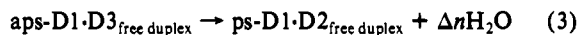


molecules, which will depend upon the overall hydration of the free duplexes. Therefore, the observed entropic differences between the duplexes of the set containing all A·T base pairs should correspond entirely to hydration changes; for the second set it should correspond to changes in both hydration and release of counterions.

**Differential Thermodynamic Profiles Suggest a Lower Hydration State for the Ligand-Free ps-D1·D2 Duplex.** If each of the thermodynamic parameters for the association of netropsin to the ps-D1·D2 duplex are subtracted from the corresponding parameters of netropsin binding to the aps-D1·D3 duplex, the resulting differential thermodynamic profiles correspond to the reaction



We can use this thermodynamic cycle because binding of netropsin to the duplexes is accompanied by similar  $K_b$  values, stoichiometries, and release of counterions. In addition, we are assuming that the structures of both complexes are stabilized by similar molecular interactions, so that any differences in the type of hydrogen bonds and/or van der Waals contacts would contribute negligibly to the overall energetics. We obtain a small  $\Delta\Delta G^\circ$  of  $-0.3 \text{ kcal mol}^{-1}$ , which is the result of a compensation of an unfavorable  $\Delta\Delta H^\circ$  of  $+4.4 \text{ kcal mol}^{-1}$  and a favorable  $\Delta(T\Delta S^\circ)$  of  $+4.7 \text{ kcal mol}^{-1}$ , and a marginal differential counterion release,  $\Delta\Delta n_{\text{Na}^+}$  of  $+0.01 \text{ mol of Na}^+/\text{mol of bound ligand}$ . The positive sign of this enthalpy–entropy compensation is the same as in the differential parameters obtained on binding this ligand to poly(dA)·poly(dT) and to poly[d(AT)]·poly[d(AT)], in which we measured a higher hydration state for the homopolymer. Therefore, the  $\Delta n$  term in eq 3 is a positive quantity that corresponds to a release of water molecules and suggests that the

unligated parallel duplex is less hydrated. Furthermore, to estimate this decrease in differential hydration of the parallel duplex relative to the antiparallel duplex, we use the average value of  $0.3 \text{ kcal mol}^{-1}$  for the enthalpy of releasing 1 mol of electrostricted water from the native DNA molecule<sup>32,33</sup> and  $\Delta\Delta H = \Delta(T\Delta S^\circ) = 4.7 \text{ kcal mol}^{-1}$ . We obtain  $16 \pm 1 \text{ mol of H}_2\text{O/mol of complex}$ , or 3 to 4 mol of  $\text{H}_2\text{O}/\text{base pair}$ . If instead we use the thermodynamic profiles for the formation of the same duplexes reported previously<sup>8</sup> and a similar thermodynamic cycle, we obtain  $\Delta\Delta H = \Delta(T\Delta S^\circ) = 23 (\pm 7) \text{ kcal/mol of duplex}$ , corresponding to a differential hydration of 3 to 5 water molecules/base pair. The similarity of these numbers strongly suggests that the groove in the ps-D1·D2 duplex is less hydrated than the minor groove in aps-D1·D3. This is consistent with the increased hydration of AA/TT stretches,<sup>21,34</sup> which contain a narrower minor groove as observed in X-ray crystal structure studies.<sup>35</sup> Perhaps it is this lower hydration state of parallel DNA that is responsible for its lower stability. We are currently measuring volume changes for these association reactions, for which our calculations predict a significant differential volume change of  $10 \text{ mL/mol of base pair}$ .

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## Structure–Reactivity Correlations for Reactions of Substituted Phenolate Anions with Acetate and Formate Esters<sup>†</sup>

Dimitrios Stefanidis, Sayeon Cho, Sirano Dhe-Paganon, and William P. Jencks\*

Contribution No. 1748 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254–9110. Received September 8, 1992

**Abstract:** The reactions of substituted phenolate anions with *m*-nitrophenyl, *p*-nitrophenyl, and 3,4-dinitrophenyl formates follow nonlinear Brønsted-type correlations that might be taken as evidence for a change in the rate-limiting step of a reaction that proceeds through a tetrahedral addition intermediate. However, the correlation actually represents two different Brønsted lines that are defined by meta- and para-substituted phenolate anions and by meta- and para-substituted *o*-chlorophenolate anions. A concerted mechanism for both acetyl- and formyl-transfer reactions is supported by the absence of a detectable change in the Brønsted slope at  $\Delta pK = 0$  for the attacking and leaving phenolate anions within each class of Brønsted correlations. Regular increases in the dependence of  $\log k$  on the  $pK_a$  of the nucleophile with increasing  $pK_a$  of the leaving group correspond to a positive interaction coefficient  $p_{xy} = \partial\beta_{\text{lg}}/\partial(pK_{\text{nuc}}) = \partial\beta_{\text{nuc}}/\partial(pK_{\text{lg}})$ . The observation of two different Brønsted lines for the reactions of substituted phenolate anions with phenyl acetates is attributed to a steric effect that decreases the rate of reaction of substituted *o*-chlorophenolate anions by 25–50%. The reactions of meta- and para-substituted phenolate and *o*-chlorophenolate anions with substituted phenyl acetate esters follow values of  $\beta_{\text{nuc}} = 0.53\text{--}0.66$  and  $-\beta_{\text{lg}} = 0.50\text{--}0.63$ . The reactions of meta- and para-substituted phenolate anions with formate esters are  $\sim 10^3$  times faster and follow smaller values of  $\beta_{\text{nuc}} = 0.43\text{--}0.64$  and  $-\beta_{\text{lg}} = 0.31\text{--}0.48$ . However, the reactions of meta- and para-substituted *o*-chlorophenolate anions with the same formate esters follow larger values of  $\beta_{\text{nuc}} = 0.63\text{--}0.90$  and  $-\beta_{\text{lg}} = 0.46\text{--}0.90$ . The large values of  $\beta_{\text{nuc}}$  and  $-\beta_{\text{lg}}$  for the reactions of substituted *o*-chlorophenolate anions with formate esters may arise from destabilization by the *o*-chloro group of a stacking interaction that is present in the transition state for reactions of formate esters, but not acetate esters.

### Introduction

Acyl-transfer reactions can occur through a stepwise mechanism, with a tetrahedral addition intermediate that has a significant

lifetime, or through a concerted, one-step mechanism with a single transition state and no addition intermediate. The change from a stepwise to a concerted mechanism with changing structure of the reactants presumably occurs when the addition compound becomes so unstable that it does not have a significant lifetime; there is no significant barrier for its decomposition, and it does

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not exist for several vibrations. When this occurs, the addition compound becomes a transition state instead of an unstable intermediate.

