CHLORINATION OF *N*-PHENYLBENZENESULFONAMIDES WITH NCP IN AQUEOUS ACETIC ACID. USING THE *para*/*meta* RATIO OF SUBSTITUENT EFFECTS FOR MECHANISM ELUCIDATION

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We dedicate this paper to Professor Otto Exner on the occasion of his 80th birthday in recognition of his outstanding contributions to many aspects of physical organic chemistry.

Rate constants were measured for the oxidative chlorination reaction of *N*-phenylbenzenesulfonamide **2** and twelve *ortho*-, nine *meta*- and twelve *para*-substituted derivatives in the aniline moiety, using 1-chloro-3-methyl-2,6-diphenylpiperidin-4-one (**1**) as chlorinating agent. The kinetics was run in 50% (v/v) aqueous acetic acid acidified with perchloric acid under pseudo-first-order conditions with respect to **1** at five different temperatures between 298 and 318 K. The dependence of rate constants on temperature was analysed in terms of the isokinetic relationship (IKR). The resulting isokinetic temperature was estimated to be 513 K. Using the Linert's theory of the IKR, the experimental isokinetic temperature was interpreted as evidence for the preferential involvement of water molecules in the formation of activated complexes. The dependence of the rate constants on the substituents was analysed using the tetralinear extension of the Yukawa–Tsuno equation for the effects of *meta* and *para* substituents. A positively charged transition state was suggested by an experimental value $r^+ = 0.39$ for the resonance demand, which was found to be insensitive to temperature variation. The parameter λ for the *para*/*meta* ratio of substituent effects was estimated to be 0.952. The electrostatic modelling of λ values was re-examined in the light of the recent calculations of the energies of interaction between charged and/or dipolar groups by Exner and Böhm. Based on energy ratios, the electrostatic method was shown to remain valid for the purpose of modelling λ values. The experimental λ value for the reaction indicates the formation of an activated complex possessing an electric charge in the vicinity of the nitrogen atom of the substrate. The electrophilic attack on the substrate nitrogen atom by the protonated chlorinating reagent has been proposed as the rate-determining step, with the

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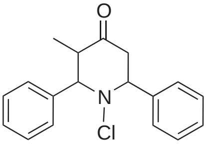
last step being the fast rearrangement of the intermediate *N*-chloro-*N*-phenylbenzenesulfonamidium cation into the products.

Keywords: Chlorinations; Electrostatic interactions; Linear free energy relationships; Reaction mechanisms; Kinetics; Substituent effects; Sulfonamides; DFT calculations.

Correlation analysis of the substituent effects on reaction rates is an established technique[1] for probing the mechanisms of organic reactions in solution. Recently, we revealed some fine details of the oxidation of benzyl alcohol with pyridinium dichromate[2] using a novel tool[3] for analysing substituent effects. In this work, we describe the application of this approach to elucidating the reaction mechanism of the chlorination of *N*-phenylbenzenesulfonamide using 1-chloro-3-methyl-2,6-diphenylpiperidin-4-one (NCP, **1**) as the chlorinating reagent. Compound **1** is an equilibrium mixture of different conformations. The reagent belongs to a family of *N*-chlorinated organic compounds that act as oxidising and chlorinating agents, and of which Chloramine-T, *N*-chloroacetamide and *N*-chlorosuccinimide are notable members. However, contrary to the latter reagents, NCP has not been included in the last edition of the March's renowned monograph[4]. Indeed, only in 1978, Ganapathy and Vijayan[5] reported the synthesis of NCP as a new compound from the reaction of 3-methyl-2,6-diphenylpiperidin-4-one with Chloramine-T. Quite surprisingly, they found NCP to have oxidising properties similar to those of *N*-chlorosuccinimide[5]. Since then, Ganapathy, his co-workers and other researchers have used NCP as an oxidant of a variety of organic substrates[6]. Besides being a versatile oxidising agent, NCP has also been shown to be a valuable chlorinating reagent[7]. Recently, Kabilan and co-workers[8] synthesised a series of novel cyclic ketones containing the same piperidine ring as NCP. They found[8] that some of these derivatives exhibited potent in vitro antibacterial or antifungal activity.



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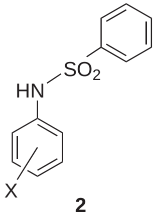

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The mechanism for the oxidative chlorination of organic substrates with NCP has been understood only in general terms. Previous studies[7] have shown that these chlorinations (or, chlorodehydrogenations[4]) are stepwise reactions initiated by the protonation of **1** in acidic solutions, followed by the attack on substrates. From an intermediate, slowly formed in the latter step, the final chlorinated products are quickly produced. For this detailed study, we chose *N*-phenylbenzenesulfonamides **2** as the substrates, since a variety of substituents can be introduced into the *ortho*, *meta* or *para* positions of its *N*-phenyl ring, thus allowing a comprehensive analysis of substituent effects on the reactivity of **2**.

We have focused on our own method[3] for modelling the parameter λ, which describes the *para*/*meta* ratio[9] of substituent inductive[10], universal electric[11] or Electra[12] effect. Experimentally, the parameter λ can be determined using a constrained tetralinear equation[13] for fitting kinetic data. The model we developed for evaluating λ values[3] is based on the electrostatic theory of substituent effects. However, this approach was recently criticised by Exner and Böhm[14], who found electrostatic interaction energies to be too small compared with quantum-chemistry interaction energies calculated in terms of the density functional theory. We have attempted to show that this limitation of the electrostatic theory is not likely to jeopardise the usefulness of our method, because the latter relies on the ratio of two, not very different interaction energies for each of a series of substituents.

In this work, we probed the reactivity of *N*-phenylbenzenesulfonamide **2** under the attack of reagent **1**, using a set of nine different neutral substituents in the *ortho*, *meta* and *para* position of the aniline part of the sulfonamide. The effect of a further set of three different neutral substituents was measured from the *ortho* and *para* position, thus totalling 34 independent reactions. These reactions were run in 50% (v/v) aqueous acetic acid solutions in the temperature range 298–313 K at the intervals of 5 K. Beside analysing the ratio between the *para* and *meta* substituent effects, the vast amount of kinetic data reported here was also analysed in terms of the isokinetic relationship[1,15] (IKR) with respect to substituent variation. The IKR is a valuable tool for the correlation analysis of a series of similar chemical reactions, which can be applied in different contexts[1,16]. In this work, we constructed isokinetic plots to examine the effect of temperature on the rate constants of each term of a series, in which the nature and position of substituents were the changing factors perturbing the basic chemical reaction being investigated.

