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Chlorination of 2-Phenoxypropanoic Acid with NCP in Aqueous Acetic Acid: Using a Novel Ortho−Para Relationship and the Para/Meta Ratio of Substituent Effects for Mechanism Elucidation

Manuel A. P. Segurado,*,† João Carlos R. Reis,‡ Jaime D. Gomes de Oliveira,§
Senthamaraikannan Kabilan,*,|| and Manohar Shanthi||

Centro de Ciências Moleculares e Materiais and Faculdade de Farmácia, Universidade de Lisboa, Av. Prof. Gama Pinto, 1649-003 Lisboa, Portugal, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Portugal, Instituto Superior de Engenharia de Lisboa, Portugal, and Department of Chemistry, Annamalai University, Annamalai Nagar 608002, India

asegurado@ff.ul.pt; kabilan@sify.com

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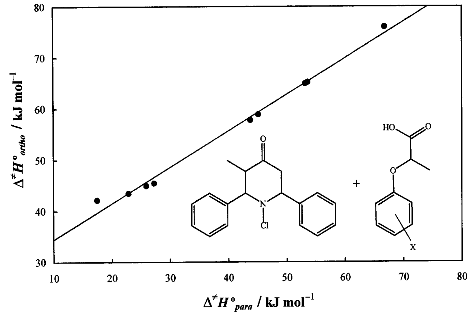

Rate constants were measured for the oxidative chlorodehydrogenation of (*R*,*S*)-2-phenoxypropanoic acid and nine ortho-, ten para- and five meta-substituted derivatives using (*R*,*S*)-1-chloro-3-methyl-2,6-diphenylpiperidin-4-one (NCP) as chlorinating agent. The kinetics was run in 50% (v/v) aqueous acetic acid acidified with perchloric acid under pseudo-first-order conditions with respect to NCP at temperature intervals of 5 K between 298 and 318 K, except at the highest temperature for the meta derivatives. The dependence of rate constants on temperature was analyzed in terms of the isokinetic relationship (IKR). For the 20 reactions studied at five different temperatures, the isokinetic temperature was estimated to be 382 K, which suggests the preferential involvement of water molecules in the rate-determining step. The dependence of rate constants on meta and para substitution was analyzed using the tetralinear extension of the Hammett equation. The parameter λ for the para/meta ratio of polar substituent effects was estimated to be 0.926, and its electrostatic modeling suggests the formation of an activated complex bearing an electric charge near the oxygen atom belonging to the phenoxy group. A new approach is introduced for examining the effect of ortho substituents on reaction rates. Using IKR-determined values of activation enthalpies for a set of nine pairs of substrates with a given substituent, a linear correlation is found between activation enthalpies of ortho and para derivatives. The correlation is interpreted in terms of the selectivity of the reactant toward para- or ortho-monosubstituted substrates, the slope of which being related to the ortho effect. This slope is thought to be approximated by the ratio of polar substituent effects from ortho and para positions in benzene derivatives. Using the electrostatic theory of through-space interactions and a dipole length of 0.153 nm, this ratio was calculated at various positions of a charged reaction center along the benzene C_1-C_4 axis, being about 2.5 near the ring and decreasing steeply with increasing distance until reaching a minimum value of −0.565 at 1.3 nm beyond the aromatic ring. Activation enthalpies and entropies were estimated for substrates bearing the isoselective substituent in either ortho and para positions, being demonstrated that they are much different from the values for the parent substrate. The electrophilic attack on the phenolic oxygen atom by the protonated chlorinating agent is proposed as the rate-determining step, this step being followed by the fast rearrangement of the intermediate thus formed, leading to products containing chlorine in the aromatic ring.

Introduction

Chlorination, as a particular case of halogenation, is a general term employed in organic chemistry to qualify the oxidative process resulting in the formation of a new carbon−chlorine bond.[1] There is, however, a variety of reaction paths leading to this structural feature, which depend on the nature of reactants and substrates, as well as on the reaction conditions.[1] Recently, we investigated the reaction mechanism for the chlorination (or

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* Corresponding author.
† Faculdade de Farmácia, Universidade de Lisboa.
‡ Faculdade de Ciências, Universidade de Lisboa.
§ Instituto Superior de Engenharia de Lisboa.
|| Annamalai University.

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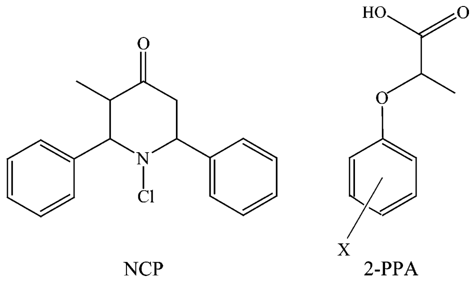
SCHEME 1. Chemical Structure of Reactants 1-Chloro-3-methyl-2,6-diphenylpiperidin-4-one (NCP) and 2-(Monosubstituted phenoxy)propanoic Acid (2-PPA)



chloro-dehydrogenation[1]) of *N*-phenylbenzenesulfonamide using an equilibrium mixture of different conformations of the racemic (*R*,*S*)-1-chloro-3-methyl-2,6-diphenylpiperidin-4-one (NCP) (Scheme 1) as chlorinating agent in aqueous acetic acid.[2] Since azacyclohexane is the alternative name of the cyclic secondary amine piperidine, NCP can also be designated as (*R*,*S*)-1-chloro-3-methyl-2,6-diphenylazacyclohexan-4-one. NCP is an interesting mild oxidant and chlorinating reagent, which was first synthesized as a new compound by Ganapathy and Vijayan[3] from the reaction of (*R*,*S*)-3-methyl-2,6-diphenylpiperidin-4-one with Chloramine-T. NCP is a very stable crystalline solid and has been used as a reactant to oxidize[3−7] or chlorinate[2,8−10] various organic substrates.

In the present research we selected the racemic (*R*,*S*)-2-phenoxypropanoic acid (2-PPA) (Scheme 1) as substrate and kept unchanged most of the reaction conditions used in the previous study.[2] We note that the effective herbicide dichlorprop is chemically (*R*,*S*)-2-(2,4-dichlorophenoxy)propanoic acid, although only the *R* enantiomer is active. Understanding the chemistry of 2-PPA, which is its parent compound, is of interest because there is an environmental concern about contamination of soil and groundwater by pesticides. To probe the mechanism of the reaction between NCP and 2-PPA, we examined substituent effects by measuring rate constants for a total of 25 substrates in 50% (v/v) aqueous acetic acid solutions in the temperature range of 298−318 K. The correlation analysis of this extensive kinetic data was made in terms of the isokinetic relationship (IKR),[11−13] the para/meta ratio of substituent effects,[14−16] and a new ortho−para relationship. The term ortho effect has a long tradition in organic chemistry.[17] In a broad sense, it is used for identifying the peculiarity of substituent effects on rates and equilibria of ortho-substituted benzene derivatives. We address the ortho effect from a restricted point of view. Instead of attempting a conventional Hammett-like approach using ortho-substituent constants, or a multiparametric correlation including steric constants, we focus on extrathermodynamic correlations among activation parameters for ortho and para derivatives within a single reaction series. This approach may be seen as an application of the isoselective relationship[18,19] if we think in terms of competition between ortho and para derivatives toward a given reactant. From an isokinetic temperature of 382 K, we infer an activated complex preferentially solvated by molecules of water. From the effect of meta and para substitution on reaction rates, we find evidence for the presence of a positive electric charge near the ether oxygen atom in the transition state. From a stimulating linear correlation of IKR-determined activation enthalpies for ortho-substituted substrates against para-substituted substrates with the same substituent, we develop a method for addressing the ortho effect and enquire into the ortho/para ratio of polar substituent effects. By drawing together the results of these analyses, we propose a three-step mechanism for the chlorination of 2-PPA with NCP.