The observation of  $^{18}\text{O}$  exchange from water into the carbonyl group of alkyl esters undergoing hydrolysis strongly suggests that a tetrahedral addition intermediate is formed along the reaction path, because this reaction requires the making or breaking of four O-H as well as two C-O bonds.<sup>1</sup> It is not likely that all of these processes can occur in a single transition state. On the other hand, S. L. Johnson has argued that the observation of general base catalysis for the ethanolysis of ethyl trifluoroacetate requires a concerted reaction mechanism.<sup>2</sup>

A two-step mechanism for the reaction of phenolate ions with phenyl esters would be expected to follow a nonlinear structure-reactivity correlation of  $\log k$  with the  $\text{p}K_{\text{a}}$  of the attacking nucleophile if it proceeds through an addition intermediate. The slope is expected to decrease with increasing  $\text{p}K_{\text{a}}$  of the attacking phenolate ion when the  $\text{p}K_{\text{a}}$  values of the attacking and leaving phenolate ions become equal and there is a change from rate-determining expulsion of the leaving group to rate-determining attack of the nucleophile.

A. Williams and his co-workers showed that a Brønsted-type correlation of  $\log k$  for the reaction of substituted phenolate anions with *p*-nitrophenyl acetate is linear for a series of phenolate ions with  $\text{p}K_{\text{a}}$  values above and below that of *p*-nitrophenol.<sup>3</sup> There is no indication of the increase in the slope of the correlation at  $\Delta\text{p}K_{\text{a}} = 0$  that would be expected for a stepwise reaction mechanism when the rate-determining step changes from nucleophilic attack, by basic phenolate ions, to expulsion of the leaving group from the tetrahedral addition intermediate, for attacking phenolate ions that are less basic than the leaving group. Subsequently, it was shown that the dependence of  $\log k$  on the  $\text{p}K_{\text{a}}$  of the attacking phenolate ion,  $\beta_{\text{nuc}}$ , increases with increasing  $\text{p}K_{\text{a}}$  of the leaving group. This shows that there is an interaction of the attacking phenolate ion with the leaving group in the rate-determining transition state, and is consistent with a fully concerted mechanism.<sup>4</sup> However,  $\beta_{\text{nuc}}$  could also increase with increasing  $\text{p}K_{\text{a}}$  of the leaving group as a result of a change in transition-state structure in a stepwise mechanism through a "Hammond effect" i.e., a later transition state for nucleophilic attack on a less reactive ester.

We report here an examination of the reactions of a series of substituted phenolate anions with substituted phenyl formates. Phenyl formates are much more reactive toward nucleophilic reagents compared with the corresponding acetate esters because of decreased steric hindrance and the absence of hyperconjugation from the methyl group of acetate esters. These factors should also stabilize a tetrahedral addition intermediate. The equilibrium constant for hydration is approximately 3000 times more favorable for formaldehyde than for acetaldehyde,<sup>5</sup> and a similar increase in stability can be expected for tetrahedral addition intermediates formed from formate compared with acetate esters, so that it should be possible to obtain evidence for the tetrahedral addition intermediate if it exists.

Our results show no evidence for a change in rate-limiting step with changing  $\text{p}K_{\text{a}}$  of the attacking phenolate ion for reactions of substituted phenyl acetates and phenyl formates with a series of substituted phenolate ions that includes compounds with  $\text{p}K_{\text{a}}$  values that are above and below the  $\text{p}K_{\text{a}}$  of the leaving phenolate

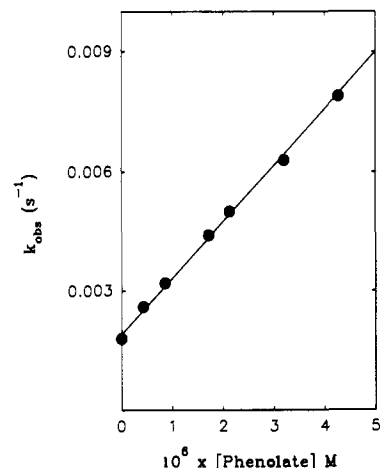


Figure 1. Dependence of the pseudo-first-order rate constants for the release of *p*-nitrophenol from *p*-nitrophenyl formate (PNPF) on the concentration of phenolate anion at 25 °C and ionic strength 1.0 M (KCl).

ion. However, the reactions of substituted *o*-chlorophenolate ions with formate esters follow a larger value of  $\beta_{\text{nuc}}$  than do other substituted phenolate ions. We conclude that there is no tetrahedral intermediate and that substituted phenyl formates, as well as phenyl acetates, react with phenolate anions through a concerted reaction mechanism.

#### Experimental Section

**Materials.** *p*-Nitrophenyl acetate (Aldrich Chemical Co.) and *p*-nitrophenyl formate (Lancaster Synthesis) were purified by recrystallization from hexanes. *m*-Nitrophenyl acetate and 3,4-dinitrophenyl acetate were prepared from acetyl chloride and phenols as previously described.<sup>6</sup> *m*-Nitrophenyl formate (mp 35–36 °C, lit. mp 37–38 °C) was prepared from acetic formic anhydride and *m*-nitrophenol by the method of Sofuku et al.,<sup>7</sup> and 3,4-dinitrophenyl formate was synthesized from formic acid, 3,4-dinitrophenol, and *N,N'*-dicyclohexylcarbodiimide as described by Okawa and Hase.<sup>8</sup>

All phenols were redistilled or recrystallized before use. The  $\text{p}K_{\text{a}}$  values of phenols used in this study were determined spectrophotometrically in CHES, HEPES, MOPS, or MES<sup>9</sup> buffers at 25 °C and  $I = 1 \text{ M}$  (KCl) by the general procedure described by Albert and Serjeant.<sup>10</sup>

**Kinetics Methods.** Pseudo-first-order rate constants were determined at 25 °C and  $I = 1 \text{ M}$  (KCl). Rate measurements were made with a Perkin-Elmer Lambda 4B or a Milton Roy Spectronic 1001 spectrophotometer by measuring the change in absorbance with time due to phenol release from the ester. Formation of the substituted phenol was observed at 350 nm; the phenolate anions were followed at 400 nm. The initial concentrations of esters were between  $10^{-5}$  and  $10^{-4} \text{ M}$ . The pH of the reaction was maintained with 0.015 M HEPES, MOPS, or MES buffers.