The correlation of the substituent effects on the reaction rates of *meta*- and *para*-substituted benzene derivatives was at the origin of the Hammett equation. Herein we use the tetralinear extension[13b] of the Yukawa–Tsuno equation to describe the reactivity of *N*-phenylbenzenesulfonamide as a function of substituent and to examine the resonance demand at different temperatures.

From a comprehensive analysis of the temperature and substituent effects, we have proposed a three-step mechanism for the oxidative chlorination of *N*-phenylbenzenesulfonamide with NCP in an acidic aqueous solution.

EXPERIMENTAL

Reagents and Solvents

Substituted anilines from Aldrich Chemical Co. were the starting compounds for the synthesis of the corresponding *N*-phenylbenzenesulfonamides using standard procedures. These substrates were purified by repeated recrystallisation and their purity checked by recording the melting points. Reagent **1** was prepared by passing gaseous chlorine through a solution of 3-methyl-2,6-diphenylpiperidin-4-one (in the form of its hydrochloric salt) in aqueous ethanol[5]. After recrystallisation from ethanol, **1** was dried over anhydrous calcium chloride in a vacuum desiccator (m.p. 190–191 °C). All other reagents were of AR grade. Deionised water was distilled twice using an all-glass apparatus, the second distillation being from potassium permanganate. Two litres of glacial acetic acid were partially frozen. After removing the liquid phase, the residue was melted, heated at reflux with 30 g of chromium trioxide and fractionally distilled. The portion distilling in the range 116–118 °C was subjected to the same treatment. The fraction with b.p. 117–118 °C was collected and kept in brown glass bottles.

Kinetic Measurements

Flasks containing **1** in acetic acid, and known amounts of the benzenesulfonamides and perchloric acid in an aqueous acetic acid solution were placed in a thermostat for 30 min to attain thermal equilibration. A given volume of the solution of **1** was transferred at time zero to a flask with sulfonamide and shaken well. The temperature was held constant to ±0.01 °C. The rate of the disappearance of **1** was monitored by iodometric estimation of the non-reacted **1**. Aliquots (2 cm^3) were withdrawn at appropriate time intervals. These samples were quenched by adding an ice-cold mixed aqueous solution prepared from 1% (w/w) potassium iodide (5 cm^3) and 0.5 mol dm^{-3} sulfuric acid (5 cm^3). The liberated iodine was titrated with sodium thiosulfate to a starch endpoint. Triplicate kinetic runs were carried out in each case.

Computation

Least-squares analysis was executed on a Pentium-inside PC-compatible computer. Calculation methods are referred to in the context of the programmes used in resolving different equations.

Product Analysis

The following experiments were performed in order to identify the final reaction products. After about 70% conversion, the reaction mixture from an actual kinetic run with the unsubstituted benzenesulfonamide was extracted with trichloromethane. This extract was well shaken with an equal volume of water. As a result, a white solid residue was separated. The solid was shown to be 3-methyl-2,6-diphenylpiperidin-4-one based on the determination of the mixed melting point and on the basis of its IR spectrum. After drying over anhydrous sodium sulfate, the rest of the solvent was evaporated under reduced pressure. The remaining reaction mixture was monitored by TLC on neutral alumina, along with authentic samples of *N*-phenylbenzenesulfonamide (R_F 0.43), *N*-(*o*-chlorophenyl)benzenesulfonamide (R_F 0.52) and *N*-(*p*-chlorophenyl)benzenesulfonamide (R_F 0.63). The spots were eluted with a (4:5:1) butan-1-ol–water–acetic acid mixture and made visible by exposure to iodine vapour. The R_F values measured for the reaction mixture matched exactly those of the authentic samples. This identification was confirmed by GC-MS analysis. Column chromatography was used with neutral alumina as adsorbent. The products extracted with trichloromethane were eluted with ethyl acetate. GC-MS analysis of this fraction unambiguously proved the presence of the isomers *N*-(*o*-chlorophenyl)benzenesulfonamide and *N*-(*p*-chlorophenyl)-benzenesulfonamide, and of the non-reacted substrate. Taking the chloro, methoxy and nitro groups as representatives of the set of substituents used, the procedure described above was repeated using substrates containing each of the selected substituents in the *ortho*, *meta* and *para* positions of the *N*-phenyl ring. As the reaction products in these nine additional experiments, *para*-chlorinated products formed from *ortho*- and *meta*-substituted substrates, and *ortho*-chlorinated products from *para*-substituted derivatives were found.

RESULTS AND DISCUSSION

Kinetic Data

The chlorination of thirty-four benzenesulfonamides (BS) with NCP in the presence of perchloric acid was studied in aqueous acetic acid at five different temperatures between 298 and 318 K. Conditions of pseudo-first order kinetics were implemented by using a large excess of BS over NCP. The rate of disappearance of NCP was monitored by the iodometric estimation of the non-reacted NCP. Experimental rate constants k_{obs} were obtained from good quality linear plots describing the first-order rate law. Preliminary experiments at 303 K also showed first-order kinetics with respect to BS and to the hydronium ion. In the latter experiments, the concentration of perchloric acid in the reacting solution was varied between 12.5 and 87.5 mmol dm^{-3}. The corresponding pH was determined to vary between 1.9 and 1.1, respectively. The rate constants observed were found to decrease as the pH increased. At fixed perchloric acid concentration, second-order rate constants k_2 were calculated according to Eq. (*1*), where $[\mathrm{BS}]_0$ stands for the initial concentration of the substrate at ambient temperature.

$$k_2 = k_{obs}/[BS]_0 \tag{1}$$

Rate constants k_2, expressed in dm^3 mol^{-1} s^{-1}, are shown in Table I, where benzenesulfonamides are classified according to the special[9] or normal[18] nature of the substituent on the *N*-phenyl ring.