Results and Discussion

Rate Constants. Experimental pseudo-first-order rate constants with respect to NCP, k_{obs}, were determined at temperatures between 298 and 318 K for the chlorination of 25 2-phenoxypropanoic acids (2-PPA) with NCP in aqueous acetic acid further acidified with perchloric acid (150 mmol dm^{-3}). Preliminary experiments at 303 K also demonstrated first-order kinetics with respect to 2-PPA and to the hydronium ion. For the latter experiment, which showed that the reaction is acid-catalyzed, the concentration of perchloric acid was varied between 50 (pH = 1.30) and 250 mmol dm^{-3} (pH = 0.60). At pH = 0.80, second-order rate constants k_2 were calculated according to eq 1, where [2-PPA]$_0$ stands for the initial concentration of the substrate at ambient temperature. In fact, under these acidic conditions, substrates, which are weak organic acids, should remain undissociated during the course of the reaction.

$$k_2 = k_{obs}/[\text{2-PPA}]_0 \qquad (1)$$

Rate constants k_2, expressed in the temperature-independent units[20] dm^3 mol^{-1} s^{-1}, are reported in Table 1, where 2-phenoxypropanoic acids are classified according to the special[14] or normal[23] nature of the substituent on the phenyl ring.

Isokinetic Relationship. The isokinetic relationship is a powerful tool for the correlation analysis of reaction series.[11−13]

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TABLE 1. Second-Order Rate Constants k_2 at Different Temperatures for the Chlorination of 25 2-(Monosubstituted phenoxy)propanoic Acids (2-PPA) with NCP in 50% (v/v) Aqueous Acetic Acid Acidified with Perchloric Acid

			$k_2/(10^{-3}\ \mathrm{dm^3\ mol^{-1}\ s^{-1}})$				
substituent	$\sigma^{0\ a}$	$\sigma^{\mathrm{BA}\ b}$	298.15 K	303.15 K	308.15 K	313.15 K	318.15 K
special							
m-OCH_3	0.102		5.96	7.94	11.92	15.89	
m-Cl	0.365		2.101	2.81	4.21	5.62	
m-Br	0.369		1.67	2.231	3.342	4.463	
p-OCH_3		−0.28	30.23	35.5	41.5	48.28	55.9
p-OC_2H_5			19.26	23.1	27.56	32.71	38.61
p-Cl		0.22	2.99	4.143	5.69	7.72	10.48
p-Br		0.22	2.65	3.708	5.15	7.06	9.58
o-OCH_3			3.915	5.00	6.35	8.04	9.97
o-OC_2H_5			3.507	4.50	5.75	7.27	9.21
o-Cl			0.865	1.32	1.98	2.927	4.305
o-Br			0.815	1.22	1.88	2.622	3.78
normal							
H	0		6.50	8.13	10.11	12.43	15.8
m-CH_3	−0.062		11.89	15.86	23.78	31.69	
m-NO_2	0.713		0.480	0.630	0.950	1.261	
p-CH_3	−0.135		15.12	18.21	21.79	25.94	30.72
p-C_2H_5	−0.127		13.39	16.29	19.7	23.68	28.33
p-CHO	0.437		1.383	2.051	3.008	4.366	6.23
p-CO_2H	0.440		1.227	1.836	2.72	3.99	5.75
p-CO_2CH_3	0.441		1.277	1.905	2.813	4.112	5.93
p-NO_2	0.814		0.417	0.650	1.00	1.513	2.27
o-CH_3			2.93	3.90	5.16	6.78	8.85
o-C_2H_5			2.70	3.70	5.00	6.71	8.85
o-CO_2H			0.465	0.731	1.13	1.72	2.585
o-CO_2CH_3			0.484	0.751	1.15	1.74	2.585
o-NO_2			0.176	0.300	0.500	0.822	1.323

[a] Unified σ^0 substituent constants.[21] [b] Hammett, benzoic acid reactivity σ^{BA} substituent constants,[22] for those substituents where σ^{BA} differs from σ^0.

In this similarity technique, the effect of temperature on the series reaction constants is tested using[11,24]

$$\log(k_{ij}/T_j) = a_{\mathrm{IKR}} + b_i(T_j^{-1} - \beta_{\mathrm{IKR}}{}^{-1}) \tag{2}$$

If the latter equation is statistically validated, then the reaction series is described by a set of straight lines having slopes b_i, which intersect at a common point. The temperature corresponding to the intersecting point is designated as the isokinetic temperature, β_{IKR}, the ordinate being $\log(k_{\mathrm{iso},\beta(\mathrm{IKR})}/\beta_{\mathrm{IKR}})$. This ordinate has been termed by Linert and Sapunov[25] as an "invariant point" for a given chemical reaction series. Indeed, as shown by these authors,[25] this ordinate value will be the same in different isoparametric relationships representing temperature-dependent data for the reaction series and may be used for estimating the isosubstituent Hammett constant.[26]

β_{IKR} is also the slope for the linear correlation between standard enthalpies of activation $\Delta^{\ddagger}H_i^{\circ}$ and standard entropies of activation $\Delta^{\ddagger}S_i^{\circ}$ of the individual reactions in the series, according to

$$\Delta^{\ddagger}H_i^{\circ} = h_{\beta(\mathrm{IKR})} + \beta_{\mathrm{IKR}}\Delta^{\ddagger}S_i^{\circ} \tag{3}$$

We note that, in spite of recent doubts,[13] the validation of an IKR in terms of eq 2 necessarily entails the occurrence of an enthalpy−entropy compensation effect as expressed by eq 3. In view of eq 4 where $\Delta^{\ddagger}G_i^{\circ}$ is the standard Gibbs energy of activation, the intercept $h_{\beta(\mathrm{IKR})}$ in eq 3 equals $\Delta^{\ddagger}G_i^{\circ}$ ($T = \beta_{\mathrm{IKR}}$), which is a substituent-independent constant. Brown[27] interpreted this quantity as an "intrinsic" Gibbs energy of activation because it would equal the activation enthalpy of a hypothetical derivative having zero activation entropy.

$$\Delta^{\ddagger}G_i^{\circ} = \Delta^{\ddagger}H_i^{\circ} - T\,\Delta^{\ddagger}S_i^{\circ} \tag{4}$$

We tested for an IKR our kinetic data for the parent compound and all of its ortho and para derivatives, totaling 20 reactions at five different temperatures. Equation 2 was fitted to these data in Table 1 using the program IKR-80-20 for the least-squares linear regression with a common point of intersection.[24] This program yielded standard deviations $s_{00} = 0.0027$ for unconstrained straight lines in terms of eq 5, which expresses Eyring's plots, and $s_0 = 0.0168$ for the IKR-constrained straight lines in eq 2. Although these statistics would imply rejecting an isokinetic relationship, in terms of Exner's Ψ-test,[28,29] the IKR equation is validated as an approximate relationship ($\Psi = 0.031$). The strict criterion used in the IKR-80-20 program has been noted before by various authors,[2,24,30] and the possible occurrence of an IKR is sometimes assessed by visual appraisal of an Arrhenius plot for the reaction series.[31,32]

$$\log(k_j/T_j) = a + bT_j^{-1} \tag{5}$$

For the probable IKR describing the 20 chlorination reactions under examination, the main best fitting parameters in eq 2 are

