the sulfur thereby preventing it. On the other hand, electron-donating substituents facilitate the nucleofuge departure, increasing the negative charge density at the Cl ($|\delta-| \uparrow$), which also promotes the Cl- - -H hydrogen bond formation that helps forming the cyclic TS. Electron-withdrawing substituents reduce the relative negative charge density on the Cl ($|\delta-| \downarrow$), which make difficult the formation of the Cl- - -H bond. From this point of view, the reason for the very similar rates of alcoholysis observed for benzenesulfonyl chloride and 4-Me-benzenesulfonyl chloride becomes clear: methyl group promotes stabilization of the cycle and eliminates its negative impact on S···O bond-forming, and as a consequence, the reactivity remains practically unchanged.

Likely, the reason for the observed variability in TS is the large steric hindrance of bulky *iso*-propyl groups that prevents the formation of cyclic TS. The high reaction order on the nucleophile ($b \sim 3$) in *iso*-propanol points to a TS involving three alcohol molecules, that could also be described according to an



Scheme 3. Cyclic transition state of sterically hindered 2,4,6-trimethylbenzenesulfonyl chloride involving two methanol molecules (cS_N2s_2)

S_N2-like mechanism in which one molecule is playing the role of a general base catalyst (Scheme 2b).[5,9,18]

Depending on the number of solvent molecules involved in the solvent network, it should be renamed cyclic-S_N2s_n (or cS_N2s_n) (Scheme 2a), where "s" stands for the solvent and "n" would be the number of solvent molecules involved, or simply S_N2s_n, (Scheme 2b). For "n," it is suggested either the closest integer or half-integer to the reaction order relative to the solvent or the proposed number of solvent molecules taking part in the TS in computational studies.

The "positive" *ortho*-effect can be explained through the spatial requirements of the TS: *ortho*-alkyl groups limit free rotation around the C-S bond of the sulfonyl chloride,[11,36–39] leaving the S in a position that favors the formation of cyclic TS (Scheme 3). TS of unhindered substrates, although having less steric constraints, can also be cyclic.

Considering the results presented in this paper, the alcoholysis of sterically hindered *ortho*-alkyl arenesulfonyl chlorides ($X\text{-}ArSO_2Cl$) proceeds through an S_N2-nucleophilic substitution mechanism involving a network, cyclic or open, of alcohol molecules, the structure of the TS being mostly determined by solvation interactions. A notation is proposed to inform about solvent molecules playing a role in the TS, thus avoiding the controversial mechanistic notation S_N3.

CONCLUSIONS

Mechanistic details and features of the TS for solvolytic processes at the sulfonyl sulfur have been discussed. The existence of different possible kinds of TS for the S_N2 substitution is assumed and described.

The sensitivity to media polarity *U* growing inversely with the polarity of the alcohol indicates the TS is more solvated than the reactants. The TS's for methanolysis and ethanolysis of sulfonyl chlorides are similar, and much less polar than for *iso*-propanolysis. Most of substrates showed a reaction order $b \sim 2$ with respect to the nucleophile (methanol and ethanol) and $b \sim 3$ in *iso*-propanol. The reaction order with respect to the nucleophile, *b*, increases with the volume of nucleophile (alcohol) and is not related uniquely to the electronic nature of the X substituent group. The higher sensitivity to nucleophilicity of medium for all substrates points to the bimolecular S_N2-like mechanism. We propose that cyclic polymolecular TSs can take place. The electronic nature of the benzene ring substituent and the interactions of the sulfonyl group with *ortho*-alkyl substituents explain the significant difference in the reactivity of substrates with different structures within the same mechanism of solvolysis. The structure and

molecularity of TS with nucleophilic assistance of solvent depends strongly on the structure of nucleophile. The TS can be cyclic for unbranched alcohols (methanol, ethanol) or linear (S_N3-like mechanism) for alcohols with bulky alkyl groups (*iso*-propanol). In the case of 2,4,6-*i*-Pr_3-benzenesulfonyl chloride, a large steric volume of o-alkyl groups promotes the formation of linear TS of S_N3-type that facilities the removal of steric hindrance to the nucleophile attack, which is reflected on its reactivity.

Our recent studies have shown that arenesulfonyl chlorides alcoholysis takes place through a spectrum of S_N2 TSs of cyclic or linear structure with participation of a network of additional solvent molecules, mimicking a general base catalysis process. cS_N2s_n or S_N2s_n notations are proposed to represent solvolytic processes undergoing bimolecular nucleophilic substitutions involving solvent molecules at the TS, cyclic (c) or linear. "n" is either the closest integer or half-integer to the reaction order relative to the solvent or, in computational studies, the proposed number of solvent molecules taking part in the TS.

EXPERIMENTAL

Chemical kinetic studies were carried out spectrophotometrically under pseudo-first order with respect to the nucleophile on a Cary 1E UV-Vis spectrophotometer, in a thermostated quartz cuvette ($l = 1$ cm) at 323 K.

Benzenesulfonyl chloride, 4-Me-benzenesulfonyl chloride, 4-Br-benzenesulfonyl chloride, and 2,4,6-trimethylbenzenesulfonyl chloride were purchased from Sigma-Aldrich and recrystallized from hexane prior to their use. 2,4,6-*i*-Pr_3-benzenesulfonyl chloride, 2,4,6-Me_3-3-NO_2-benzenesulfonyl chloride, 2,4-Me_2-benzenesulfonyl chloride, 2,6-Me_2-4-*t*-Bu-benzenesulfonyl chloride, 2,3,5,6-Me_4-benzenesulfonyl chloride, and 2,4,6-$(OMe)_3$-benzenesulfonyl chloride were prepared from the corresponding benzene derivatives as follows.[40] Under constant stirring (T = 0 °C), 1 mol of hydrocarbon, dissolved in 450 mL of an inert solvent ($CHCl_3$, CCl_4 and hexane), was added to crystalline NaCl (1 mol) and then chlorosulfonic acid (5 mol) was slowly added dropwise over half an hour. After 3–4 h, the reaction mixture was poured onto ice, treated with chloroform, the extract dried over $CaCl_2$ or Na_2SO_4, and filtered. The filtrate evaporated under vacuum. The resulting sulfonyl chloride was distilled under vacuum (2–5 mmHg) with a fractionating column; the middle fraction was collected and recrystallized from hexane (yield 65–85%). 2,4,6-Me_3-3-NO_2-benzenesulfonyl chloride, was synthesized analogously, but at a higher temperature (20–30°C).

Alcohols were purchased of analytical grade (Sigma-Aldrich). Molecular sieves (3 Å) were used for dehydration. All alcohols were redistilled immediately before the kinetic experiments at the temperatures specified in the literature ($b.p._{MeOH} = 64.4$°C; $b.p._{EtOH} = 78.32$°C; $b.p._{i\text{-}PrOH} = 82.6$°C at 760 mmHg). Hexane was purified as follows.[41] The hydrocarbon was washed with concentrated sulfuric acid and then with water and dried, and finally distilled from sodium metal (b.p. = 68°C). The distillate was stored over 3 Å molecular sieves. The composition of the alcohol-hexane mixtures varied for each alcohol (Supporting Information).

Structure and purity of the obtained sulfonyl compounds were confirmed by NMR spectroscopy and monocrystal X-ray diffraction (Supporting Information).

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