Slow kinetics for reactions of acetate esters with weakly nucleophilic phenols were determined by measuring the initial rate of phenol release. The absorbance at the end point was determined by hydrolyzing an aliquot of the ester solution at high pH, neutralizing the solution, and then adding an appropriate amount of buffer, phenol nucleophile, and KCl so that the absorbance was measured under conditions identical with those of the kinetics runs.

#### Results

The observed pseudo-first-order rate constants for reactions of substituted phenolate anions with substituted phenyl esters were found to follow a linear dependence on the concentration of the nucleophiles; a typical result is shown in Figure 1. Second-order

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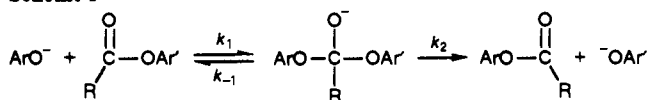
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**Table I.** Second-Order Rate Constants for the Reactions of Substituted Phenolate Anions with *m*-Nitrophenyl (MNPF), *p*-Nitrophenyl (PNPF), and 3,4-Dinitrophenyl (DNPF) Formate in Aqueous Solution at 25 °C, *I* = 1.0 M

substituted phenolate nucleophile	$pK_a^a$	$k_2, M^{-1} s^{-1}$		
		MNPF	PNPF	DNPF
2-CH <sub>3</sub>	10.13	590	1000	
4-CH <sub>3</sub>	10.09	1900	2200	13 000
H	9.81	850	1400	8000
4-NHCOCH <sub>3</sub>	9.53	780		
3-NHCOCH <sub>3</sub>	9.39	530		
4-Cl	9.26	480	1100	6300
3-Cl	8.87	280	570	3400
2-Cl-4,5-(CH <sub>3</sub> ) <sub>2</sub>	8.75	180	440	
2-Cl-4-CH <sub>3</sub>	8.68	160	410	3300
2-F	8.48	120	320	
3,4-Cl <sub>2</sub>	8.44	160	380	2500
2-Cl	8.32	55	160	1600
3,5-Cl <sub>2</sub>	8.03	68	170	1400
4-COCH <sub>3</sub>	7.91	22		
4-CN	7.80	22		
2,4-Cl <sub>2</sub>	7.75	23	88	980
3,4,5-Cl <sub>3</sub>	7.69	50	140	1200
2,3-F <sub>2</sub>	7.68	25	100	
2,3-Cl <sub>2</sub>	7.51	9.4	41	530
2,6-F <sub>2</sub>	7.12	4.4	28	
2,4,5-Cl <sub>3</sub>	6.88	2.6	15	300
2,3,5-Cl <sub>3</sub>	6.58	1.5	6.5	120
2,3,5,6-F <sub>4</sub>	5.41	0.031	0.29	15
2,3,4,5,6-F <sub>5</sub>	5.33	0.068	0.39	

<sup>a</sup> Determined in this study at 25 °C, *I* = 1.0 M.**Scheme I**

rate constants for the reactions of phenolate anions with the esters were calculated from the slopes of plots of  $k_{\text{obsd}}$  against the concentration of phenolate anion. The concentrations of phenolate anion at a given pH value were calculated from the concentration and the  $pK_a$  of the phenol. The  $pK_a$  values were determined by spectrophotometric titration under conditions identical with those of the kinetics measurements. The second-order rate constants for the reactions of substituted phenolate anions with *m*-nitrophenyl acetate (MNPA), *p*-nitrophenyl acetate (PNPA), and 3,4-dinitrophenyl acetate (DNPA) are given in Table II, and second-order rate constants for the reactions of substituted phenolate anions with *m*-nitrophenyl formate (MNPF), *p*-nitrophenyl formate (PNPF), and 3,4-dinitrophenyl formate (DNPF) are given in Table I.

**Discussion**

**Brønsted Correlations: The Mechanism of Formyl and Acetyl Transfer.** A stepwise mechanism for the nucleophilic reaction of phenolate anions with phenyl acetate or phenyl formate esters proceeds in two steps through a tetrahedral addition intermediate on the reaction path, as shown in Scheme I. Nucleophilic attack is rate-determining when the nucleophile,  $\text{ArO}^-$ , is more basic than the leaving group of the ester ( $k_2 > k_{-1}$ , Scheme I), and expulsion of the leaving group is rate-determining when the leaving group is more basic than the nucleophile ( $k_2 < k_{-1}$ , Scheme I). A Brønsted-type plot for a stepwise mechanism is described by eq 1, in which the  $C_1$  and  $C_2$  terms define the second-order rate constants when  $k_1$  and  $k_2$ , respectively, are rate-determining, and  $\beta_1$  and  $\beta_2$  describe the corresponding Brønsted slopes. The  $pK_a$  at which the change in rate-limiting step occurs and each step is 50% rate-limiting,  $pK_0$ , is given by eq 2.<sup>11</sup> When the nu-

$$k_{\text{obsd}} = \frac{C_1 C_2 (10^{(\beta_1 + \beta_2)(pK_a)})}{C_1 (10^{\beta_1(pK_a)}) + C_2 (10^{\beta_2(pK_a)})} \quad (1)$$

$$pK_0 = \log(C_1/C_2)/(\beta_2 - \beta_1) \quad (2)$$

**Table II.** Second-Order Rate Constants for the Reactions of Substituted Phenolate Anions with *m*-Nitrophenyl (MNPA), *p*-Nitrophenyl (PNPA), and 3,4-Dinitrophenyl (DNPA) Acetate in Aqueous Solution at 25 °C, *I* = 1.0 M

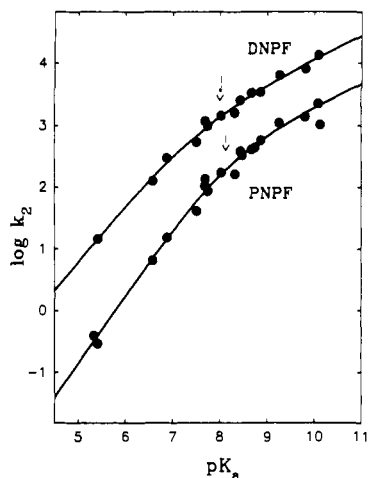
substituted phenolate nucleophile	$pK_a^a$	$k_2, M^{-1} s^{-1}$		
		MNPA	PNPA	DNPA
2-CH <sub>3</sub>	10.13		0.47	4.90
4-CH <sub>3</sub>	10.09	0.63	1.34	17
H	9.81	0.45	0.83	9.9
4-NHCOCH <sub>3</sub>	9.53		0.79	
4-Cl	9.26	0.17	0.57	
3-Cl	8.87	0.12		3.3
2-Cl-4-CH <sub>3</sub>	8.68	0.049	0.12	2.0
2-F	8.48		0.16	
2,4-F <sub>2</sub>	8.40		0.28	
3,4-Cl <sub>2</sub>	8.44	0.062	0.18	2.5
2-Cl	8.32	0.017	0.056	0.92
3,5-Cl <sub>2</sub>	8.03	0.029	0.08	1.1
4-CN	7.80		0.024	
2,4-Cl <sub>2</sub>	7.75	0.01	0.029	0.54
3,4,5-Cl <sub>3</sub>	7.69	0.016	0.055	0.81
2,3-F <sub>2</sub>	7.68		0.041	
2,3-Cl <sub>2</sub>	7.51	$4.8 \times 10^{-3}$	0.015	0.31
2,6-F <sub>2</sub>	7.12	$4.4 \times 10^{-3}$	0.018	
2,4,5-Cl <sub>3</sub>	6.88	$2.6 \times 10^{-3}$	$7.4 \times 10^{-3}$	0.17
2,3,5-Cl <sub>3</sub>	6.58		$2.8 \times 10^{-3}$	
2,3,5,6-F <sub>4</sub>	5.41		$3.8 \times 10^{-4}$	
2,3,4,5,6-F <sub>5</sub>	5.33		$6.3 \times 10^{-4}$	