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$a_{IKR} = -0.730$ and $\beta_{IKR} = 382$ K. At 95% confidence level, the isokinetic temperature is expected to be between 376 and 398 K. We interpret this value for β_{IKR} in terms of Linert's theory,[33−36] according to which solvents act as heat baths for activated processes in solution. Linert's expression between isokinetic temperatures and active vibration frequencies of solvent molecules has been recast[37] in terms of wavenumbers $\tilde{\nu}$ as in eq 6. For $\beta_{IKR} = 382$ K, eq 6 yields the wavenumber of 265 cm^{-1}.

$$\tilde{\nu}_{\text{heat bath}}/\text{cm}^{-1} = 0.695(\beta_{IKR}/\text{K}) \qquad (6)$$

The present kinetics were run in a mixture of water and acetic acid. Having examined the infrared spectrum of acetic acid, only absorption bands at wavenumbers larger than 450 cm^{-1} were observed. On the other hand, liquid water presents an intense absorption band from 300 to 900 cm^{-1}, which has been ascribed to the bending of hydrogen bonds.[38] Following the suggestion by a reviewer, we also examined the Raman spectrum of liquid water. At 303 K, Carey and Korenowski[39] observed a Raman peak centered at 425 cm^{-1}, which corresponds to one of the three intermolecular librational modes that are Raman active. The value of 265 cm^{-1} compares well with active vibrational wavenumbers for various chemical reactions in water,[40,41] and, although displaced to lower wavenumbers, it is in fair agreement with the wavenumber of 357 cm^{-1} found for a similar chlorination reaction series in the same solvent mixture.[2] On the basis of the foregoing discussion, we interpret the isokinetic temperature of 382 K as indicating preferential solvation of activated complexes by water molecules.

Activation Parameters. Standard enthalpies and entropies of activation were computed for all of the 25 chlorination reactions from the individual temperature dependence of their rate constants in terms of the Eyring equation written in the form of eq 5. As Lente et al.[42] commented recently, $\Delta^{\ddagger}S^{\circ}$ values calculated from the best fitting parameters in eq 5 are as reliable as the corresponding $\Delta^{\ddagger}H^{\circ}$ values. These activation parameters and their standard deviations are given in Table 2 along with of the corresponding IKR-constrained values for the 20 reactions examined with this technique. Isokinetic activation enthalpies and entropies were calculated from the best fitting parameters in eq 2 using eqs 7 and 8, in which R is the gas constant, h is the Planck constant, and k_B is the Boltzmann constant.

$$\Delta^{\ddagger}H_i^{\circ} = -2.303Rb_i \qquad (7)$$

$$\Delta^{\ddagger}S_i^{\circ} = -2.303R[\log(h/k_B) + a_{IKR} - b_i/\beta_{IKR}] \qquad (8)$$

TABLE 2. Standard Enthalpies of Activation $\Delta^{\ddagger}H^{\circ}$ and Standard Entropies of Activation $\Delta^{\ddagger}S^{\circ}$ Derived from Equations 2 and 5 for the Chlorination of 2-Phenoxypropanoic Acids with NCP in Aqueous Acetic Acid

	$\Delta^{\ddagger}H^{\circ}/(\text{kJ mol}^{-1})$		$\Delta^{\ddagger}S^{\circ}/(\text{J K}^{-1}\text{ mol}^{-1})$	
substituent	eq 2	eq 5	eq 2	eq 5
special				
m-OCH_3		52.06 ± 2.20		−113.2 ± 7.2
m-Cl		52.14 ± 2.14		−121.6 ± 7.0
m-Br		52.09 ± 2.16		−123.7 ± 7.0
p-OCH_3	17.44	21.69 ± 0.01	−215.1	−201.3 ± 0.1
p-OC_2H_5	22.83	24.87 ± 0.01	−201.0	−194.4 ± 0.1
p-Cl	43.77	46.83 ± 0.15	−146.2	−136.2 ± 0.5
p-Br	45.13	48.14 ± 0.04	−142.6	−132.8 ± 0.2
o-OCH_3	42.15	34.43 ± 0.17	−150.4	−175.5 ± 0.6
o-OC_2H_5	43.45	35.46 ± 0.14	−147.0	−173.0 ± 0.5
o-Cl	57.80	60.64 ± 0.10	−109.4	−100.2 ± 0.4
o-Br	58.88	57.94 ± 1.14	−106.6	−109.6 ± 3.7
normal				
H	35.97	32.14 ± 0.66	−166.6	−179.0 ± 2.2
m-CH_3		52.05 ± 2.21		−107.5 ± 7.2
m-NO_2		51.76 ± 2.50		−135.2 ± 8.2
p-CH_3	25.91	25.39 ± 0.01	−192.9	−194.6 ± 0.1
p-C_2H_5	27.25	26.99 ± 0.01	−189.4	−190.3 ± 0.1
p-CHO	52.27	56.85 ± 0.07	−123.9	−109.0 ± 0.3
p-CO_2H	53.60	58.44 ± 0.08	−120.4	−104.7 ± 0.3
p-CO_2CH_3	53.15	58.01 ± 0.07	−121.6	−105.8 ± 0.3
p-NO_2	66.78	64.23 ± 0.05	−85.9	−94.2 ± 0.2
o-CH_3	44.94	41.02 ± 0.11	−143.1	−155.9 ± 0.4
o-C_2H_5	45.44	44.23 ± 0.15	−141.8	−145.7 ± 0.5
o-CO_2H	65.20	65.10 ± 0.09	−90.0	−90.4 ± 0.3
o-CO_2CH_3	64.93	63.56 ± 0.08	−90.7	−95.2 ± 0.3
o-NO_2	76.03	76.99 ± 0.13	−61.7	−58.6 ± 0.5

In relation to Eyring's values, the isokinetic values of activation enthalpies and entropies generally differ by less than 10%, except for $\Delta^{\ddagger}H^{\circ}$ of four reactions and $\Delta^{\ddagger}S^{\circ}$ of five reactions. We note that both *o*-alkoxy derivatives are included in these exceptions, a situation also encountered in a similar study.[2] These deviations may reflect the possible formation of intermolecular hydrogen bonds between *o*-alkoxy groups and protic solvent molecules near the reaction site.[43] We also note that the magnitude and sign of the activation entropy of a second-order reaction in solution depend on the chosen standard state,[44] which can be identified from the units expressing rate constants.

In a reaction series, Exner[11,45] has suggested IKR-constrained activation parameters to be nearer to "true" values than conventional values individually calculated in terms of Eyring equation. In support of Exner's proposal, Segura[46] found for a certain reaction series that experimental isokinetic activation enthalpies correlated much better with theoretically computed energies using an ab initio molecular-orbital method than do experimental Eyring's activation enthalpies. The discussion that follows will be based on isokinetic activation parameter values, although it refers occasionally to Eyring's values.