Isokinetic Relationship

The IKR is a technique in similarity analysis, in which the temperature dependence of the rate constants for a series of reactions is examined in terms[15] of Eq. (*2*).

$$\log (k_{ij} / T_j) = a + b_i (T_j^{-1} - \beta^{-1}) \tag{2}$$

In a plot of log (k/T) as a function of T^{-1}, Eq. (*2*) describes a set of straight lines having slopes b_i, which may intersect at a common point. In such a case, the corresponding temperature is referred to as the isokinetic temperature, β. This temperature is also the proportionality constant between the increments in standard activation enthalpies $\Delta^{\neq}H°$ and standard activation entropies $\Delta^{\neq}S°$ along the reaction series, according to Eq. (*3*).

$$\delta\Delta^{\neq} H° = \beta\,\delta\Delta^{\neq} S° \tag{3}$$

In general, a reaction series can be constructed in different ways. Herein, we have used slight structural changes in the substrate by varying the nature and position of the substituents. Following Whalley and co-workers[19], parameter β is then designated as the isokinetic temperature with respect to a substituent. On different occasions, changes with respect to reactant[20] and solvent[21] variation have been studied. In the former case[20], substantial structural changes in the reactant were deemed responsible for a failure to observe an IKR. In the latter case[21], clear IKRs were found for two quaternisation reactions along a homologous series of aliphatic alcohols. Equation (*2*) was fitted to the data in Table I using a programme for the least-squares linear regression with a common point of intersection[15c]. This programme has been implemented on a Microsoft EXCEL97 spreadsheet, readily available on the Web[22]. An isokinetic relationship was tested encompassing all the kinetic data in Table I for these 34 chlorination reactions. The IKR-80-20 programme[22] yielded standard deviations s_{00} = 0.0021

TABLE I

Second-order rate constants k_2 at different temperatures (in K) for the chlorination of thirty-four *N*-(monosubstituted phenyl)benzenesulfonamides (BS) with NCP in 50% (v/v) aqueous acetic acid acidified with perchloric acid[a]

Substituent	σ^0 [b]	σ^+ [c]	k_2, 10^{-3} dm^3 mol^{-1} s^{-1}				
			298.15	303.15	308.15	313.15	318.15
			Special				
m-OCH_3	0.102	–	9.10	14.3	22.2	33.8	51.0
m-F	0.335	–	3.33	5.40	8.70	13.9	21.8
m-Cl	0.365	–	2.83	4.70	7.70	12.3	19.6
m-Br	0.369	–	2.60	4.30	7.00	11.2	17.8
m-I	0.343	–	3.10	5.10	8.26	13.1	20.6
p-OCH_3	–0.120	–0.780	64.4	92.7	131.3	185.9	260.0
p-OC_2H_5	–	–	49.1	71.5	102.9	147.2	207.6
p-F	0.151	–0.070	12.1	18.7	28.5	42.9	63.7
p-Cl	0.242	0.110	6.37	10.1	15.8	24.3	36.9
p-Br	0.265	0.150	4.70	7.65	12.3	19.4	30.2
p-I	0.277	0.130	4.30	6.99	11.2	17.7	27.6
o-OCH_3	–	–	9.70	14.6	21.7	32.0	46.6
o-OC_2H_5	–	–	9.50	14.4	21.6	32.1	47.1
o-F	–	–	2.50	4.10	6.50	10.2	15.7
o-Cl	–	–	1.20	2.00	3.30	5.40	8.70
o-Br	–	–	1.10	1.80	3.00	4.80	7.70
o-I	–	–	0.940	1.60	2.70	4.40	7.20
			Normal				
H	0	–	12.0	18.8	28.5	42.7	64.7
m-CH_3	–0.062	–	22.2	33.6	50.2	74.0	107.8
m-CO_2H	0.356	–	2.83	4.68	7.60	12.2	19.1
m-CO_2CH_3	0.349	–	2.82	4.70	7.70	12.4	19.6
m-NO_2	0.713	–	0.580	1.02	1.80	3.00	5.00
p-CH_3	–0.135	–0.310	35.4	53.0	78.3	114.4	165
p-C_2H_5	–0.127	–0.300	30.7	45.7	67.2	97.6	140.2
p-CO_2H	0.440	[d]	1.95	3.30	5.50	9.05	14.6
p-CO_2CH_3	0.441	[d]	2.04	3.40	5.60	8.995	14.3
p-$CO_2C_2H_5$	–	–	2.07	3.50	5.80	9.50	15.3
p-NO_2	0.814	[d]	0.417	0.75	1.33	2.30	3.98
o-CH_3	–	–	7.90	12.2	18.6	28.0	41.6
o-C_2H_5	–	–	6.10	9.50	14.5	21.9	32.6
o-CO_2H	–	–	0.466	0.807	1.37	2.30	3.79
o-CO_2CH_3	–	–	0.485	0.841	1.40	2.40	4.00
o-$CO_2C_2H_5$	–	–	0.488	0.842	1.40	2.38	3.80
o-NO_2	–	–	0.109	0.201	0.365	0.650	1.14

[a] $[BS]_0$ = 7–33 mmol dm^{-3}; $[NCP]_0$ = 0.2–0.9 mmol dm^{-3}; $[HClO_4]$ = 62.5 mmol dm^{-3}. [b] Unified σ^0 substituent constants taken from lit.[17]. [c] From lit.[1], p. 61. [d] The same as the corresponding σ^0 value.

for unconstrained lines in terms of Eq. (*4*) and s_0 = 0.0102 for straight lines constrained by Eq. (*2*).

$$\log (k_i / T) = a_i + b_i T^{-1} \qquad (4)$$

However, at 95% confidence level, the *F*-test gave *F* = 92.68, which would mean the rejection of an isokinetic relationship. Notwithstanding this, the IKR equation was validated as an approximate relationship using the Exner's ψ-test[23], which yielded ψ = 0.016. The reason underlying these apparently conflicting results can be attributed to the relatively high experimental precision, as indicated by the s_{00} value. Exner and his colleagues[15c] have also encountered similar examples. For the reaction series consisting of all 34 chlorination reactions, an isokinetic temperature of β = 513 K was determined, although its confidence interval (497–532 K) is large. An analogous situation was observed when the reaction series was restricted to the subset of *meta* and *para* derivatives comprising only 22 reactions, which is illustrated in Fig. 1. In this instance, β = 480 K and a confidence interval of 474–487 K was obtained. Even though their confidence intervals do not overlap, these estimates of the isokinetic temperature do not seem to be disparate.