<sup>a</sup> Determined in this study at 25 °C, *I* = 1.0 M.

cleophilic phenolate ion is more basic than the leaving group and the attack step is rate-determining, there will be partial neutralization of the negative charge on the attacking phenolate anion in the transition state. This change in charge should give a slope of  $\beta_{\text{nuc}} \leq 1.0$  for a plot of  $\log k$  against the  $pK_a$  of the substituted phenolate nucleophile. As the  $pK_a$  of the phenolate nucleophile is decreased to below that of the leaving phenolate, the rate-determining step will change from nucleophilic attack to expulsion of the leaving group from the addition intermediate. In the transition state of the second step the negative charge on the attacking phenolate anion has disappeared, and there may be some development of positive charge, if electron donation from oxygen contributes to expulsion of the leaving group. This will give a larger value of  $\beta_{\text{nuc}}$ , which is expected to be  $\geq 1.0$ . Therefore, a stepwise mechanism for the reaction of phenolate anions with phenyl acetate or phenyl formate, as defined by eq 1, results in a nonlinear Brønsted plot. The Brønsted slope for weakly basic phenolate ions is expected to be  $\beta_{\text{nuc}} \geq 1.0$ , because the bond to the carbonyl carbon atom is fully formed and leaving group expulsion from the tetrahedral intermediate is rate-limiting. A value of  $\beta_{\text{nuc}} \leq 1.0$  is expected for strongly basic phenolate ions, because nucleophilic attack is rate-limiting and the bond to the carbonyl carbon atom is only partially formed in the transition state. The change in slope occurs at  $pK_0$ , the  $pK_a$  of the leaving group, as the rate-limiting step changes from expulsion of the leaving group to attack of the nucleophile on the ester.

Brønsted-type correlations for the reactions of substituted phenolate anions with *p*-nitrophenyl and 3,4-dinitrophenyl formates are shown in Figure 2. The solid lines were calculated from eq 1 with the following parameters: the reactions of *p*-nitrophenyl formate follow  $\beta_1 = 0.38 \pm 0.04$ ,  $\beta_2 = 1.09 \pm 0.03$ ,  $C_1 = 0.35 \pm 0.28$ , and  $C_2 = (4.7 \pm 2) \times 10^{-7}$ , and the reactions of 3,4-dinitrophenyl formate follow  $\beta_1 = 0.38 \pm 0.08$ ,  $\beta_2 = 0.94 \pm 0.1$ ,  $C_1 = 2 \pm 2$ , and  $C_2 = (2 \pm 2) \times 10^{-4}$ . The curves are calculated for a change in the rate-determining step at  $pK_0 = 8.0$  for DNPF and 8.1 for PNPF. A similar curve for the reaction of MNPF (not shown) was calculated from  $\beta_1 = 0.48 \pm 0.6$ ,  $\beta_2 = 1.16 \pm 0.04$ ,  $C_1 = (2.7 \pm 2) \times 10^{-2}$ ,  $C_2 = (2.8 \pm 2) \times 10^{-8}$ , and  $pK_0 = 9 \pm 1$ . The rate constants for substituted 2,6-difluorophenolate ions fall close to the correlation for other ortho-substituted phenolate ions.

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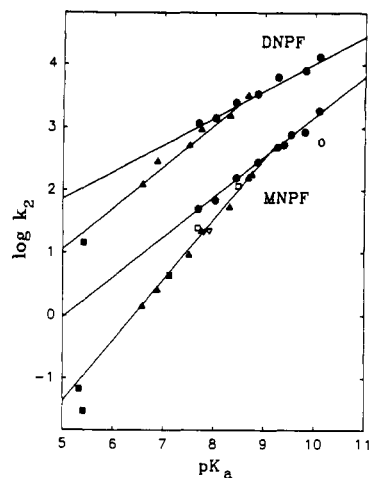


**Figure 2.** The dependence on basicity of the nucleophile of the second-order rate constants,  $k_2$ , for the reactions of substituted phenolate anions with 3,4-dinitrophenyl formate (DNPF) and *p*-nitrophenyl formate (PNPF). The solid lines were calculated from eq 1 with the values of  $\beta_1$ ,  $\beta_2$ ,  $C_1$ , and  $C_2$  that are given in the text.

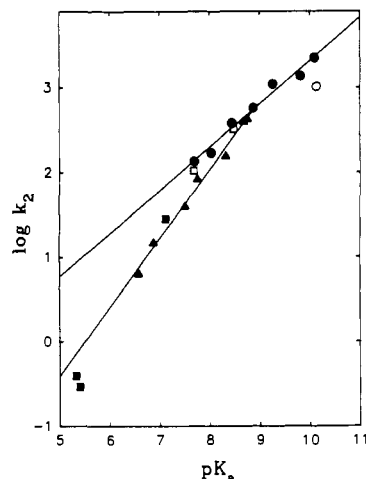
Although these parameters provide a fair fit to the data, they are not in the range that is expected for a stepwise mechanism that proceeds through a tetrahedral addition intermediate. The change in the slope of the Brønsted-type correlation occurs at  $pK_0 = 8$  for 4-nitrophenyl formate, which is well above the  $pK_a$  of 7.0 for the leaving group. Furthermore, the change in the Brønsted slope for reaction with 3,4-dinitrophenyl formate occurs at the same  $pK_0$  value of 8, although the leaving group of this ester has a  $pK_a$  of 5.3 and differs from that of 4-nitrophenyl formate only by the addition of the *m*-nitro group. This result is important because the large value of  $pK_0$  for 4-nitrophenyl formate might be attributed to imbalance between bond breaking and delocalization of negative charge into the 4-nitro substituent by resonance in the transition state.<sup>11,12</sup> The absence of an effect of the 3-nitro substituent on  $pK_0$  suggests that the anomalous value of  $pK_0$  for *p*-nitrophenyl formate does not arise from such imbalance. Finally, the value of  $pK_0 = 9.0$  for *m*-nitrophenyl formate is significantly larger than the  $pK_a$  of 8.2 for this leaving group, which is not expected to be significantly perturbed by conjugation with the *m*-nitro substituent.