Tetralinear Analysis of Meta and Para Substituent Effects. The Hammett-like analysis of substituent effects from meta and para positions on the present chlorination reaction was done using our tetralinear approach,[15] in which the meta−para interrelationship is constrained by a hyperbolic model.[14] Since this approach has been described before in detail and applied to various reaction series,[2,15,16,47,48] only a brief account is given

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TABLE 3. Tetralinear Analysis of the Chlorination Rates of 2-(*m*- and *p*-Monosubstituted phenoxy)propanoic Acids with NCP in Aqueous Acetic Acid at Different Temperatures[a]

parameter	temperature/K 298.15	303.15	308.15	313.15
λ	0.967 ± 0.058	0.900 ± 0.056	0.912 ± 0.042	0.846 ± 0.067
γ	0.474 ± 0.037	0.454 ± 0.039	0.432 ± 0.037	0.415 ± 0.037
γ/γ^0	-2.105 ± 0.180	-2.016 ± 0.184	-1.919 ± 0.178	-1.8422 ± 0.175
s^b	0.064	0.066	0.063	0.066

[a] Data from Table 1 in the form $\log(k_{2,X}/k_{2,H})$ fitted to the constrained tetralinear equation (eqs 9−12) using σ^0 constants[21] and σ^{BA} constants.[22] Data points for the *m*-CH_3 derivative were excluded at 308.15 and 313.15 K. [b] Standard deviation of the fit.

herein. Thus, normal substituents, which are defined by Exner[23] as dipolar groups bearing a full octet without lone pairs of electrons on the atom next to the aromatic ring, are treated separately from special substituents,[14] which either bear a lone electron pair or an incomplete electron octet on that atom. Because this separation applies to both meta and para positions, there are four basic linear correlations, each involving only meta normal (3n), para normal (4n), meta special (3s), or para special (4s) substituents.

In its version for Hammett analyses, the basic tetralinear equation is given by[15]

$$\log(k_{3n}/k_H) = \delta_{3n} + \rho_{3n}\sigma_{3n}{}^{\circ} \tag{9}$$

$$\log(k_{4n}/k_H) = \delta_{4n} + \rho_{4n}\sigma_{4n}{}^{\circ} \tag{10}$$

$$\log(k_{3s}/k_H) = \delta_{3s} + \rho_{3s}\sigma_{3s}{}^{\circ} \tag{11}$$

$$\log(k_{4s}/k_H) = \delta_{4s} + \rho_{4s}\sigma_{4s}{}^{BA} \tag{12}$$

Although there are eight fitting parameters in eqs 9−12, only four of them are independent parameters by virtue of four constraining equations deduced from the hyperbolic model for the meta−para interrelationship of substituent effects.[15] Two of these constraints yield the relevant model parameters λ and γ in terms of eqs 13 and 14, where $\lambda^{\circ} = 0.961$ and $\gamma^{\circ} = -0.225$ are constants for the hyperbolic model applied[14,16] to the unified σ° scale.[21] Parameter λ is effectively $\lambda_{p/m}$, i.e., the para/meta ratio of polar, inductive substituent effects, and the quantity γ/γ° has been shown to be an analogue of the Hammett reaction constant after excluding through-resonance substituent effects.[2,15,16,48]

$$\rho_{4n}/\rho_{3n} = \rho_{4s}/\rho_{3s} = \lambda/\lambda^{\circ} \tag{13}$$

$$2\delta_{4n} - \delta_{3n}\lambda + \rho_{4n}\gamma^{\circ} = 2\delta_{4s} - \delta_{3s}\lambda + \rho_{4s}\gamma^{\circ} = \gamma \tag{14}$$

We used our nonlinear least-squares computing program[15,16] for the constrained fitting of eqs 9−12 to the kinetic data in Table 1 at each of the experimental temperatures where meta and para derivatives were investigated. However, the *p*-OC_2H_5 derivative was excluded from this analysis for lack of the corresponding σ^{BA} constant. We searched for outlier data points exhibiting a deviation larger than twice the standard deviation of the fit. This search identified the *m*-CH_3 derivative at 308.15 and 313.15 K. After removing these two data points, the best values for the tetralinear parameters of the present reaction series are reported in Table 3, together with their standard deviations calculated using a Monte Carlo procedure previously described.[16,47]

The λ values in Table 3 do not show significant dependence on temperature. In fact, the difference between any two of these values is within the combined standard errors. They will be used in the electrostatic modeling of parameter $\lambda_{p/m}$ determined by charged activated complexes formed during the oxidative chlorination of the 2-phenoxypropanoic acid. Since γ/γ° can be interpreted as a Hammett reaction constant ρ, its relatively large and negative value indicates the presence of an electron-deficient center in transition states. Preliminary fitting experiments using the Yukawa−Tsuno version of the tetralinear equation[16] showed that the present reaction series could be equally well-described using the σ^+ scale of substituent constants in conjunction with a resonance-demand parameter r^+ of 0.28. We have already shown that the σ^{BA} scale is equivalent to the σ^+ scale with $r^+ = 0.215$.[16] We conclude that there is a moderate through-resonance demand toward a partial positive charge during the course of the chlorination reaction under examination.

For approximately locating the reaction site, we resort to the information contained in parameter λ. This is done using a previously developed treatment for the para/meta ratio of polar substituent effects in terms of the electrostatic theory,[15,47] which was recently reexamined[2] in the light of Exner and Böhm's calculation of interaction energies using the density functional theory.[49,50] We note that, since about 56% of the total interaction energy between a dipole μ_X and a charge can be described by direct through-space electrostatic interactions,[2] then for interactions of a given type the ratio of electrostatic energies should give a reliable measure of the relative total interaction energy. This modeling is based on eq 15 for $\lambda_{p/m}$,[15,47] where distance r_+ is measured from the positive pole, which can be either on the substituent charge center or on a ring carbon atom, to the charge on the reaction site, and similarly for distance r_-.

$$\lambda_{p/m}(\mu_X, \text{charge}) = (1/r_+ - 1/r_-)_{para}/(1/r_+ - 1/r_-)_{meta} \tag{15}$$

For the experimental parameter λ, in Table 3 we report values ranging between 0.846 and 0.967. Modeling of these values with eq 15 gives a broad range of positions for locating the charge. However, disregarding the λ value at the highest temperature, we obtain an average value of 0.926, which indicates a position 0.136 nm away the benzene ring on its C_1−C_4 axis. Incidentally, this is equal to the interatomic distance C_1−O. Hence, this analysis points to the presence of an electric charge very near the oxygen atom belonging to the phenoxy group of activated complexes.

The evidence so far collected strongly suggests the electrophilic attack of protonated NCP on the substrate phenolic oxygen atom as the rate-determining step of this chlorination reaction.

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TABLE 4. Correlation Analysis of an Interdependence between Activation Enthalpies for Ortho and Para Derivatives in Terms of Equation 16 for Two Reaction Series

chlorination reaction series	n^a	$\Delta^{\ddagger}H^{\circ}$ calculated using	h_{α}/(kJ mol^{-1})	a	r^b
2-phenoxypropanoic acids	9	eq 2	27.24 ± 0.97	0.713 ± 0.026	0.995
	9	eq 5	16.46 ± 2.79	0.884 ± 0.071	0.978
N-phenylbenzenesulfonamides^c	12	eq 2	14.16 ± 1.07	0.928 ± 0.018	0.998
	12	eq 5	11.31 ± 3.12	0.913 ± 0.051	0.985

[a] Number of data points. [b] Correlation coefficient. [c] Activation enthalpy values taken from ref 2.