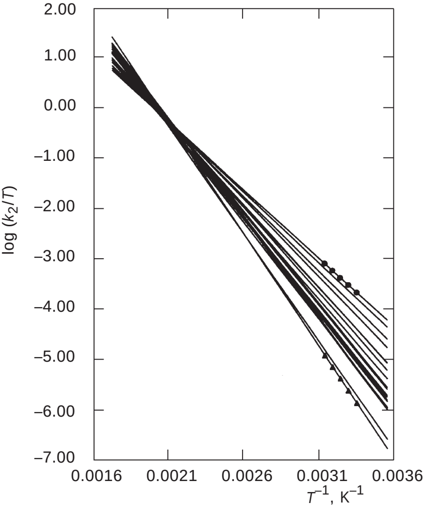

FIG. 1

Isokinetic plot of the data in Table I according to Eq. (*2*) for the chlorination reaction of *N*-(*meta*- or *para*-substituted phenyl)benzenesulfonamides with NCP. For the sake of clarity, only data points for the fastest reaction, *p*-OCH_3 (●) and the slowest reaction, *p*-NO_2 (▲) are shown

According to the Linert's theory[24], solvents act as heat baths in relation to chemical processes in solution. Linert derived an expression for the link between active vibrational frequencies of solvent molecules and isokinetic temperatures. Recently, Pinheiro et al.[21] reformulated this expression into the form of Eq. (*5*), which is a more practical equation using wavenumbers $\tilde{\nu}$.

$$\tilde{\nu}_{\text{heat bath}} \, / \, \text{cm}^{-1} = 0.695 \, (\beta \, / \, \text{K}) \qquad (5)$$

Using Eq. (*5*), the wavenumber of 357 cm^{-1} corresponds to β = 513 K. Although the kinetics was run in aqueous acetic acid, we paid attention to the electromagnetic spectrum of liquid water. In their classical monograph, Eisenberg and Kauzmann[25] refer to an intense absorption band in the far infrared region, which should arise from intermolecular modes. This band, extending from 300 to 900 cm^{-1}, has a maximum near 685 cm^{-1} at 303 K. It was attributed to molecular librations and, in particular, to the bending of hydrogen bonds. Interestingly, the band maximum shifts to lower wavenumbers with rising temperature, thus indicating that the hydrogen bonds in water are more easily bent at higher temperatures[25]. Hence, the experimental value for the isokinetic temperature may be attributed to the preferential solvation of activated complexes by the highly polar water molecules.

Activation Parameters

From the regression coefficients for Eyring's plots in terms of Eq. (*4*), standard enthalpies and entropies of activation were calculated. Their values and respective standard deviations are shown in Table II together with the corresponding IKR-constrained values. In relation to Eyring values, the constrained values for the activation enthalpies do not deviate more than 5%, except for the two *ortho*-alkoxy derivatives. This comparison was not so favourable when activation entropies were examined. Indeed, for five reactions, the deviation exceeds 20% and increases up to 60% for the *p*-NO_2 derivative.

For the reactions in this series, the activation entropies are large and negative. In the context of the activation entropies for a given second-order reaction in solution, we would like to note that their magnitude and sign depend on the choice of the standard states[26]. In addition, the importance of specifying the ideal thermodynamic process associated with the formation of activated complexes has been demonstrated[27]. Standard states are im-

TABLE II
Standard enthalpies of activation $\Delta^{\neq}H°$ and standard entropies of activation $\Delta^{\neq}S°$ derived from Eq. (*2*) (IKR equation) and Eq. (*4*) (Eyring equation) for the chlorination of thirty-four *N*-(monosubstituted phenyl)benzenesulfonamides with NCP in aqueous acetic acid

Substituent	$\Delta^{\neq}H°$, kJ mol^{-1}		$\Delta^{\neq}S°$, J K^{-1} mol^{-1}	
	Eq. (*2*)	Eq. (*4*)	Eq. (*2*)	Eq. (*4*)
		Special		
m-OCH$_3$	64.49	65.39(0.07)	–67.6	–64.7(0.2)
m-F	70.46	71.63(0.26)	–56.0	–52.1(0.9)
m-Cl	71.30	73.68(0.15)	–54.3	–46.6(0.5)
m-Br	71.88	73.24(0.11)	–53.2	–48.8(0.4)
m-I	70.84	72.08(0.09)	–55.2	–51.2(0.3)
p-OCH$_3$	53.04	52.45(0.18)	–89.9	–91.8(0.6)
p-OC$_2$H$_5$	54.62	54.32(0.10)	–86.8	–87.8(0.3)
p-F	62.87	62.95(0.01)	–70.8	–70.5(0.1)
p-Cl	66.67	66.72(0.05)	–63.4	–63.2(0.2)
p-Br	68.29	70.82(0.06)	–60.2	–52.0(0.2)
p-I	68.87	70.76(0.05)	–59.1	–52.9(0.2)
o-OCH$_3$	64.58	59.34(0.11)	–67.4	–84.5(0.4)
o-OC$_2$H$_5$	64.62	60.60(0.12)	–67.4	–80.4(0.4)
o-F	72.36	69.80(0.31)	–52.3	–60.6(1.0)
o-Cl	76.66	75.61(0.28)	–43.9	–47.3(0.9)
o-Br	77.33	74.30(0.44)	–42.6	–52.4(1.4)
o-I	78.03	77.64(0.25)	–41.2	–42.5(0.8)
		Normal		
H	62.86	63.54(0.41)	–70.8	–68.6(1.3)
m-CH$_3$	59.25	59.75(0.02)	–77.8	–76.2(0.1)
m-CO$_2$H	71.36	72.81(0.15)	–54.2	–49.5(0.5)
m-CO$_2$CH$_3$	71.29	73.92(0.12)	–54.3	–45.8(0.4)
m-NO$_2$	80.71	82.44(0.53)	–36.0	–30.4(1.7)
p-CH$_3$	56.39	58.14(0.02)	–83.4	–77.7(0.1)
p-C$_2$H$_5$	57.37	57.33(0.01)	–81.5	–81.6(0.1)
p-CO$_2$H	73.43	76.88(0.07)	–50.2	–39.0(0.2)
p-CO$_2$CH$_3$	73.34	74.23(0.13)	–50.3	–47.4(0.4)
p-CO$_2$C$_2$H$_5$	73.09	76.31(0.05)	–50.8	–40.4(0.2)
p-NO$_2$	82.55	86.29(0.25)	–32.4	–20.2(0.8)
o-CH$_3$	65.60	62.96(0.02)	–65.4	–74.0(0.1)
o-C$_2$H$_5$	67.19	63.50(0.08)	–62.3	–74.3(0.3)
o-CO$_2$H	82.32	80.09(0.08)	–32.8	–40.1(0.3)
o-CO$_2$CH$_3$	82.07	80.54(0.69)	–33.3	–38.3(2.2)
o-CO$_2$C$_2$H$_5$	82.13	78.60(0.57)	–33.2	–44.7(1.9)
o-NO$_2$	90.82	90.02(0.10)	–16.3	–18.9(0.3)