These results contrast with the structure–reactivity behavior that was observed for the reactions of thiol anions with substituted phenyl acetates. These reactions show nonlinear Brønsted-type correlations of  $\log k$  with the  $pK_a$  of the nucleophile and an increase in  $pK_0$  with increasing  $pK_a$  of the leaving group. This is the behavior that is expected for a stepwise reaction mechanism that proceeds through a tetrahedral addition intermediate.<sup>11</sup>

However, Figures 3 and 4 show a correlation of the data for the reaction of phenolate anions with phenyl formates that takes into account the fact that two different classes of phenolate anions are used in the Brønsted correlations. The change in slope depends on the presence or absence of an ortho substituent, rather than on the  $pK_a$  of the phenol. Each Brønsted-type correlation in Figures 3 and 4 is described by two Brønsted lines: the first line (solid circles) is defined by meta- and para-substituted phenolate anions and has  $\beta_{\text{nuc}}$  values in the range 0.43–0.64, and the second line (solid triangles) is defined by meta- and para-substituted *o*-chlorophenolate anions and has  $\beta_{\text{nuc}}$  values in the range 0.66–0.90. The two lines intersect at  $pK = 8.4, 8.9,$  and  $9.1$  for the reactions of 3,4-dinitrophenyl, *p*-nitrophenyl, and *m*-nitrophenyl formates, respectively. These values of the intersection points show only a small dependence on the  $pK_a$  of the leaving group and are similar to the  $pK_0$  values that were obtained from the fit to eq 1. The changes in the Brønsted slopes with changing  $pK$  of the phenol in Figures 3 and 4 are not caused by the change in  $pK$ ; they are simply a consequence of the fact that the values



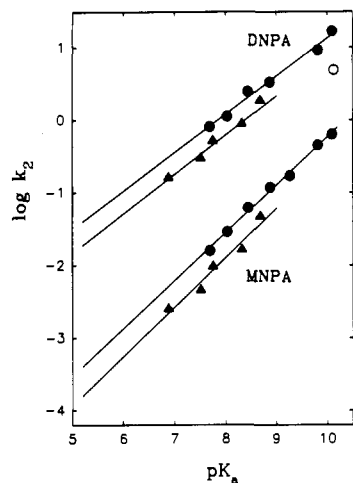
**Figure 3.** The dependence on basicity of the nucleophile of the second-order rate constants,  $k_2$ , for the reactions of substituted phenolate anions with 3,4-dinitrophenyl formate (DNPF) and *m*-nitrophenyl formate (MNPF). Each reaction is described by two Brønsted lines, which are defined by meta- or para-substituted phenolate anions (filled circles) and meta- or para-substituted *o*-chlorophenolate anions (filled triangles). The filled squares refer to meta- or para-substituted 2,6-difluorophenolate anions, and the open symbols refer to meta- or para-substituted *o*-fluorophenolate anions; however, the open triangle refers to 4-cyano- and 4-acetylphenolate anions.



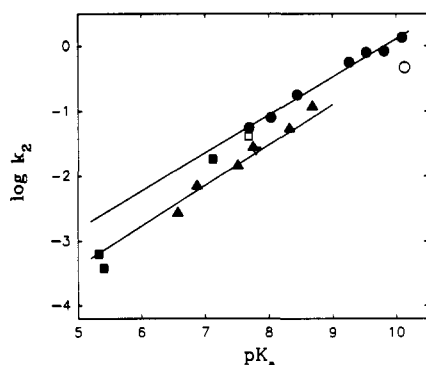
**Figure 4.** Brønsted plots for the reactions of PNPf with meta- or para-substituted phenolate anions (upper line) and meta- or para-substituted *o*-chlorophenolate anions (lower line). The symbols are identified in the caption to Figure 3.

of  $\beta_{\text{nuc}}$  for the reactions of these esters with ortho-substituted phenolate anions are larger than the values of  $\beta_{\text{nuc}}$  for the reactions of meta- and para-substituted phenolate anions, and the substituted *o*-chlorophenolate anions are less basic than most of the other phenolate anions. This results in a nonlinear Brønsted plot when *o*-chloro as well as meta- and para-substituted phenolate nucleophiles are used in the Brønsted correlations. The Brønsted correlations are best described by linear plots for each of the two classes of phenolate ions, and the intersection points of the two lines increase by only 0.7  $pK$  units when the  $pK$  values of the leaving groups increase by 3  $pK$  units. We conclude that the data provide no support for a change in rate-determining step in a stepwise mechanism and that all of the reactions follow a concerted reaction mechanism.

We do not know the reason that the sensitivity of the rate constants to substituents on the attacking phenolate ion is larger for reactions of formate esters with substituted *o*-chlorophenolate ions compared with meta- and para-substituted phenolate ions (Figures 3 and 4). No such difference is found for the reactions with acetate esters. Inspection of space-filling molecular models indicates that the *o*-chloro substituent restricts the number of



**Figure 5.** Brønsted plots of the second-order rate constants,  $k_2$ , for the reactions of substituted phenolate anions with DNPA and MNPA. The symbols are identified in the caption to Figure 3.



**Figure 6.** Brønsted plots of the second-order rate constants,  $k_2$ , for the reactions of *p*-nitrophenyl acetate with anions of meta- and para-substituted phenolates. The symbols are identified in the caption to Figure 3.

conformations of a tetrahedral intermediate or transition state that can be reached without interference from unfavorable non-bonding interactions; in one of these conformations the substituted benzene rings of the attacking and leaving phenolates are aligned parallel to each other, and it is possible that dipolar interactions or "microscopic medium effects" between the attacking and leaving substituted phenolate ions in the lowest energy conformation of the transition state are responsible for the enhanced sensitivity of the transition state to substituents on the nucleophile. Molecular models show that the methyl group of acetate esters interferes with a parallel alignment of the substituted benzene rings in a tetrahedral intermediate or transition state, so that interactions of this kind are not likely to occur with ring-substituted phenyl acetates.