Ortho−Para Relationship. We use the unclear[51] term ortho effect as a short name for the change on chemical properties of benzene derivatives occurring on replacement of an *o*-hydrogen by different substituents. A variety of treatments have been developed over decades to tackle this elusive effect. We refer to Exner and associate[51−53] and Pytela and co-workers[54,55] for concise accounts of older approaches to the ortho effect. Here we follow a modern trend which concentrates on comparing the reactivity of ortho and para derivatives within a given reaction series.[51,52,55,56] Indeed, excluding specific interactions with the reaction center, substituent effects from the alternating ortho and para positions have the same nature, as Pytela and Prusek[55] have noted. Curiously, the idea that the reactivity of para derivatives provides a basis for interpreting the reactivity of ortho derivatives is a revival of the very first approach to the ortho effect.[17]

Ortho versus Para Activation Enthalpies. The present chlorination reaction series contains nine different substituents s in both the ortho and para positions, and an IKR holds approximately in this series. Hence, two subreaction series can be formed in which the common variable is the substituent nature. For reasons discussed later, the “substituent” hydrogen is not included in this analysis. Aiming at probing a possible correlation between $\Delta^{\ddagger}H^{\circ}_{\text{ortho}-\text{s}}$ and $\Delta^{\ddagger}H^{\circ}_{\text{para}-\text{s}}$, we tested a linear model in terms of eq 16 where both variables are interdependent.

$$\Delta^{\ddagger}H^{\circ}_{\text{ortho}-\text{s}} = h_{\alpha} + \alpha\Delta^{\ddagger}H^{\circ}_{\text{para}-\text{s}} \tag{16}$$

For the correlation analysis of chemical data with similar experimental errors on either variable, Exner and Zvára[57] recommend using the squared perpendicular distances from the regression line as the least-squares condition. In the context of nonlinear regressions, we have already used the least sum of rectangle areas defined by the orthogonal distances from the regression curve.[14,58] In the linear case of eq 16 both methods become identical for regression lines of unit slope. For convenience we preferred the least-rectangles linear regression analysis, details of which are given in the Experimental Section.

This analysis was performed with isokinetic and Eyring activation enthalpies for the present and a related reaction series. Results are summarized in Table 4 and shown in Figure 1 for the 2-phenoxypropanoic acid series.

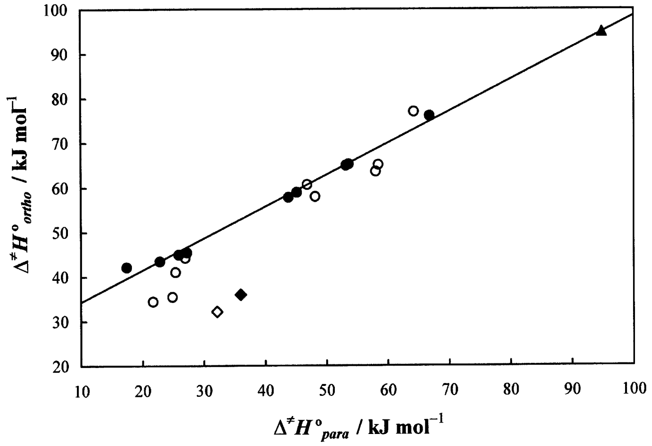

FIGURE 1. Correlation of activation enthalpies for the chlorination of 2-(*o*- versus *p*-monosubstituted phenoxy)propanoic acids. Data points from Table 2: filled circles, IKR values (eq 2); full line, best straight line through filled circles; open circles, Eyring values (eq 5); filled diamond, IKR value for the parent 2-PPA; open diamond, Eyring value for the parent 2-PPA. Filled triangle, calculated common ortho and para activation enthalpies for derivatives bearing the isoselective substituent (see later).

These interesting linear correlations prompted us to develop an extrathermodynamic formalism to frame these results. In the following we explore the consequences of eq 16 being obeyed within a given reaction series. Since both ortho and para subsets pertain to the same IKR, then eqs 17 and 18 hold. In other words, eqs 17 and 18 are particular cases of eq 3.

$$\Delta^{\ddagger}H^{\circ}_{\text{ortho}-\text{s}} = h_{\beta(\text{IKR})} + \beta_{\text{IKR}}\Delta^{\ddagger}S^{\circ}_{\text{ortho}-\text{s}} \tag{17}$$

$$\Delta^{\ddagger}H^{\circ}_{\text{para}-\text{s}} = h_{\beta(\text{IKR})} + \beta_{\text{IKR}}\Delta^{\ddagger}S^{\circ}_{\text{para}-\text{s}} \tag{18}$$

Combination of eqs 16−18 yields eq 19, in which the intercept s_{α} is given by eq 20.

$$\Delta^{\ddagger}S^{\circ}_{\text{ortho}-\text{s}} = s_{\alpha} + \alpha\Delta^{\ddagger}S^{\circ}_{\text{para}-\text{s}} \tag{19}$$

$$s_{\alpha} = [h_{\alpha} - (1 - \alpha)h_{\beta(\text{IKR})}]/\beta_{\text{IKR}} \tag{20}$$

Additionally, in view of the general thermodynamic relationship given in eq 4, activation Gibbs energies $\Delta^{\ddagger}G^{\circ}_{\text{ortho}}$ and $\Delta^{\ddagger}G^{\circ}_{\text{para}}$ became linked by eq 21, the intercept g_{α} being defined in eq 22.

$$\Delta^{\ddagger}G^{\circ}_{\text{ortho}-\text{s}} = g_{\alpha} + \alpha\Delta^{\ddagger}G^{\circ}_{\text{para}-s} \tag{21}$$

$$g_{\alpha} = h_{\alpha} - Ts_{\alpha} \tag{22}$$

Interestingly, linear eqs 16, 19, and 22 have the same slope, α. As Exner commented,[45] if the IKR holds for a reaction series, $\Delta^{\ddagger}G^{\circ}$, $\Delta^{\ddagger}H^{\circ}$, and $\Delta^{\ddagger}S^{\circ}$ change in a parallel manner so that

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anyone of these activation parameters provide essentially the same information. However, relative errors in activation enthalpies are smaller than in activation entropies. On the other hand, although the intercepts h_α and s_α are temperature-independent, g_α is not. For these reasons we preferred using eq 16 to compute h_α and α values.

Since the isokinetic temperature β_{IKR} is independently determined in terms of the IKR, a complete description of the ortho−para relationship requires knowledge of the intercept $h_{\beta(\mathrm{IKR})}$ appearing in eq 3 for use in eq 20. This parameter is conveniently derived from eqs 2, 7, and 8, being related to β_{IKR} and a_{IKR} by

$$h_{\beta(\mathrm{IKR})} = -2.303R\beta_{\mathrm{IKR}}[\log(h/k_{\mathrm{B}}) + a_{\mathrm{IKR}}] \qquad (23)$$

Isoselective Relationship. There is a striking analogy between the foregoing analysis of the ortho−para relationship and the formalism developed for the isoselective relationship (ISeR). The ISeR is a similarity technique[18,19] for analyzing the temperature effect on two reaction series possessing a common variable that is useful in various chemical contexts.[18,19,37,59] Selectivities should be expressed as the logarithm of the ratio fast-to-slow reaction rate constants, and their temperature dependence should follow a simple rule: the higher the temperature, the lower the selectivity. We can thus define the selectivity of a given reactant toward the para or ortho substitution position in the substrate. In these terms the corresponding ISeR is expressed by an analogue of eq 2, which is written here in the form of eq 24 for application to the OPR.

$$\log(k_{\text{para}-sj}/k_{\text{ortho}-sj}) = a_{\mathrm{ISeR}} + b_{\mathrm{s}}(T_j^{-1} - \beta_{\mathrm{ISeR}}^{-1}) \qquad (24)$$

In the latter equation β_{ISeR} is designated as the isoselective temperature with respect to substituent variation. At this temperature, the selectivity equals a_{ISeR} and will remain unchanged upon substituent variation.