plicit in the concentration units used for expressing the second-order rate constants. Hence, the standard changes in activation entropy reported in Table II refer to processes at constant temperature and pressure involving separate ideal solutions containing 1 mol dm^{-3} of reactants and activated complexes.

Since the isokinetic temperature is positive, then, according to Eq. (*3*), an increase in the value for activation enthalpies is accompanied by a decrease in the magnitude of activation entropies. Within each of the three subsets of reactions characterised by fixed positions of substitution (i.e. *ortho*, *meta* or *para*), the highest values for $\Delta^{\neq}H°$ and $\Delta^{\neq}S°$ were found for the nitro group. This observation confirms the peculiar chemical properties of this substituent[28]. From Table II we also note that, for a given substituent, the highest activation enthalpies are generally associated with *ortho* substitution, although not in the case of special substituents, i.e. the methoxy group and fluorine. This analysis of the activation parameters suggests the operation of a bimolecular mechanism, in which the formation of activated complexes is accompanied by charge development.

Tetralinear Analysis of meta and para Substituent Effects

The constrained tetralinear approach to describing the substituent effects in benzene derivatives can be seen as an extension[13] of both the Hammett and Yukawa–Tsuno equations, in which the *meta–para* interrelationship is constrained by a hyperbolic model[9]. In the correlation analysis of a given reaction series, substituents are grouped into four subsets, namely *meta* normal (3n), *para* normal (4n), *meta* special (3s) and *para* special (4s). Exner[18] has defined normal substituents as dipolar groups in which the atom adjacent to the aromatic ring possesses a full octet, but no lone pair of electrons. By contrast, special substituents[9] are those bearing a lone electron pair or an incomplete electron octet in that atom.

In its version for Yukawa–Tsuno analyses, the basic tetralinear equation is given by Eqs (*6*)–(*9*).

$$\log(k_{3n}/k_H) = \delta_{3n} + \rho_{3n}\sigma^0_{3n} \tag{6}$$

$$\log(k_{4n}/k_H) = \delta_{4n} + \rho_{4n}[\sigma^0_{4n} + r^+(\sigma^+_{4n} - \sigma^0_{4n})] \tag{7}$$

$$\log(k_{3s} / k_H) = \delta_{3s} + \rho_{3s}\sigma^0_{3s} \tag{8}$$

$$\log(k_{4s} / k_H) = \delta_{4s} + \rho_{4s}[\sigma^0_{4s} + r^+(\sigma^+_{4s} - \sigma^0_{4s})] \tag{9}$$

In this approach, *meta* derivatives are treated separately from *para* derivatives. In addition, different equations are used for normal and special derivatives. There is a total of nine fitting parameters in Eqs (*6*)–(*9*). However, their values can be constrained in terms of a hyperbolic model for the *meta–para* interrelationship of the substituent effects[9]. According to this model, a pair of conjugate rectangular hyperbolae can be drawn, having asymptotes defined by[13] lim ($k_4/k_H \to \infty$) log (k_4/k_3) = λ and lim ($k_4/k_3 \to \infty$) log (k_4/k_H) = γ. Four constraining equations arise from this model[13a], which therefore leaves only five independent parameters in the set of Eqs (*6*)–(*9*). Two of the constraints yield the model parameters λ and γ in terms of, respectively, Eqs (*10*) and (*11*), where $\lambda^0 = 0.961$ and $\gamma^0 = -0.225$ are the constants for the hyperbolic model applied[9,13b] to the unified σ^0 scale[17].

$$\rho_{4n} / \rho_{3n} = \rho_{4s} / \rho_{3s} = \lambda / \lambda^0 \tag{10}$$

$$2\delta_{4n} - \delta_{3n}\lambda + \rho_{4n}\gamma^0 = 2\delta_{4s} - \delta_{3s}\lambda + \rho_{4s}\gamma^0 = \gamma \tag{11}$$

The important quantities characterising a given reaction series are parameter λ yielding the *para*/*meta* ratio of inductive or Electra substituent effects, parameter γ giving[13] an absolute measure of the Hammett reaction constant if the contributions from through-resonance are excluded, and the Yukawa–Tsuno parameter r^+ for the through-resonance demand relative to the σ^+ scale.

We used our non-linear least-squares computing programme[13] to fit the constrained tetralinear equation (Eqs (*6*)–(*9*)) to the data in Table I for *meta* and *para* derivatives. However, the derivatives bearing *p*-OC_2H_5 and *p*-$CO_2C_2H_5$ were excluded from this analysis, because the corresponding σ^0 constants are not available. On the other hand, the unsubstituted substrate was regarded as containing substituent H and included twice, both in 3n and 4n subsets. Preliminary fitting experiments using σ^0, σ^{PhCOOH} and σ^+

constants indicated that the σ^+ scale was the most appropriate substituent scale to describe the chlorination reactions under study. This aspect is in line with the finding by two of us[29] that through-resonance is the main electronic effect influencing the chemical shifts of UV absorption frequencies for the *N*-(*p*-substituted phenyl)benzenesulfonamides used as substrates in this study.