**Reactions of Phenolate Anions with Nitrophenyl Acetates.** In contrast to the reactions of nitrophenyl formates, the reactions of substituted phenolate anions with *m*-nitrophenyl, *p*-nitrophenyl, and 3,4-dinitrophenyl acetate follow linear Brønsted-type correlations with similar or identical slopes for the reactions of substituted phenolate anions and substituted *o*-chlorophenolate anions, as shown in Figures 5 and 6. The slower reaction of the *o*-chloro- and *o*-methyl-substituted nucleophiles with phenyl acetates, by a factor of 1.5–2, may be accounted for by steric hindrance from the ortho substituent. There is also little or no steric effect of one or two *o*-fluoro substituents in the reaction with *p*-nitrophenyl acetate. However, the 2,3,5,6-tetrafluorophenolate and pentafluorophenolate ions show negative deviations from the correlation by a factor of 3 (Figure 6, solid squares), which could represent a steric effect or, possibly, a steeper slope of the Brønsted correlations for fluorine-substituted phenolate ions. The observed trend of steric effects,  $\text{CH}_3 > \text{Cl} > \text{F}$ , is consistent with Taft's

**Table III.** Brønsted  $\beta_{\text{nuc}}$  Values for the Reactions of Substituted Phenolate Anions with Substituted Phenyl Acetates and Formates

ester	$\beta_{\text{nuc}}$		$\text{p}K_{\text{lg}}$
	substituted phenolate anions <sup>a</sup>	substituted <i>o</i> -chlorophenolate anions <sup>a</sup>	
Phenyl Acetates			
MNPA	0.66	0.63	8.19
PNPA	0.59	0.73	7.15
3,4-DNPA	0.53	0.58	5.28
Phenyl Formates			
MNPF	0.64	0.90	8.19
PNFF	0.51	0.81	7.15
3,4-DNPF	0.43	0.63	5.28

<sup>a</sup>Substituents at the meta or para positions.

$E_s$  steric parameters,<sup>13</sup> which are derived from rate constants for acid-catalyzed ester hydrolysis, and with  $S^0$  ortho steric parameters,<sup>14</sup> which are derived from the reactions of substituted pyridines with methyl iodide.

The linear Brønsted-type correlations for the reactions of substituted phenolate ions with 3-nitrophenyl acetate, 4-nitrophenyl acetate, and 3,4-dinitrophenyl acetate that are shown in Figures 5 and 6 show no evidence for the break near  $\Delta\text{p}K = 0$  that is expected for a stepwise mechanism that proceeds through a tetrahedral intermediate. The data are consistent with an associative concerted mechanism of substitution in which attack of the nucleophile and departure of the leaving group are coupled, in agreement with the conclusion of Williams and co-workers.<sup>3,4</sup>

Our results differ from the earlier work in that separate correlation lines are followed for the reactions of meta- and para-substituted phenolate ions and for *o*-chloro-substituted phenolate ions. One significant difference between the current study and the earlier work<sup>3,4</sup> is that the Brønsted correlations reported here are based upon rate constants and  $\text{p}K_a$  values of phenols that were determined under identical conditions.

Chrystiuk and Williams have shown that the reactions of substituted pyridines with *N*-(methoxycarbonyl)isoquinolinium ion follow a linear Brønsted-type correlation with  $\beta_{\text{nuc}} = 0.58$  for pyridines with  $\text{p}K_a$  values above and below the  $\text{p}K_a$  of the leaving group, consistent with a concerted reaction mechanism.<sup>15</sup>

Guthrie has concluded from an analysis by the Marcus treatment that there is essentially no barrier for the collapse of the tetrahedral intermediate  $\text{T}^-$  formed from essentially all aryl acetates with  $\text{p}K_a$  values of  $< 11$  for the leaving groups.<sup>16</sup>

**Structure-Reactivity Correlations and Interaction Coefficients.** The slopes of Brønsted-type correlations of  $\log k$  against the  $\text{p}K_a$  of the nucleophile,  $\beta_{\text{nuc}}$ , for reactions of the formate and acetate esters with meta- and para-substituted phenolate ions and with meta- and para-substituted *o*-chlorophenolate ions are summarized in Table III. The values of  $\beta_{\text{nuc}}$  for the reactions with phenyl acetates are in the range 0.5–0.7 and do not differ significantly for the two classes of nucleophile. The values of  $\beta_{\text{nuc}}$  and  $-\beta_{\text{lg}}$  for the reactions with phenyl formates are slightly smaller compared with  $\beta_{\text{nuc}}$  and  $-\beta_{\text{lg}}$  for the less reactive phenyl acetates.

However, the values of  $\beta_{\text{nuc}}$  in the range 0.6–0.9 for reactions of the phenyl formates with substituted *o*-chlorophenolate anions are significantly larger compared with the values of  $\beta_{\text{nuc}} = 0.4$ –0.6 for reaction with meta- and para-substituted phenolate anions. The values of  $\beta_{\text{nuc}}$  for reaction with the substituted phenyl acetates are smaller than those reported by Williams and co-workers,<sup>4</sup> possibly because these workers included ortho- and para-substituted phenolate nucleophiles in the same correlation.

The slopes of Brønsted-type correlations of  $\log k$  against the  $\text{p}K_a$  of the leaving group,  $-\beta_{\text{lg}}$ , are summarized in Table IV. The values of  $-\beta_{\text{lg}}$  are in the range 0.3–0.9 and, with one exception, are larger for the acetate than for the formate esters. The formate

(13) Taft, R. W. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956.

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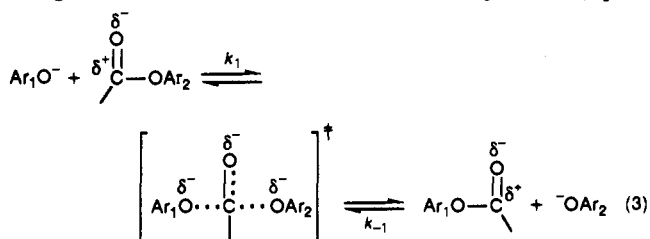
(16) Guthrie, J. P. *J. Am. Chem. Soc.* 1991, 113, 3941–3949.