Exner and Giese[60] established the conditions for the observation of an ISeR between two reaction series complying with the IKR. One condition requires the same isokinetic temperature for both series, in which case there exists an ISeR and β_{ISeR} equals the common β_{IKR}. A different and more general condition requires the activation enthalpies of both series to be linearly related to each other. Evidently, the former requirement is automatically fulfilled in our approach to the OPR and the latter requirement has been validated experimentally for two series of chlorination reactions. Indeed, since ortho and para subseries follow eq 2, we can write

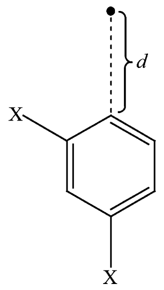
$$\log(k_{\text{para}-sj}/T_j) = a_{\mathrm{IKR}} + b_{\text{para}-\mathrm{s}}(T_j^{-1} - \beta_{\mathrm{IKR}}^{-1}) \qquad (25)$$

$$\log(k_{\text{ortho}-sj}/T_j) = a_{\mathrm{IKR}} + b_{\text{ortho}-\mathrm{s}}(T_j^{-1} - \beta_{\mathrm{IKR}}^{-1}) \qquad (26)$$

Hence subtraction of eqs 25 and 26 yields an isoselective equation having the form of eq 24, where $b_{\mathrm{s}} = b_{\text{para}-\mathrm{s}} - b_{\text{ortho}-\mathrm{s}}$ and $\beta_{\mathrm{ISeR}} = \beta_{\mathrm{IKR}}$. Furthermore, in this particular case of an ISeR between two subseries belonging to the same IKR, the intercept $a_{\mathrm{ISeR}} = a_{\mathrm{IKR}} - a_{\mathrm{IKR}}$ should ideally equal zero.

The versatile program IKR-80-20 has already been employed for testing the ISeR.[37] However, it gave poor correlation statistics for the direct fit of eq 24 to our kinetic data; for example, Ψ = 0.110. No doubt this fact mirrors the increase in relative experimental error occurring when passing from individual rate constants to the ratio of rate constants.

SCHEME 2. Geometric Basis for Estimating the Ortho/Para Ratio of Substituent Effects According to Equation 28



Equation 27 is another consequence of an ISeR holding for the OPR, which can be derived from eqs 17 and 18.

$$\Delta^{\ddagger}H^{\circ}_{\text{ortho}-\mathrm{s}} - \Delta^{\ddagger}H^{\circ}_{\text{para}-\mathrm{s}} = \beta_{\mathrm{ISeR}}(\Delta^{\ddagger}S^{\circ}_{\text{ortho}-\mathrm{s}} - \Delta^{\ddagger}S^{\circ}_{\text{para}-\mathrm{s}}) \qquad (27)$$

Using isokinetic activation enthalpy and entropy values in Table 2, we confirmed that the enthalpy−entropy plot of eq 27 gives the expected strictly linear fit ($n = 9$, intercept = −36 pJ mol^{-1}, β_{ISeR} = 382 K, r = 1.000). We note the vanishing intercept value and an isoselective temperature equal to the isokinetic temperature. Intriguingly, the excluded case of substituent hydrogen would be accurately described by eq 27. However, we shall present compelling arguments against including substituent hydrogen in the ortho/para relationship (OPR).

Ortho/Para Ratio of Polar Substituent Effects. In relation to the para position, polar substituents in the ortho position are nearer to the reaction center and their dipole orientation is much different. These aspects of the ortho substitution are, of course, well-known.[17,61−63]

Our electrostatic treatment of the para/meta ratio of polar substituent effects is now extended to the OPR. Following Dewar et al.,[64] a polar substituent is approximated by a point charge at its center of charges and an opposite point charge at the neighbor carbon atom in the ring. From an average over 26 representative polar substituents,[15] a dipole length of 0.153 nm was estimated.[47] In terms of the electrostatic theory underpinning this model,[47] the ortho/para ratio of electrostatic interaction energies between a polar substituent X and a charged reaction site, $\lambda_{o/p}(\mu_{\mathrm{X}}, \text{charge})$, is given by eq 28, which is an analogue of eq 15.

$$\lambda_{o/p}(\mu_{\mathrm{X}}, \text{charge}) = (1/r_{+} - 1/r_{-})_{ortho}/(1/r_{+} - 1/r_{-})_{para} \qquad (28)$$

The latter equation is obtained on the reasonable assumption of identical effective permittivities for field effects from ortho and para positions.

We calculated the parameter $\lambda_{o/p}$ for charged reaction centers at various distances d away the benzene ring along its C_1−C_4 axis, as depicted in Scheme 2. Duplicate calculations were also

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TABLE 5. Electrostatically Calculated Ortho/Para and Para/Meta Ratios of Interaction Energy between a Charged Site and Polar Substituents in Benzene Derivatives

benzene derivative	d/nm	$\lambda_{o/p}$	$\lambda_{p/m}$
pyridinium ion	0.000	2.538	0.835
	0.100	1.441	0.898
anilinium ion	0.135	1.048	0.925
phenolate ion	0.136	1.038	0.926
	0.1397	1.000	0.929
	0.1463	0.934	0.934
	0.147	0.928	0.934
	0.1594	0.810	0.944
	0.170	0.713	0.952
	0.200	0.482	0.976
benzoate ion	0.213	0.397	0.985
phenylacetate ion	0.229[a]	0.296	0.998
	0.2322	0.279	1.000
	0.292	0.000	1.045
	0.300	−0.028	1.050
	0.400	−0.282	1.119
	1.300	−0.565	1.482
	∞	−0.500	2.000

[a] For the orthogonal projection of charge center on the C_1-C_4 axis.

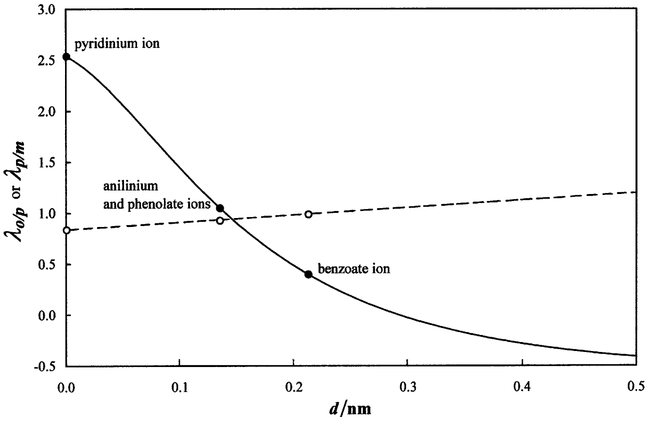

FIGURE 2. Dependence of parameters $\lambda_{o/p}$ (full line) and $\lambda_{p/m}$ (dashed line) on distance d defined in Scheme 2, according to eqs 28 and 15, respectively.

performed for the parameter $\lambda_{p/m}$. The result of this exercise is reported in Table 5 for some typical benzene derivatives and other distances of interest.