The best values for the tetralinear parameters, which correlate the oxidative chlorination rates of 9 *meta* and 10 *para* derivatives of *N*-phenylbenzenesulfonamide with NCP at 5 different temperatures are reported in Table III. The standard deviations associated with these experimental values were calculated using a previously described Monte Carlo procedure[3,13b]. The price to be paid for obtaining reliable λ, γ and r^+ values is thus the experimental effort in determining the rate constants for a large number of derivatives, evenly distributed by the 3n, 4n, 3s and 4s subsets of substituents.

The λ values for the chlorination reaction are given in Table III. These λ values are very stable over the small experimental temperature range of 20 K, in accordance with a similar finding already reported for the oxidation of benzyl alcohol with pyridinium dichromate at different temperatures[2]. The average value of 0.952 has been used (vide infra) in our attempt to shed light on the nature of the activated complexes involved in the oxidative chlorination of the benzenesulfonamides.

We have shown[2,13] that the quantity γ/γ^0 has the meaning of the Hammett reaction constant ρ in the absence of through-resonance effects. It is evident from Table III that negative γ/γ^0 values decrease in magnitude

TABLE III

Tetralinear analysis of the chlorination rates of *N*-(*meta*- and *para*-monosubstituted phenyl)benzenesulfonamides in aqueous acetic acid at different temperatures[a]

Parameter	Temperature, K				
	298.15	303.15	308.15	313.15	318.15
λ	0.955(0.039)	0.953(0.037)	0.953(0.038)	0.952(0.039)	0.949(0.038)
γ	0.448(0.050)	0.426(0.049)	0.410(0.048)	0.393(0.048)	0.370(0.043)
γ/γ^0	–1.986	–1.889	–1.821	–1.743	–1.641
r^+	0.391(0.074)	0.390(0.073)	0.386(0.078)	0.392(0.080)	0.395(0.077)
s^b	0.056	0.052	0.052	0.051	0.046

[a] Data from Table I in the form of log ($k_{2,X}/k_{2,H}$) fitted to the constrained tetralinear equation (Eqs (*6*)–(*9*)) using σ^0 constants[17] and σ^+ constants[1]. [b] Standard deviation of the fit.

with increasing temperature. Exner[15a,23b] discussed the validity of the relationships between the isokinetic temperature and the temperature dependence of the Hammett reaction constants according to Eq. (*12*) where ρ_∞ represents the limiting value of ρ at infinite temperature, and demonstrated[23b] that the observation of an IKR for a given reaction series is a necessary condition for the Hammett correlation to hold at different temperatures.

$$\rho = \rho_\infty (1 - \beta T^{-1}) \tag{12}$$

Herein we attempted to evaluate the temperature dependence of parameter γ and its relationship to the isokinetic temperature. By analogy with Eq. (*12*), we set out Eq. (*13*). Using the data from Table III, the linear regression suggested by Eq. (*13*) yields γ_∞/γ^0 = 3.331 and β = (476 ± 11) K, its correlation coefficient being –0.997.

$$\gamma / \gamma^0 = (\gamma_\infty / \gamma^0)(1 - \beta T^{-1}) \tag{13}$$

Exner[23b] has stated that Eq. (*12*) is inappropriate for determining isokinetic temperatures. For the same reasons, Eq. (*13*) can only yield indicative estimates of β. Nonetheless, the value of 476 K indicated by Eq. (*13*) is in good agreement with the value of β = 480 K obtained from Eq. (*2*) when applied to our kinetic data for *meta* and *para* derivatives. This finding lends further support to the view that the values for γ/γ^0 can be discussed in the same terms as for the Hammett reaction constants. On this basis, negative γ/γ^0 values point to the presence of an electron-deficient centre in transition states.

The outstanding feature of the original Yukawa–Tsuno equation[30] is the treatment of *meta* and *para* derivatives at different levels of complexity[31]. In fact, an extra parameter is required to describe the substituent effects from the *para* position on the reactions sensitive to through-resonance electronic interactions. Previously, the tetralinear extension of the Yukawa–Tsuno correlation was tested at a single temperature[13b]. Herein, we report for the first time r^+ values measured at five different temperatures for the same reaction series (Table III). The resonance demand appears to be insensitive to temperature variation, at least over the experimental range of 20 K. Although Monte Carlo estimates give a relative error of about 20% in the r^+ values, which is much larger than the errors in the λ and γ values, as a first approximation, we consider the through-resonance effects to be temperature independent. The average value of r^+ = 0.391 means that the resonance demand in the chlorination reaction is about 39% of that in the reference benzyl cation system. This finding strongly suggests that a partial positive charge develops in the course of the oxidative chlorination of benzenesulfonamides by NCP, which is in agreement with the information obtained above from γ/γ^0 values.

Electrostatic Modelling of Parameter λ

Experimental values for the parameter λ describing the *para*/*meta* ratio of substituent Electra effects have been previously modelled[2,3,13] in terms of through-space electrostatic interactions. However, Exner and Böhm[14] have recently calculated the interaction energies between the pairs of substituents by the density functional theory (DFT). They performed these quantum chemistry computations for conveniently designed homodesmotic reaction series involving 1,4-disubstituted derivatives of bicyclo[2.2.2]octane, the molecule of which possesses a rigid structure. (Homodesmotic reactions are isodesmic reactions in which the hybridisation states of atoms are conserved[32].) Exner and Böhm[14b] also calculated the energies using the classical electrostatic formulas for charge–charge, charge–dipole and dipole–dipole interactions, and have demonstrated that the electrostatic energies are too small in comparison with DFT energies, particularly for weak interactions. More recently, Exner and Böhm[33] used the technique of principal component analysis in examining the DFT energies of an extended set of homodesmotic reactions leading to the formation of 1,4-disubstituted bicyclo[2.2.2]octanes. These authors[33] found that the set should be divided into one subset for compounds containing at least one charged substituent and another subset for those containing only dipolar substituents.