**Table IV.** Brønsted  $\beta_{lg}$  Values for the Reactions of Substituted Phenolate Anions with Substituted Phenyl Formates and Acetates

substituted phenolate nucleophile	$pK_{nuc}$	$-\beta_{lg}$	
		formates	acetates
4-CH <sub>3</sub>	10.09	0.31	0.50
H	9.81	0.34	0.48
4-Cl	9.26	0.39	
3-Cl	8.81	0.38	
3,4-Cl <sub>2</sub>	8.44	0.42	0.56
3,5-Cl <sub>2</sub>	8.03	0.46	0.55
3,4,5-Cl <sub>3</sub>	7.63	0.48	0.59
2Cl-4-CH <sub>3</sub>	8.68	0.46	0.56
2-Cl	8.32	0.51	0.60
2,4-Cl <sub>2</sub>	7.75	0.56	0.60
2,3-Cl <sub>2</sub>	7.51	0.60	0.63
2,4,5-Cl <sub>3</sub>	6.88	0.71	0.63
2,3,5-Cl <sub>3</sub>	6.58	0.66	
F <sub>3</sub>	5.41	0.92	

esters show a large increase in the sensitivity of the rate to the  $pK_a$  of the leaving phenolate ion, from  $\beta_{lg} = -0.3$  to  $-0.9$ , with a decrease in the basicity of the attacking phenolate ion from  $pK_a = 10.1$  to 5.4. There is a similar, but much smaller, increase in the magnitude of  $\beta_{lg}$  for reactions with the acetate esters, from  $-0.5$  to  $-0.6$ , with a decrease in the basicity of the attacking phenolate ion from 10.1 to 6.9.

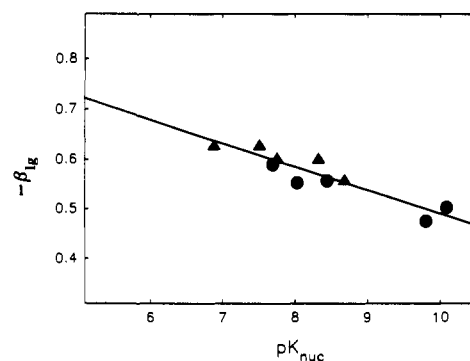
The interpretation and "bookkeeping" of structure-reactivity correlations is facilitated by their description in terms of "effective charges" on the reactants, transition state, and products (eq 3).



Thus, the effective charge,  $\delta^-$ , on an attacking phenolate ion in the transition state of a reaction with  $\beta_{nuc} = 0.7$  is  $-(1.0 - 0.7) = -0.3$ . The equilibrium constants for the formation of acetate esters at equilibrium are described by  $\beta_{eq} = 0.7$  for the reaction with substituted phenols or  $\beta_{eq} = 1.7$  for reaction with substituted phenolate ions.<sup>11</sup> The esters behave *as if* there is 0.7 more positive charge on the phenolic oxygen atom in the ester than in the free phenol, as a consequence of the strong electron-withdrawing effect of the carbonyl group.

The values of  $\beta_{nuc}$  and  $\beta_{lg}$  are generally in the same range for a given reaction class. To the extent that these parameters are measures of bond formation and bond breaking in the transition state, this suggests that the reactions are neither strongly associative nor strongly dissociative. However, there is an apparent inconsistency, or *imbalance*, of the structure-reactivity coefficients and effective charges in the transition states of these reactions.<sup>17</sup> The coefficients for the forward and reverse reactions are related to  $\beta_{eq}$  for the effect of substituents on the equilibrium constant according to  $\beta_{lg} = \beta_{nuc} - \beta_{eq}$ . Therefore, a value of  $\beta_{nuc} = 0.6$  for the attack of substituted phenolate ions on a phenyl ester requires a value of  $\beta_{lg} = \beta_{nuc} - \beta_{eq} = 0.6 - 1.7 = -1.1$  for the reaction of a phenolate ion with a series of substituted phenyl esters. This value is much larger in magnitude than the observed values of  $\beta_{lg}$  in the range  $-(0.3-0.7)$ , with the exception of one value of  $\beta_{lg} = -0.9$  (Table IV).

This imbalance may be attributed to the fact that all of the leaving groups are nitrophenyl esters. The low  $pK_a$  values of *o*- and *p*-nitrophenols arise in large part from resonance delocalization of the negative charge of the phenolate anion into the nitro substituent, and there is an imbalance in the amount of this delocalization of charge in the transition state compared with the product *p*-nitrophenolate ion. Thus, if there is 50% rehybridization

**Figure 7.** The dependence of the Brønsted  $\beta_{lg}$  on the  $pK_a$  of the phenolate nucleophile for the reactions of phenyl acetates with meta- or para-substituted phenolate anions (circles) and meta- or para-substituted *o*-chlorophenolate anions (triangles).

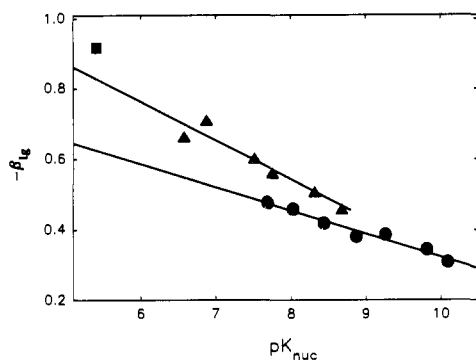
and 50% delocalization of negative charge in the product and 50% bond breaking in the transition state, there will be only  $0.5 \times 25\% = 12.5\%$  delocalization in the transition state if rehybridization and solvation of the developing negative charge on the nitro group have proceeded by 50% in the transition state.<sup>17</sup> Consequently the effective  $pK_a$  of the *p*-nitrophenolate anion in the transition state can be much larger than would be expected from its  $pK_a$  value at equilibrium, the difference between this effective  $pK_a$  and the  $pK_a$  of *m*-nitrophenol will be smaller, and the absolute value of  $\beta_{lg}$  will be larger.

**Cross-Correlation Coefficients and Changes in Transition-State Structure.** The value of a cross-correlation coefficient,  $p_{xy}$ , which is defined as  $\partial\beta_{lg}/\partial(pK_{nuc}) = \partial\beta_{nuc}/\partial(pK_{lg})$ , reflects the degree to which the bond making with the attacking nucleophile and the bond breaking of the leaving group are coupled in the transition state. A positive value of  $p_{xy}$  is expected for an associative concerted mechanism, in which there is a significant interaction between the leaving and attacking groups, and a zero value of  $p_{xy}$  is expected for a stepwise dissociative mechanism, in which the bond-making and bond-breaking events are completely uncoupled, because this mechanism requires that the bond to the leaving group must be completely broken before the bond to the attacking nucleophile is made. This difference can be used to distinguish between a concerted and a stepwise *dissociative* reaction mechanism.