The dependence of parameters $\lambda_{o/p}$ and $\lambda_{p/m}$ on distance d can be visually appreciated in Figure 2, from which it is clear that the effect of distance on $\lambda_{o/p}$ is much more pronounced than on $\lambda_{p/m}$. The lines describing these dependencies intersect for the chemically interesting distance of 0.1463 nm, where $\lambda_{o/p} = \lambda_{p/m}$. At distances greater than 0.2922 nm, there is a reversal in the polar effect exerted by an ortho substituent in relation to lower distances, or else when it is moved from the ortho to the para position. These predicted opposite substituent effects add to previously identified similar reversals.[62,63] In this negative region, parameter $\lambda_{o/p}$ attains a minimum value of −0.565 at the not too great distance of 1.300 nm and then increases slowly up to the asymptotic limit of −0.500 at very great distances.

According to Table 5, nearly equal polar effects are expected to arise from substituents in the ortho and para positions for the protonation of aniline and the dissociation of phenol but not for the dissociation of benzoic acid. From the slope of theoretically calculated acidity of benzoic acids, Böhm et al.[51] estimated the ortho/para ratio of polar effects to be 0.81. However, our electrostatic modeling for the benzoate ion suggests a value of 0.397 for this ratio. Nonetheless, the corresponding $\lambda_{p/m}$ values would be 0.944 and 0.985, respectively, which show only a moderate disagreement. Approaching again slope α in eq 16 by parameter $\lambda_{o/p}$, similar comparisons for the two chlorination reaction series under examination give a rough agreement. Thus, $\lambda_{p/m} = 0.926$ for the chlorination of 2-phenoxypropanoic acid corresponds to $\lambda_{o/p} = 1.038$ (see Table 5), although we report $\alpha = 0.713$ in Table 4. For the chlorination of *N*-phenylbenzenesulfonamide, we estimated[2] $\lambda_{p/m} = 0.952$, from which Table 5 indicates $\lambda_{o/p} = 0.713$. The latter value should be compared with $\alpha = 0.928$ in Table 4.

From this exploratory analysis based on scarce experimental data, we draw the following conclusions. As advanced by Exner and co-workers,[51] slope α in eq 16 is determined, to a large extent, by the ortho/para ratio of polar substituent effects. However, the electrostatic modeling of slope α in terms of $\lambda_{o/p}$ did not give satisfactory concordance. Because $\lambda_{o/p}$ values are very sensitive to geometric conditions, this modeling should be based on extremely accurate experimental data for rate and equilibrium constants. Additionally, and perhaps more importantly, we should question the validity of assuming an average dipole length for describing the polar effect of a collection of different substituents from the ortho position in benzene derivatives. This problem may also be compounded with the remarkable recent finding by Exner and Böhm[65] that an electronegativity term in the inductive effect of uncharged groups becomes more important at short distances.

Case of "Substituent" *o*-Hydrogen. It is generally recognized that approaches to the ortho effect based on Hammett-like equations were the least successful.[55] For example, Bowden and Manser[66] excluded the unsubstituted benzoic acid while attempting to correlate the effect of ortho substituents with σ constants for the corresponding para substituents. And Chapman and co-workers[67] noted that, in multiparametric extensions of the Hammett equation for describing the ortho effect, the intercept term often deviates from the value for the unsubstituted compound, which notionally corresponds to hydrogen as an ortho substituent.

By addressing the latter awkward and puzzling aspect of the ortho effect from the viewpoint of the ISeR, we will argue that the parent compound does not belong to the series of ortho-substituted reactants. However, as noted in the context of eq 27, some features of the substituent hydrogen apparently fit into the framework we have developed for the OPR. Thus, its selectivity would be nil at all temperatures so that it could be described by eq 24 as the isoselective substituent in the series. The situation is very different when focusing on the linear relationships between ortho and para activation parameters. It is our contention that the isoselective substituent, denoted as ISS, should be characterized in terms of parameters that conform to eqs 16 and 19. Equating $\Delta^{\ddagger}H^{\circ}_{\text{ortho}-\text{ISS}} = \Delta^{\ddagger}H^{\circ}_{\text{para}-\text{ISS}}$ ($=\Delta^{\ddagger}H^{\circ}_{\text{ISS}}$), eq 16 in conjunction with Table 3 for the chlorination of 2-phenoxypropanoic acids, gives $\Delta^{\ddagger}H^{\circ}_{\text{ISS}} = h_{\alpha}/(1 - \alpha) = 94.9$ kJ mol^{-1}. This high activation enthalpy for the isoselective derivatives is marked in Figure 1. Similarly, from $\Delta^{\ddagger}S^{\circ}_{\text{ortho}-\text{ISS}} = \Delta^{\ddagger}S^{\circ}_{\text{para}-\text{ISS}}$ ($=\Delta^{\ddagger}S^{\circ}_{\text{ISS}}$), eqs 19, 20, and 23, together with the required numerical constants, we obtain $\Delta^{\ddagger}S^{\circ}_{\text{SS}} = s_{\alpha}/(1 - \alpha) = 10.6$ J K^{-1} mol^{-1}. At 298 K, these activation

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parameters determine a rate constant $k_{ISS} = 0.8 \times 10^{-9}$ dm^3 mol^{-1} s^{-1}, which indicates that the isoselective substituent would exert a very retarding effect in relation to the parent substrate for which $k_H = 6.5 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. In other words, this value clearly shows that no isoselective substituent can possibly be found for the present chlorination reaction. We conclude that, in the analysis of the ortho effect, it is not appropriate to regard a parent compound as both *o*-hydrogen and *p*-hydrogen derivatives.

Conclusions

The chlorination reaction of 2-phenoxypropanoic acid with NCP was investigated in aqueous acetic acid at pH near 0.8. Hence, for the first step of this reaction is proposed the protonation of the chlorination agent according to eq 29, where NCP is chemically denoted as >NCl.

$$>\mathrm{NCl} + \mathrm{H}^+ \overset{K}{\rightleftharpoons} >\mathrm{N}^+\mathrm{HCl} \qquad (29)$$

An IKR was found to hold approximately for a series of 20 reactions with various ortho and para substituents at five different temperatures. From the corresponding isokinetic temperature of 382 K, the preferential solvation of activated complexes by water molecules is suggested. The effects of meta and para substitution were well-described by the tetralinear equation using Hammett σ constants, and this analysis indicated a positively charged reaction center near the oxygen atom belonging to the phenoxy group. Hence, for the second and rate-determining step is proposed the electrophilic attack of the protonated agent NCPH$^+$ on the ether oxygen atom of the substrate leading to the reversible formation of a chlorinated cationic intermediate according to eq 30, where >NH stands for 3-methyl-2,6-diphenylpiperidin-4-one.

$$>\mathrm{N}^+\mathrm{HCl} + \mathrm{XC_6H_4OCH(CH_3)CO_2H} \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} \mathrm{XC_6H_4O^+ClCH(CH_3)CO_2H} + >\mathrm{NH} \qquad (30)$$

For the third and last step in this mechanism, is proposed a fast, irreversible chlorination of the phenolic ring according to eq 31, where $k'_2 \gg k'_{-1}$.

$$\mathrm{XC_6H_4O^+ClCH(CH_3)CO_2H} \xrightarrow{k'_2} \mathrm{X(Cl)C_6H_3OCH(CH_3)CO_2H} + \mathrm{H}^+ \qquad (31)$$

Reported second-order rate constants k_2 are then composite quantities given by $k_2 = k'_1K\,[\mathrm{H}^+]$, which explains the experimentally observed acid-catalytic effect.