Undoubtedly, there is a need for revaluation of our electrostatic modelling of λ values, even though only the ratios of electrostatic energies are used in our estimations. In effect, parameter λ_e can be defined in terms of Eq. (*14*) as the ratio of two electrostatic interaction energies.

$$\lambda_e = \Delta E_{e,\,para} \,/\, \Delta E_{e,\,meta} \tag{14}$$

In the case where DFT calculations could be performed for complicated chemical entities, a DFT parameter λ_{DFT} would then be appropriately defined as in Eq. (*15*).

$$\lambda_{DFT} = \Delta E_{DFT,\,para} \,/\, \Delta E_{DFT,\,meta} \tag{15}$$

In the event, ΔE_e energies were found to be proportional to ΔE_{DFT} ones. Equation (*16*) then holds, and therefore, λ_e values are equal to λ_{DFT} ones.

$$\Delta E_{e,\,para} \,/\, \Delta E_{DFT,\,para} = \Delta E_{e,\,meta} \,/\, \Delta E_{DFT,\,meta} \qquad (16)$$

To this end, we subjected Exner and Böhm's data[14b,33] to further analysis. DFT and electrostatic energies have been reported in Table I of lit.[14b] for a total of 27 homodesmotic reactions, which can be subdivided according to the interaction type into 5 reactions for charge–charge, 10 for charge–dipole and 12 for dipole–dipole interactions. For each interaction type, we plotted ΔE_e values[14b] against the corresponding slightly corrected ΔE_{DFT} values given in[33]. The outcome of this exercise is summarised in Table IV, and Fig. 2 illustrates the linear correlation for the case of charge–dipole interactions. Table IV shows that good linear correlations hold between ΔE_e and ΔE_{DFT} energies referring to a given interaction type. Intercept values are modest, representing only 2.0, 1.5 and 5.5% of the average ΔE_e values for charge–charge, charge–dipole and dipole–dipole interactions, respectively. Besides, DFT-calculated energies, which are obtained as a small difference between two large values, are themselves subjected to uncertainties estimated to be of the order[14] of 1 kJ mol^{-1}. As pointed out by Exner and Böhm[14b], it is difficult to estimate the impact of effective permittivities on electrostatic energies. Fortunately, since the electrostatic modelling of parameter λ relies necessarily on the relative energy values for the same type

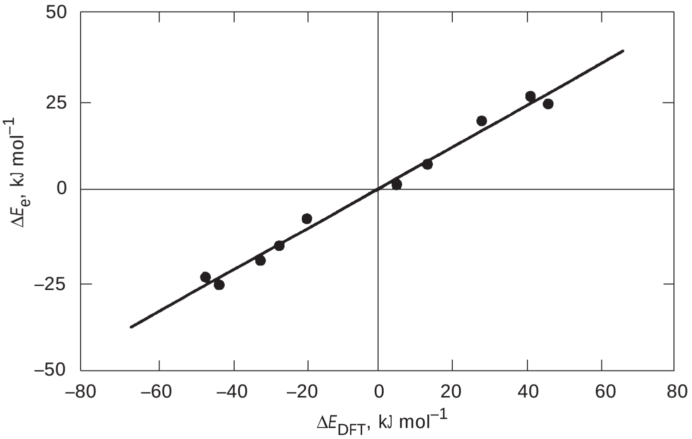

FIG. 2
Electrostatic energies, ΔE_e, as a function of DFT-calculated energies, ΔE_{DFT}, for the ten isodesmic reactions exhibiting charge–dipole interactions (according to[14b,33])

of interaction, the actual values are not needed for electrical charges and effective permittivities.

As regards the slope values in Table IV, taking ΔE_{DFT} energies as a measure of the total interaction energies, we interpret these slopes as the part of the total energies described by the classical through-space electrostatic formulas. Thus, 70% of the charge–charge interaction energies in the 1,4-disubstituted derivatives of bicyclo[2.2.2]octane should be attributed to direct interactions between electrical charges. In turn, we ascribe 56% of the energy values for the weaker charge–dipole and dipole–dipole interactions to direct through-space electrostatic interactions. In other words, ΔE_e values appear as the leading term contributing to total interaction energies. These findings suggest that the interactions between charged groups should be treated separately from those between dipolar groups, in agreement with Exner and Böhm's analysis[33]. However, it is not so clear whether the mixed case, involving the interactions between charged and dipolar groups, should be treated separately as well. We believe that, for the most part, electrostatic interaction energies arising from a successive polarisation of the intervening covalent chemical bonds between charged or dipolar substituents can account for the remaining terms. Incidentally, the latter interaction mechanism is at the heart of the Lewis's original concept of the inductive effect[10e,32]. Our contention may gain some support from the remarkable finding by Exner and Böhm[33] that a part of the DFT energy for dipole–dipole interactions significantly correlates with the electronegativity of the first atom of a substituent. Hence, some assurance has been provided for our electrostatic model of reproducing the experimentally determined values of parameter λ.

TABLE IV
Linear dependence of electrostatic energies, ΔE_e, on DFT-calculated energies, ΔE_{DFT}, according to the interaction type for the isodesmic reactions in[14b,33]

Interaction type	Intercept, kJ mol^{-1}	Slope	Correlation coefficient
Charge–charge	3.985	0.699	0.999
Charge–dipole	0.261	0.564	0.994
Dipole–dipole	–0.136	0.561	0.940

Information Contained in Parameter λ

We found an average value of 0.952 for the *para*/*meta* ratio of the Electra substituent effects, as given by parameter λ. Having restored our confidence in the electrostatic modelling of λ values, we turned our attention to evaluating the nature and geometry of possible molecular structures, for which electrostatically calculated λ_e values equal the experimentally determined λ value.

We collected strong experimental evidence showing the formation of a positive partial charge on activated complexes for the reaction under study. We could also confirm independently that the reaction site is electrically charged, rather than possessing a dipole. To this end, we used the previously derived[3] Eq. (*17*) for the ratio of electrostatic interaction energies between a point charge and a given dipolar substituent from the *para* and *meta* positions; the interaction distances r_+ and r_- refer to the corresponding point charges in the dipole.

$$\lambda_e = \left(\frac{1}{r_+} - \frac{1}{r_-}\right)_{para} \Bigg/ \left(\frac{1}{r_+} - \frac{1}{r_-}\right)_{meta} \qquad (17)$$