However, a value of  $p_{xy} > 0$  may be observed in a stepwise *associative* mechanism, in which a tetrahedral addition intermediate is formed on the reaction pathway. Because the bond to the leaving group is still present in the transition state leading to the tetrahedral intermediate, there can be a significant interaction between the leaving group and the attacking nucleophile that results in a nonzero value of the cross-correlation coefficient. Therefore, a positive value of  $p_{xy}$  may be observed in both the stepwise associative and the concerted mechanisms and does not distinguish between the two mechanisms.

Figure 7 shows that there is a significant decrease in  $-\beta_{lg}$  with increasing  $pK$  of the nucleophile for reactions of phenolate ions with a series of substituted phenyl acetates. This decrease corresponds to a value of  $p_{xy} = \partial\beta_{lg}/\partial(pK_{nuc}) = \partial\beta_{nuc}/\partial(pK_{lg}) = 0.04$  and shows that there is a significant interaction between the nucleophile and the leaving group in the transition state that causes a change in the structure of the transition state. There is no significant difference in the behavior of the meta- and para-substituted phenolate anions (circles) and the meta- and para-substituted *o*-chlorophenolate anions (triangles). Hengge has recently shown that there is a significant secondary <sup>15</sup>N isotope effect in the reaction of phenoxide ion with *p*-nitrophenyl acetate containing <sup>15</sup>N in the leaving group. This result shows that there is a significant interaction between the attacking phenoxide ion and the leaving group in the rate-determining transition state and is also consistent with a concerted displacement mechanism.<sup>18</sup> A

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**Figure 8.** The dependence of the Brønsted  $\beta_{lg}$  on the  $pK_a$  of the phenolate nucleophile for the reactions of phenyl formates with meta- or para-substituted phenolate anions (circles), meta- or para-substituted *o*-chlorophenolate anions (triangles), and 2,3,5,6-tetrafluorophenolate anion (square).

$^{15}\text{N}$  isotope effect does not provide rigorous proof of a concerted mechanism, because there may be a decrease in the C–N bond order in a transition state for rate-determining attack of the nucleophile to form a tetrahedral intermediate. However, there is no detectable isotope effect in the reaction with hydroxide ion, which presumably represents rate-limiting nucleophilic attack.<sup>18</sup>

Figure 8 shows that the reactions of phenyl formates show a larger change in transition-state structure with increasing  $pK_a$  of the nucleophile, and this change is different for meta- and para-substituted phenolate anions (circles) and meta- and para-substituted *o*-chlorophenolate anions (triangles). The change in  $-\beta_{lg}$  is consistent with  $p_{xy} = 0.07$  for the reactions of meta- and para-substituted phenolate anions (circles) and  $p_{xy} = 0.11$  for the reactions of meta- and para-substituted *o*-chlorophenolate anions and 2,3,5,6-tetrafluorophenolate ions (triangles). This difference provides additional evidence that the structures of the transition states for the reactions of the two classes of phenolate ions are different.

Buncel and Hoz have shown that the rate constants for reactions of substituted phenolate ions with phenyl acetates in a series of different solvents follow a correlation with  $\sigma$ , not  $\sigma^-$ . This shows that there is not a measurable amount of electron donation by resonance into the aromatic system of the leaving phenolate ion in the transition state of the reaction.<sup>19</sup> However, this result does not show that the reaction is not concerted, because this resonance may not develop to a measurable extent until the bond to the leaving group is largely broken. It is likely that there is *imbalance* between the amount of C–O cleavage and the development of electron delocalization.<sup>17</sup>

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## Identification of the Active Catalyst in the Rhodium Porphyrin-Mediated Cyclopropanation of Alkenes

David W. Bartley and Thomas Kodadek\*

Contribution from the Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712. Received July 24, 1992

**Abstract:** Iodorhodium porphyrins are extremely active catalysts for the cyclopropanation of alkenes by diazo esters. Mechanistic studies of this reaction have resulted in the spectroscopic characterization of several potential organometallic intermediates in the reaction, including a novel metal diazonium complex resulting from alkylation of the rhodium center by ethyl diazoacetate. This compound is thought to decompose to a metal carbene that subsequently transfers the carbene fragment to the substrate. While our studies have led to a satisfactory general picture of the reaction mechanism, the axial ligation state of the metal under typical catalytic conditions remains unclear. We show here that the predominant active species is an iodoalkylrhodium complex that results from attack of the metal carbene by iodide. Iodination of the carbene is competitive with cyclopropanation even though the substrate is present in a vast excess. The partition ratio (cyclopropanation events/iodination events) is approximately 100:1.

Callot and co-workers reported that iodorhodium porphyrins are efficient catalysts for the cyclopropanation of alkenes by diazo esters.<sup>1</sup> The porphyrin-catalyzed reactions exhibit an unusual propensity to provide mostly the *syn* diastereomer when bulky macrocycles are used. We have been interested in developing asymmetric versions of this system using chiral porphyrin ligands, since optically pure *syn* cyclopropyl esters are not readily accessible with current methodology. Unfortunately, the enantioselectivities obtained to date are not synthetically useful.<sup>2,3</sup> In order to rationally design more selective catalysts, we recently initiated a detailed investigation of the reaction mechanism, with an emphasis on the characterization of intermediates in the catalytic cycle. In particular, stoichiometric reaction between iodorhodium tetra-*p*-tolylporphyrin (RhTTPI) and ethyl diazoacetate (EDA) led to the spectroscopic characterization of the diazonium complex **2** (see Scheme I) at low temperatures.<sup>4</sup> When this species was

allowed to warm in the presence of an alkene, a 68% yield of cyclopropanes was obtained with concomitant evolution of 1 equiv of nitrogen.<sup>4</sup> When the diazonium complex is warmed in the absence of alkene, the previously characterized<sup>5,6</sup> iodoalkyl complex **4** is produced in quantitative yield.<sup>4</sup> These observations strongly implicate the intermediacy of metallocarbene **3** as the reactive intermediate (Scheme I). Cyclopropanes and iodoalkyl complex **4** represent the two possible products of nucleophilic attack on the carbene carbon, in the first case by an alkene and in the latter by iodide. In addition to the diazonium complex, both mono- and bis-alkene  $\pi$  complexes of RhTTPI have been observed (Scheme I). A kinetic analysis of the reaction suggests that these complexes are not attacked directly by ethyl diazoacetate but rather compete with the carbene precursor for ligation to rhodium. Another possibility is that the nature of a coordinated alkene might affect

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(4) Maxwell, J. L.; Brown, K. C.; Bartley, D.; Kodadek, T. *Science* **1992**, *256*, 1544.  
 (5) Callot, H. J.; Schaeffer, J. *J. Chem. Soc., Chem. Commun.* **1978**, 937.  
 (6) Maxwell, J.; Kodadek, T. *Organometallics* **1991**, *10*, 4.