The actual chlorine position on the ring will depend on the nature and position of substituent X in the substrate.

The ortho substitution effect was examined in terms of a novel analysis using isokinetic activation enthalpies. A specific ortho effect was detected for alkoxy substituents on the basis of large differences between isokinetic and Eyring values for activation enthalpies. Isokinetic activation enthalpies for ortho-substituted substrates were found to be linearly correlated with those for equally substituted substrates in the para position, the slope of this straight line being probably related to the ortho/para ratio of polar substituent effects. When an IKR holds for a reaction series containing ortho and para isomers, it is shown that an isoselective relationship also holds for the selectivity of a given reactant toward the para- or ortho-substituted substrates with the same substituent. The corresponding isoselective temperature is demonstrated to be equal to the isokinetic temperature. For the present reaction series, the substrate containing the isoselective substituent is not the parent substrate, and this aspect is viewed as an argument against using "substituent" *o*-hydrogen in the correlation analysis of ortho substitution.

Experimental Section

Materials. All chemicals were reagent grade products. Substituted phenols and 2-chloropropanoic acid were the starting compounds for the synthesis of the corresponding substituted 2-phenoxypropanoic acids using the procedure developed by Koelsch[68] for obtaining 2-(monosubstituted phenoxy)acetic acids. This is described for the parent substrate. A solution of sodium hydroxide (20 g, 0.5 mol) in water (125 cm^3) was added to 2-chloropropanoic acid (54.2 g, 0.5 mol) in an ice bath, the temperature of the reacting mixture being kept below 30 °C. To the resultant solution was added a solution of phenol (47 g, 0.5 mol) in aqueous sodium hydroxide (5 mol dm^{-3}, 100 cm^3). After heating the mixture for 20 h in a steam bath, a good yield in sodium 2-phenoxypropanoate was obtained. The reaction mixture was cooled, acidified to pH = 2 with concentrated hydrochloric acid, and extracted several times with diethyl ether. The combined organic extracts were then extracted three times with 5% aqueous monosodium carbonate. After removal of dissolved ether in a vacuum, the combined aqueous extracts were acidified to pH = 2 with concentrated hydrochloric acid. The oily precipitate solidified to give the free acid. Substrates were purified by repeated recrystallization from suitable solvents. NCP was prepared by passing gaseous chlorine through a solution of (*R,S*)-3-methyl-2,6-diphenylpiperidinium-4-one chloride in aqueous ethanol,[3] recrystallized from ethanol, and dried in a vacuum desiccator over calcium chloride. The purity of these reagents was checked by determining their melting points. The purification of solvents water and acetic acid is described elsewhere.[2]

Kinetic Measurements. Reactions were conducted in 50% (v/v) acetic acid−water solvent containing perchloric acid (150 mmol dm^{-3}). Conditions of pseudo-first-order kinetics with respect to NCP were implemented by using concentrations of 2-PPA 10- to 30-fold the concentration of NCP. For the parent substrate at 303.15 K, $[\mathrm{NCP}]_0 = 1$ mmol dm^{-3} and $[\mathrm{2\text{-}PPA}]_0 = 30$ mmol dm^{-3}. Appropriate volumes of thermally equilibrate, separate reagent solutions were poured into iodine flasks and glass-stoppered. The temperature was kept constant within ±0.01 °C. The rate of disappearance of NCP was monitored by titration. Aliquots (5 cm^3) were withdrawn from the reaction flask at suitable time intervals, quenched into a freshly prepared ice-cold aqueous solution made up with potassium iodide (2% (w/w), 10 cm^3) and sulfuric acid (5 mol dm^{-3}, 10 cm^3). Oxidation of iodide ions with the nonconsumed NCP liberated molecular iodine, which was titrated using standard sodium thiosulfate solution to a starch end point. Experimental rate constants were obtained from the slope of least-squares linear fits to the logarithmic first-order rate law, which gave high correlation coefficients. Duplicate kinetic measurements were carried out for all the experiments. Reported rate constants are average values with an estimated reproducibility of 3% or better.

Product Analysis. The reaction products resulting from the attack of NCP on 2-PPA were subjected to a detailed analysis. After about 70% conversion, the reaction mixture from an actual kinetic experiment was extracted with trichloromethane and shaken vigorously with an equal volume of water. A white precipitate was separated and shown to be 3-methyl-2,6-diphenylpiperidin-4-one (or 3-methyl-2,6-diphenylazacyclohexan-4-one) by means of IR spectrometry and mixed melting point determination. The liquid extract was dried over anhydrous sodium sulfate and the organic solvent removed under reduced pressure. The residue was monitored

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[68] Koelsch, C. F. *J. Am. Chem. Soc.* **1931**, *53*, 304−305.

by thin-layer chromatograpy (TLC) on neutral alumina, along with authentic samples of 2-PPA and its *o*-chloro and *p*-chloro derivatives. The spots were eluted with a (4:5:1) butan-1-ol−water−acetic acid mixture and developed by exposure to iodine vapor. The three R_F values measured for the residue matched exactly those of the aforementioned authentic samples. This identification was further confirmed by ^{13}C NMR spectrometry of extracts of the TLC spots.

Computation. Least-squares and least-rectangles analyses were performed. Calculation procedures using linear and nonlinear regressions have been described in the context of the computer programs used for solving a given equation. The method of least-rectangles linear regression was used in the cases where both variables are loaded with similar errors. Given the general straight line $y = a + bx$, best fitting parameters and their standard errors can be computed from the related common linear regressions of y on x, $y = a_1 + b_1x$, and of x on y, $x = a_2 + b_2y$. Slopes b_1 and b_2 have necessarily the same sign. Then slope b is given by their geometric mean $\pm(b_1/b_2)^{1/2}$, its sign being determined by the sign common to b_1 and b_2. Alternatively and equivalently, the best slope can be calculated as $b = \pm s(y)/s(x)$, where $s(y)$ and $s(x)$ are the standard deviations obtained for the above common linear regressions. Since the least-rectangles or orthogonal straight line must go through the point defined by the mean-value coordinates ($\bar{x}$,$\bar{y}$), then intercept a is computed as $a = \bar{y} - b\bar{x}$. For a given set of experimental data, an identical correlation coeficcient r is obtained for the least-squares linear regressions of y on x and of x on y, and therefore for the linear least-rectangles linear correlation between x and y. Standard deviations of best fitting parameters, $s(a)$ and $s(b)$, were estimated using the following equations,[69,70] where n is the number of data points and $\bar{x}$ is the mean value of x.

$$s(a) = \sqrt{\frac{s^2(y)}{n}(1 - r)[2 + \bar{x}(1 + r)/s^2(x)]}$$

$$s(b) = \sqrt{\frac{b^2(1 - r^2)}{n - 2}}$$

These calculations were implemented on a Microsoft Excel spreadsheet using the LINEST function.

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