For a positive charge situated on the C_1–C_4 axis of the *N*-phenyl moiety, the value of $\lambda_e = 0.952$ points to a position at 0.1672 nm beyond the C_1 atom. Since the interatomic distance C_1–N is[34] 0.136 nm, this λ_e value is consistent with a positive charge at 0.0312 nm past the nitrogen atom. On the other hand, we also used the appropriate electrostatic formula[3] for modelling $\lambda_e = 0.952$ in the case of a dipolar reaction site 0.1 nm in length localised along the *N*-phenyl 1,4 axis. This modelling experiment localised the reaction-centre middle-point 0.459 nm past the *N*-phenyl ring, which is clearly unrealistic. Both models are depicted in Fig. 3. Hence, we focused further discussion on a charged reaction site. However, activated complexes are not exactly molecular entities having well-defined geometry and centre of charge. Drawing on the tetrahedral structure around nitrogen atoms, the most likely positions where to find the positive charge are on the bond axes at angles of 70.5° with the reference C_1–C_4 axis. Modelling of parameter λ_e for these positions is complicated by the expected free rotation about the C_1–N bond, characterised by the rotational angle ϕ. On other occasions[2,3], we resolved similar problems. Thus, the positive charge is described by a circle line having radius *r* on a plane at distance *h* from the nitrogen atom, with the aforementioned value of 0.0312 nm providing an upper limit for *h*; the geometrical parameters *h* and *r* can be visualised, as depicted in Fig. 4. Since λ_e values depend on the rotational angle ϕ, individual values at different rotations ϕ were calculated by introducing analytically determined distances into Eq. (*17*), which was then averaged in terms of Eq. (*18*).

$$\bar{\lambda}_e(\phi) = \int_0^{2\pi} \lambda_e(\phi)\, d\phi / 2\pi \tag{18}$$

Using successive approximations, we found that the average value of $\bar{\lambda}_e(\phi)$ = 0.952 emerged from a position defined by h = 0.0234 nm and r = 0.0662 nm, with individual λ_e estimates being between 0.968 and 0.939.

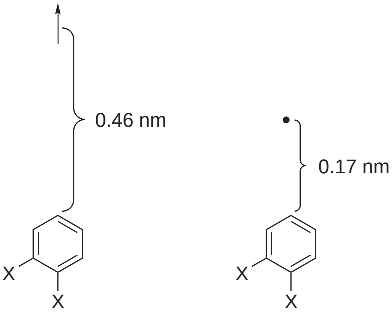

FIG. 3
Models for dipole–dipole and dipole–charge interactions in benzene derivatives yielding λ = 0.952

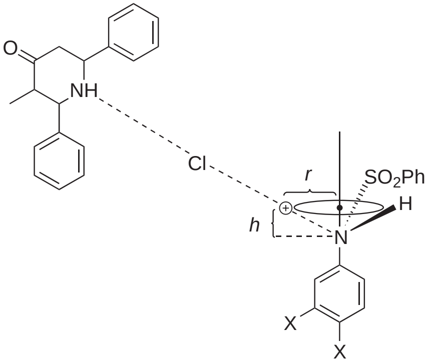

FIG. 4
Proposed structure for the activated complex showing a positive charge and the formation of a new Cl–N covalent bond

In chemical terms, our electrostatic modelling of parameter λ identified an electrical charge on activated complexes, which is situated 0.070 nm away from the nitrogen atom of benzenesulfonamides along a given bond axis.

Reaction Mechanism

The chlorination reactions were carried out in acidic aqueous solution at low pH. The latter property was estimated to be lower than 2, and relatively stable during the course of the reaction. Furthermore, the reaction was accelerated when pH decreased. Under these conditions, the nitrogen atom of the chlorinating agent NCP, here chemically denoted as >NCl, should be highly protonated (Eq. (*19*)).

$$>NCl + H^+ \rightleftarrows >N^+HCl \qquad (19)$$

In other words, Eq. (*19*) expresses the well-known acid-catalytic effect, which has also been observed in similar reactions[7].

For the rate-determining step, we obtained a wealth of information from the analysis of rate constants using different physical organic chemistry techniques. Thus, the values for activation enthalpies and entropies suggested a bimolecular mechanism and the IKR analysis indicated a reaction centre preferentially solvated by water molecules. In turn, the tetralinear analysis of *meta* and *para* substituent effects identified a partial positive charge in the transition state. More specifically, modelling of parameter λ placed this charge in the vicinity of the nitrogen atom belonging to *N*-phenylbenzenesulfonamide. All this information strongly suggests that the slow step in this mechanism is the electrophilic attack of the protonated agent $NCPH^+$ on the nitrogen atom of the substrate leading to the reversible formation of the corresponding chlorinated ion (Eq. (*20*)).

$$>N^+HCl + XC_6H_4NHSO_2C_6H_5 \rightleftarrows XC_6H_4N^+HClSO_2C_6H_5 + >NH \qquad (20)$$

In Eq. (*20*), >NH stands for 3-methyl-2,6-diphenylpiperidin-4-one. In this second step, we envisage an activated complex (Fig. 4) in which the heterolytic breaking of the covalent N^+–Cl bond in the reagent is accompanied by the formation of a new covalent Cl–N^+ bond in the substrate, using the lone electron-pair on its nitrogen atom. Indeed, modelling of the λ value for this reaction indicated a transition state, where the centre of positive charges is only 0.07 nm from its final position in the cationic intermediate. On the basis of this value, we propose an intermediate-like, rather than reactant-like, transition state for this step, with this view gaining further support from the relatively high values of the activation enthalpies.

The third and last step in this mechanism proposal is a fast, irreversible chlorination of the *N*-phenyl ring (Eq. (*21*)).

$$XC_6H_4N^+HClSO_2C_6H_5 \rightarrow X(Cl)C_6H_3NHSO_2C_6H_5 + H^+ \qquad (21)$$

In this context, it is worthy to note that the electron-acceptor ability of the $SO_2C_6H_5$ moiety as a substituent[35] contributes to the destabilisation of the cationic intermediate, which will quickly undergo an intra- or intermolecular rearrangement[4] resulting in the chlorination of the aromatic *N*-phenyl ring. The final products of these reactions then depend on the nature and position of the substituent on the sulfonamide used as the substrate (for the characterisation of end products, see Experimental).

Our three-step mechanism proposal is consistent with the main features of the previously proposed mechanisms for similar reactions[7]. However, in this instance we collected additional information, which shed more light on the nature of the chemical entities proposed as intermediates in these chlorination reactions.

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